NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Regorafenib for previously treated hepatocellular carcinoma [ID1519] (rapid review TA514)

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Regorafenib for previously treated hepatocellular carcinoma (rapid review TA514) [ID1519]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

NICE guidance

Regorafenib for previously treated 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 are 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.

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

1 Recommendations

1.1 Regorafenib is not recommended for treating advanced unresectable hepatocellular carcinoma in adults who have had sorafenib.

1.2 This recommendation is not intended to affect treatment with regorafenib 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.

Why the committee made these recommendations

In the NHS, advanced unresectable hepatocellular carcinoma is mostly treated with sorafenib. For people who cannot tolerate sorafenib, or whose disease progresses with sorafenib, the only current option is best supportive care. Regorafenib is a possible treatment option after sorafenib instead of best supportive care, in line with its marketing authorisation.

Clinical trial evidence in people with advanced hepatocellular carcinoma who have already had sorafenib, have an Eastern Cooperative Oncology Group (ECOG) performance status score of either 0 or 1, and Child-Pugh grade A liver impairment shows that people having regorafenib live longer than people having best supportive care. However, the survival benefit with regorafenib is unclear in people who cannot tolerate sorafenib, have a poorer ECOG performance status or more severe liver disease. These people were not included in the trial so it is uncertain whether the results of the trial would translate into similar benefits in the NHS.

The company responded to the committee's preferred assumptions after consultation and submitted a further model incorporating these assumptions for overall survival extrapolation, full dose and pooled resource use surveys.

Regorafenib meets NICE's criteria to be considered a life-extending treatment at the end of life. The most plausible cost-effectiveness estimates are higher than those NICE normally considers an acceptable use of NHS resources for end-of-life treatments. Therefore regorafenib cannot be recommended for routine use in the NHS.

Regorafenib is not recommended through the Cancer Drugs Fund because the uncertainties in the clinical and cost effectiveness cannot be resolved by data collection in the Cancer Drugs Fund, and regorafenib does not have plausible potential to be cost effective.

2 Information about regorafenib

Marketing authorisation	Regorafenib (Stivarga, Bayer) is indicated as 'monotherapy for the treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib'. 'Regorafenib is not recommended for patients with severe hepatic impairment (Child-Pugh grade C) because it has not been studied in this population'.
Dosage in the marketing authorisation	160 mg (4×40 mg tablets) orally once daily for 3 weeks followed by 1 week off therapy. A 4-week period is considered a treatment cycle.
Price	The list price per treatment cycle for 160 mg of regorafenib is £3,744.00 (excluding VAT; British national formulary online [accessed October 2017]). The company has agreed a patient access scheme with the Department of Health. If regorafenib had been recommended, this scheme would provide a simple discount to the list price of regorafenib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 4) considered evidence submitted by Bayer and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Unmet need

People with advanced hepatocellular carcinoma would welcome a new treatment option

3.1 Advanced unresectable hepatocellular carcinoma is often diagnosed late in life and has a poor survival prognosis. It is a debilitating condition with many distressing symptoms. The clinical and patient experts noted that people with advanced unresectable hepatocellular carcinoma have limited treatment options and will have been through many unsuccessful treatments in a long treatment pathway. They noted that improving quality of life and even small extensions to length of life are of considerable importance to this patient group. The committee agreed that people with advanced unresectable hepatocellular carcinoma who have already had sorafenib have an unmet clinical need, and would welcome other treatment options.

Treatment pathway

Regorafenib is a potential option for advanced unresectable hepatocellular carcinoma after sorafenib

3.2 If surgical or locoregional treatments fail or are unsuitable, systemic therapy with sorafenib is the only active treatment option available for people with hepatocellular carcinoma. NICE technology appraisal guidance on sorafenib recommends it as an option for treating advanced hepatocellular carcinoma only in people with Child-Pugh grade A liver impairment. During the appraisal of sorafenib, the committee noted that people need both adequate liver function and performance status to have sorafenib in clinical practice in England, and that treatment should be restricted to people with Child-Pugh grade A liver function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. The clinical expert explained that best supportive care or clinical trials are the only options for people whose disease progresses despite taking sorafenib, or who cannot tolerate it. There are no second-line therapies

available and a palliative care approach is taken for these patients. The committee noted that regorafenib offers a potential second-line treatment option for people who cannot tolerate, or whose disease progresses on, sorafenib.

Clinical evidence

Regorafenib is more clinically effective than best supportive care in the clinical trial population

3.3 The company's clinical evidence came from 1 trial. RESORCE (n=573) was an international, phase III, multicentre, randomised, double-blind, placebo-controlled trial comparing regorafenib (plus best supportive care) with placebo (plus best supportive care). The trial included people whose disease had progressed on sorafenib, who had either 160 mg regorafenib orally once daily for weeks 1 to 3 of each 4-week treatment cycle or best supportive care. Up to 2 regorafenib dose reductions because of toxicity were allowed (from 160 mg to 120 mg to 80 mg). The primary outcome was overall survival, with secondary outcomes including progression-free survival. The committee noted that the results showed a small and statistically significant median overall survival gain of 2.8 months for regorafenib (10.6 months; 95% confidence interval [CI] 9.1 to 12.1) compared with best supportive care (7.8 months; 95% CI 6.3 to 8.8). The committee noted that the hazard ratio for overall survival for regorafenib compared with best supportive care was 0.63 (95% CI 0.50 to 0.79) and that regorafenib offered an important survival benefit for people with advanced hepatocellular carcinoma. Median progression-free survival was statistically significantly better for regorafenib (3.1 months, 95% CI 2.8 to 4.2) than for best supportive care (1.5 months, 95% CI 1.4 to 1.6). The committee noted that the hazard ratio for progression-free survival for regorafenib compared with best supportive care was 0.46 (95% CI 0.37 to 0.56), which represented a clinically relevant reduced risk of progression for the regorafenib group. It also heard that quality-of-life scores were generally similar across treatment arms with different measures, including EQ-5D. Scores were slightly worse for regorafenib than for best supportive care but these differences did not pass the 'minimally important difference' threshold established in the literature. The committee noted that there were only 5 clinical trial centres in the UK, with 20 patients randomised to treatment in 4 of the centres. The ERG noted that RESORCE was a high-quality randomised controlled trial, with a low risk of selection,

performance, attrition and reporting bias. Therefore, the committee concluded that regorafenib offers an important gain in progression-free and overall survival compared with best supportive care.

The generalisability of the population included in the RESORCE trial to clinical practice in England is uncertain

3.4 RESORCE included people with advanced unresectable hepatocellular carcinoma who:

- previously had sorafenib
- mostly had Child-Pugh grade A liver impairment
- had an ECOG performance status score of either 0 or 1.

The committee noted that regorafenib's marketing authorisation is broader than the trial population, because the trial did not include people who:

- had Child-Pugh grade B liver impairment
- had an ECOG performance status of 2 or more
- cannot tolerate sorafenib.

The clinical expert noted that RESORCE included a highly selective population who could tolerate sorafenib well and also highlighted that post-trial studies investigating survival outcomes for sorafenib, which included patients outside of the strict trial criteria, showed lower survival than predicted in the main sorafenib trial. The clinical expert stated that the toxicity and efficacy of regorafenib in people who could not tolerate sorafenib, with Child-Pugh grade B liver impairment and with an ECOG performance status of 2 or more was unknown. The committee therefore concluded that benefits could not be extrapolated outside the trial population because of the uncertainty in survival benefit for people not included in RESORCE but covered by the broader marketing authorisation for regorafenib.

An audit of sorafenib use shows differences between the RESORCE trial population and the population in clinical practice in England

3.5 A 2017 audit of sorafenib use in the UK by King et al. found that sorafenib is used in patients who have an ECOG performance status of 2 or more and

Child-Pugh grade B liver impairment (21% and 16% of the audit population respectively). The committee noted that sorafenib is recommended as an option for treating advanced hepatocellular carcinoma only for people with Child-Pugh grade A liver impairment, but that people progressing on sorafenib are likely to have further deterioration in liver impairment (Child-Pugh status) and ECOG performance status. The clinical expert explained that because sorafenib and regorafenib are both tyrosine kinase inhibitors with similar mechanisms of action, people who cannot tolerate sorafenib may also be unable to tolerate regorafenib (although there are no data to support this at this time). Therefore, an estimated 30% to 50% of the population whose disease progressed on sorafenib would be eligible for regorafenib. The committee also noted that all patients had a treatment-related adverse event, and that quality-of-life values were only maintained rather than improved with regorafenib treatment. The committee acknowledged comments received during consultation that use of regorafenib should be restricted based on the eligibility criteria in the RESORCE trial. It concluded that given the lack of evidence in people with an ECOG performance status of 2 or more, with Child-Pugh B liver impairment and who cannot tolerate sorafenib, there is considerable uncertainty in the efficacy of regorafenib in populations not included in RESORCE but covered by its marketing authorisation.

The company's economic model

The model structure is appropriate for decision-making

3.6 The company used a partitioned survival model with 3 health states (progression free, progressed disease and death). The committee, however, noted the uncertainty in the model about people covered by the marketing authorisation for regorafenib who were excluded from RESORCE. The committee understood that all efficacy and clinical parameters in the model were derived using patient-level data from RESORCE. The committee noted that data for progression-free survival from RESORCE represented a full pattern of progression, so no extrapolation was needed and the progression-free survival curve was taken directly from the observed trial Kaplan–Meier data. The committee accepted that standard parametric curve fitting was done using patient-level data from RESORCE for overall survival.

The company submitted a model suitable for decision-making

3.7 After consultation, the company submitted a further model using the committee's preferred assumptions, specifically:

- extrapolating overall survival using a Weibull distribution
- using the full dose of 160 mg per cycle
- resource use estimates from pooled 2015 and 2007 surveys
- full extrapolation of time-to-treatment discontinuation.

This model originally contained errors, which resulted in the company submitting several iterations of the economic model and response to consultation. The committee noted this divergence from NICE processes but accepted the company's model as suitable for decision-making.

Overall survival extrapolation in the economic model

The Weibull distribution is most appropriate for extrapolating overall survival

3.8 In the company's original base case, a dependent lognormal curve was used to model overall survival. The ERG disagreed with this choice of curve and the fitting of dependent models because the lognormal function is an accelerated failure time model. The ERG also considered the choice of the lognormal curve to be inappropriate, based on its clinical expert's advice that the model-predicted sustained difference in overall survival between the regorafenib and best supportive care curves beyond 35 cycles was unrealistic in a population with progressed hepatocellular carcinoma. The committee heard from the clinical expert that the 5-year survival suggested by the lognormal curve was implausible because the modelled population was elderly, with advanced disease refractory to most previous treatments. The ERG noted that the NICE reference case places most significance on clinical plausibility and preferred the Weibull curve based on clinical opinion and goodness-of-fit to observed data. The Cancer Drugs Fund clinical lead highlighted a recent study reporting mature follow-up data on patients having sorafenib (plus other treatments) in specialist centres. This showed relatively high 5-year survival rates of 5% to 8%, suggesting that some people may have indolent disease. The committee noted that this study included a sorafenib population and that the population having

regorafenib are likely to have lower 5-year survival rates because they are further along the treatment pathway. The committee concluded that the company's preferred dependent lognormal curves were overly optimistic and technically incorrect. It preferred the use of independent Weibull curves, but recognised that these were associated with significant uncertainty.

3.9 The committee considered that the Weibull distribution remained the most appropriate choice for extrapolating overall survival because no new evidence was provided during consultation. However, in its updated analyses, the company extrapolated overall survival with independently fitted Gompertz and exponential distributions, as well as the Weibull distribution. The company noted that the ERG's clinical expert also considered the Gompertz and exponential extrapolations to be clinically plausible, so it provided cost-effectiveness results for these 3 distributions individually combined with its updated assumptions. The ERG explained that its preference for the Weibull distribution was not based only on clinical opinion of its plausibility, but also on goodness-of-fit to the observed data and the empirical hazards. The committee noted that based on the empirical hazards (particularly in the best supportive care arm), an exponential curve was not appropriate and that the Akaike information criterion/Bayesian information criterion for Weibull fit better than Gompertz by more than 5 points. The company provided no further information to support the use of an exponential or Gompertz curve. The committee reiterated that the Weibull was the most appropriate distribution for extrapolating overall survival, in preference to the Gompertz and exponential curves.

Time-to-treatment discontinuation in the economic model

Treatment discontinuation in RESORCE may not represent NHS clinical practice

3.10 The committee noted that the number of people continuing treatment with regorafenib despite disease progression was high in RESORCE and that time-to-treatment discontinuation did not equate to time to progression. The clinical expert explained that this did not represent clinical practice in England because 80% of patients would stop treatment on progression. They highlighted that the number of people continuing treatment despite disease progression and the efficacy of treatment in these patients was uncertain. The committee concluded

that the rate of treatment discontinuation in RESORCE is unlikely to represent NHS clinical practice.

Including the survival benefits but excluding the costs of post-progression treatment is unreasonable

3.11 The company agreed that most people will discontinue treatment if their disease progresses, and accepted that people would have less treatment in practice than in RESORCE. The company did a new survey which investigated post-progression treatment, and found that 8 of the 9 respondents would stop treatment at progression. In response to consultation, the company presented a scenario whereby an area under the log-logistic time-to-treatment discontinuation curve was applied adjusting for 80% of patients stopping treatment at or before progression and 20% having treatment post-progression. This resulted in people having an average of approximately 1 cycle of post-progression treatment. The ERG explained that although current practice in England may differ from that observed in RESORCE, the survival estimates observed in RESORCE may have been influenced by the post-progression treatment. Therefore, it was inappropriate to include health benefits associated with post-progression treatment, but to exclude a proportion of the costs associated with generating those health gains. The committee concluded that adjusting for cost alone for 20% of people having treatment post-progression was unreasonable.

Costs in the economic model

Assuming additional days of drug wastage to model drug cost is arbitrary and associated with significant uncertainty

3.12 The company's original base case included cost savings from dose reductions and treatment interruptions for regorafenib. The ERG's clinical advisers noted that NHS prescribing practices do not account for reduced frequency of individual prescriptions for patients with leftover pills. Cost reductions included in the company's model would therefore probably not be fully realised in clinical practice. The clinical expert explained that despite efficiency measures in the NHS, it would be reasonable to assume some drug wastage in clinical practice even if the patient's dose were reduced. This was also supported by the Cancer Drugs Fund clinical lead who stated that people are normally given a month's supply of a drug, and any leftover pills cannot be used for other

patients. Therefore, a month's supply should be modelled to take wastage into account. The company provided evidence from pharmacists from 2 of the largest tertiary centres in the UK supporting pack splitting to minimise wastage of sorafenib and other oral tyrosine kinase inhibitors. Healthcare at Home, which distributes sorafenib in England, also provided a supportive statement after consultation. The committee acknowledged that although wastage could be minimised, the pharmacists' evidence provided by the company suggested that it could not be eliminated entirely. In response to consultation, the company presented a scenario whereby costs for the actual treatment taken (as average doses in RESORCE) was modelled but with an assumption that every patient wastes additional days of medicine at the maximum daily dose over the course of their treatment. This wastage was applied as a one-off cost to every patient and reflects an assumption between the company's base case and committee's preferred assumptions. It was unclear in this scenario whether the observed reduced dosage in RESORCE reflected patients randomly missing tablets, or whether there had been a planned reduction in dose (in which case the reduction in regorafenib costs would be appropriate) because the company had not submitted any data on individual patient dosages which could reduce this uncertainty. The committee considered the assumption of drug wastage to be arbitrary and therefore associated with significant uncertainty. The ERG did 2 exploratory analyses: a pessimistic scenario in which drug costs were assumed to be 160 mg per day (full pack dose), and an optimistic scenario in which drug costs were assumed to be 160 mg multiplied by relative dose intensity (RDI) to account for this uncertainty (see section 3.18). The ERG also highlighted 2 further concerns with the company's modelling of drug costs. It noted that the projected log-logistic time-to-treatment discontinuation curve and the Weibull overall survival curves crossed at around 4 years. This is logically inconsistent because it indicates that patients are still incurring drug costs after they have died. In addition, the modelled RDI followed an unusual pattern for which no rationale was provided. The committee concluded that the company's approach to modelling drug wastage was associated with significant uncertainty.

Pooling estimates from the 2007 and 2015 surveys is appropriate for health state resource use costs

3.13 In its original base case, the company used clinician surveys to estimate resource use associated with sorafenib and best supportive care. It assumed that the sorafenib results would also apply to regorafenib. The committee noted

that the company used a survey from 2015 with 3 clinical experts to inform resource use in its original base case. The committee heard from the ERG that the company did not reference an earlier survey done in 2007 using 4 UK clinicians. It noted that the company reiterated its preference for the 2015 survey because estimates from 2007 preceded the availability of sorafenib and were not based on clinical experience. The committee considered that the new survey might have produced better estimates for the sorafenib arm because it would take into account experience with sorafenib, but noted that estimates for the best supportive care arm from the original survey should be equally valid when compared with those of the new survey. The committee was not convinced of the robustness of the surveys and noted the small number of clinicians involved and the variability in the clinicians' responses. Without any better quality data, the committee concluded that it would be more appropriate to pool estimates from the 2007 and 2015 surveys for health state resource use costs.

The hospital admission rate derived from the new survey is appropriate

3.14 In response to consultation, the company provided results from a new survey designed to better understand the rate of hospitalisations in the NHS, and to address the ERG's concerns with how questions in the original surveys may have been interpreted. The results supported the statement from the clinical expert in the appraisal consultation document that few people are admitted to hospital. These results were then incorporated in the company's updated model. The ERG was broadly satisfied with the new survey, but it noted that resources associated with patients who have post-progression treatment with regorafenib are unlikely to be generalisable to those associated with people who stop regorafenib after progression. Nevertheless, the committee concluded that the hospital admission rates derived from the new survey is the best available data.

Utility values in the economic model

Utility values derived from RESORCE using EQ-5D data are too high for a population with progressed disease

3.15 The Cancer Drugs Fund clinical lead noted that the utility values appear high for a population of patients who enter the model after progressing on sorafenib even if the patients have an ECOG performance status of 0 or 1 at entry. The clinical expert said that most patients tend to have side effects from treatment

that have a serious impact on their quality of life, which did not appear to be reflected in the utility values. The ERG had concerns about the face validity of the utility values collected in RESORCE using EQ-5D data because the utility decrement for progression (−0.048) appeared low for an advanced hepatocellular population with progressed disease. The company obtained EQ-5D data directly from the trial as recommended in the NICE methods guide. However, the ERG explained that the EQ-5D questionnaire was completed on the first day of each treatment cycle, when a patient had not had treatment for a week. So any adverse effects of regorafenib treatment may not have been fully captured. The ERG noted that reducing the health state utility values will increase the incremental cost-effectiveness ratio (ICER), although an exact figure was not provided. The committee concluded that the high utility values used in the model did not seem clinically plausible despite EQ-5D data from the trial being used and that this was likely to have resulted in an underestimate of the ICER.

The company's updated economic analysis

The company's ICER for regorafenib compared with best supportive care ranges from £42,788 to £50,456 per QALY gained

3.16 The company's updated base-case deterministic ICER, provided in response to consultation, included both the committee's preferred assumptions from the appraisal consultation document and a number of company-preferred assumptions, specifically:

- using a revised rate of hospitalisations based on the new survey
- assuming that each patient wastes additional days of medicine at the maximum daily dose
- assuming that 80% of people stop treatment at or before progression, with only 20% having treatment post-progression.

3.17 The company considered that using these assumptions and extrapolating overall survival using Weibull, Gompertz and exponential distributions would produce plausible ICERs. The deterministic ICERs range from £42,788 to £50,456 per quality-adjusted life year (QALY) gained for regorafenib compared with best supportive care (probabilistic ICERs were not provided).

The ERG's updated exploratory economic analyses

The ERG's exploratory ICER for regorafenib compared with best supportive care ranges from £55,829 to £68,137 per QALY gained

3.18 The ERG did 4 exploratory analyses that investigated the effect of individual assumptions on the ICER for regorafenib compared with best supportive care. All 4 analyses extrapolated overall survival using a Weibull distribution and included corrections of errors in the company model (specifically when additional progression-free survival data points had erroneously been excluded from calculations, and when emergency department visits accrued no cost):

- Analysis 1: using cost of full pack (160 mg) dosing.
- Analysis 2: analysis 1, plus using company-modelled RDI instead of full pack dosing.
- Analysis 3: analysis 2, plus incorporating a logical consistency constraint to account for the projected log-logistic time-to-treatment discontinuation curve and the Weibull overall survival curve crossing at around 4 years.
- Analysis 4: analysis 3, plus using last observation carried forward RDI extrapolation instead of modelling RDI for regorafenib in the unusual pattern (as in the company model).

When combining all 4 analyses, the deterministic ICER was £55,829 per QALY gained.

3.19 The ERG also presented the most optimistic (analysis 4) and pessimistic (analysis 1) scenarios in terms of drug wastage in exploratory analyses using Weibull, Gompertz and exponential distributions. The ICERs for regorafenib compared with best supportive care ranged from £55,829 to £68,137 per QALY gained for the Weibull distribution and £48,510 to £60,910 per QALY gained using the Gompertz and exponential distributions.

The updated most plausible ICER after consultation

The most plausible ICER is above the range normally considered a cost-effective use of NHS resources

3.20 The committee accepted the ERG's corrections to the errors in the company's model. It noted that the ERG's most optimistic and pessimistic scenarios (in

terms of drug wastage), using the committee-preferred Weibull distribution, produced ICERs for regorafenib compared with best supportive care of £55,829 to £68,137 per QALY gained. The committee concluded that the most plausible ICER, incorporating the confidential patient access scheme for regorafenib compared with best supportive care, was over £50,000 per QALY gained and substantially above the range normally considered a cost-effective use of NHS resources.

End of life

Regorafenib meets NICE's end-of-life criteria when used in adults who have already sorafenib

3.21 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods.

- The committee discussed whether life expectancy without regorafenib would be less than 24 months. It noted that median overall survival was 7.8 months for best supportive care in RESORCE and that the mean modelled overall survival from the company model was 10.8 months. It heard from the ERG that any changes relating to parametric overall survival functions would not change the conclusions for this end-of-life criterion. The committee concluded that the short life expectancy criterion was met.
- The committee discussed whether a survival benefit of over 3 months could be expected for regorafenib compared with best supportive care. It noted that the median survival in the regorafenib arm of RESORCE was extended by 2.8 months. It also recalled that the average number of months of life gained with regorafenib, as estimated by the company's economic model, was 6.24 months compared with best supportive care. On balance, the committee agreed that it was reasonable to assume that the survival benefit of regorafenib is likely to exceed 3 months and concluded that the extension-to-life criterion was met.

Cancer Drugs Fund

Regorafenib does not meet the criteria to be included in the Cancer Drugs Fund

3.22 Having concluded that regorafenib could not be recommended for routine use, the committee then considered if it could be recommended for treating hepatocellular carcinoma within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. The committee understood that the company had not made a specific case for regorafenib to be considered for funding through the Cancer Drugs Fund. It also considered that the most plausible ICERs were substantially higher than the range normally considered to be a cost-effective use of NHS resources and that the data presented were mostly mature. The committee discussed whether a recommendation through the Cancer Drugs Fund could allow for data collection for the full population covered by the marketing authorisation, but agreed that the relevant data to inform a decision would not be collected within 2 years. The committee therefore concluded that regorafenib did not have plausible potential to satisfy the criteria for routine use, and that the clinical uncertainties could not be resolved through data collection within the Cancer Drugs Fund. Regorafenib did not meet the criteria to be included in the Cancer Drugs Fund.

Innovation

There is no evidence of any additional benefits of regorafenib

3.23 The patient and clinical experts explained that there is a significant unmet need for people with advanced unresectable hepatocellular carcinoma because of the limited treatment options available to them. The committee noted that best supportive care is currently the only treatment option available for people whose disease progresses with sorafenib, or who cannot tolerate it, and that regorafenib offers a valuable second-line treatment option. It concluded that regorafenib would be beneficial for patients, but it had not been presented with evidence of any additional benefits that were not captured in the measurement of QALYs.

Conclusion

Regorafenib is not recommended

3.24 The committee concluded that the most plausible ICER for regorafenib compared with best supportive care was over £50,000 per QALY gained, which is higher than the range usually considered a cost-effective use of NHS resources, even for end-of-life treatments. Regorafenib also did not meet the criteria to be recommended for use in the Cancer Drugs Fund. The committee concluded that it could not recommend regorafenib for treating advanced unresectable hepatocellular carcinoma in adults who have already had sorafenib.

4 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

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.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

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

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Accreditation

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

TA514 regorafenib for previously treated advanced hepatocellular carcinoma

Patient Access Scheme submission template

Bayer plc

Commercial in confidence data is highlighted

1 Introduction

The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2014) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) is to improve patients' access to medicines at prices that better reflect their value through Patient Access Schemes.

Patient Access Schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient Access Schemes propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for Patient Access Schemes is provided in the PPRS (2014).

Patient Access Schemes are proposed by a pharmaceutical company and agreed with NHS England, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2 Instructions for companies

This document is the Patient Access Scheme submission template for technology appraisals. If companies want the National Institute for Health and Care Excellence (NICE) to consider a Patient Access Scheme as part of a technology appraisal, they should use this template. NICE can only consider a Patient Access Scheme after formal referral from NHS England.

The template contains the information NICE requires to assess the impact of a Patient Access Scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Company evidence submission template' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal April 2018. The 'User guide for company evidence submission template' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed Patient Access Scheme. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that

has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a Patient Access Scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the Patient Access Scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal'

If you are submitting the Patient Access Scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the appraisal committee considered to be most plausible. No other changes should be made to the model.

3 Details of the Patient Access Scheme

3.1 Please give the name of the technology and the disease area to which the Patient Access Scheme applies.

Drug name	Regorafenib
Brand name	Stivarga®
Indications	• Regorafenib for previously treated advanced hepatocellular carcinoma • Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours

3.2 Please outline the rationale for developing the Patient Access Scheme.

The Patient Access Scheme was developed in response to the Final Appraisal Determination (FAD) for TA514 (regorafenib for previously treated advanced hepatocellular carcinoma).

The Committee considered the plausible ICER to be in the range of £55,829 to £68,137 per QALY, with variation between estimates due to one underlying assumption, the relative dose intensity of regorafenib used in the economic model:

- The lower bound ICER estimate (£55,829/QALY) assumed costs based on patients receiving the mean dose as observed in the RESORCE clinical trial. This accounted for dose reductions, used both in the trial and in clinical practice in response to toxicity.
- The upper bound ICER (£68,137/QALY) assumed costs based on the maximum daily dose being received (160mg). This scenario accounted

for a patient receiving a full pack of regorafenib each month and disposing of all unused medication at the end of each cycle.

Incorporation of treatment wastage in the economic model

The clinical benefit modelled for regorafenib matches the relative dose intensity observed in the RESORCE trial. Should a higher dose of regorafenib be implemented into the economic model, there must be consideration on how this would affect the clinical benefit, or alternatively it must be considered that this medication is not consumed and is classified as treatment wastage. No additional clinical benefit was incorporated into the model, the following sections detail how treatment wastage is considered in the model.

Treatment wastage can be due to two factors:

a) *Patients discontinuing treatment during a cycle:*

The economic model employed a half-cycle correction, where a months supply of treatment is costed at the start of each cycle for all patients remaining on treatment. The model therefore accounts for all possible wastage due to patients terminating treatment during a cycle.

Measures such as pack-splitting and use of weekly prescriptions (where the clinician decision is to not provide a full month of treatment) may lead to the submitted approach overestimating treatment wastage.

b) *Patients disposing of all unused tablets after each cycle and receiving a full pack at the start of each new treatment cycle:*

The committee acknowledged evidence presented from two large NHS tertiary centres where wastage of unused tablets is reduced through delaying the dispensing of new packs (or use of pack splitting) when patients have tablets left-over from the previous cycle (1). This practice alone has the potential to eliminate all remaining treatment wastage.

Patients did not receive the maximum dose intensity in the RESORCE trial due largely to planned dose reductions (2). Dose reductions or interruptions

due to adverse events occurred in 68% of the patients in the regorafenib group and 31% of patients in the placebo group (3). These were in accordance with the pre-specified trial protocol for recommended dose modifications for adverse events[1]. Dose reductions are used to control toxicity and are initiated by the treating clinician; guidance on recommended dose modifications and measures are listed in the SmPC (4).

In conclusion, there is no evidence from the RESORCE trial to suggest that patients were disposing of medication, or that use of regorafenib in clinical practice is associated with treatment wastage above that already accounted for in the model. Evidence suggests that the NHS has practices that can effectively control treatment wastage, where possible this practice should be shared across trusts.

Development of the Patient Access Scheme

To inform assumptions around dose intensity Bayer conducted a review of the previous 20 technology appraisals conducted for oral oncology treatments (5-24).

In 16 (80%) appraisals (5-20) the manufacturer used the relative dose intensity (RDI) as observed in the clinical trial (as per the lower bound ICER assumption of this appraisal). Only once was this assumption not accepted by the Committee (19). In this appraisal the RDI was 82%. The committee increased this by 8% to an RDI of 90% to account for treatment wastage.

More recently published NICE appraisals (25) and those currently in consultation (26), for other drugs in this class (and indicated for HCC) have rested on a conclusion that use of the RDI as observed in the clinical trial is appropriate for decision making.

The review also identified an inconsistent application of the half-cycle correction for treatment costs across appraisals. This is turned off in the regorafenib base case to account for any wastage due to treatment

[1] Manufacturer submission pg. 37.

discontinuation during the cycle. This equates to the costs of treatment for patients who stopped treatment during a cycle being included in the modelling of regorafenib for the full cycle. These costs are not always included in NICE appraisals.

In conclusion all unavoidable drug wastage is fully costed in the economic model. A precedent suggests RDI should not be altered from that observed in the clinical trial. This introduces a wider issue regarding the consistency of decision making across appraisals, especially when variation is within a drug class.

This Patient Access Scheme reflects the Committees uncertainty as outlined in the FAD. It is hoped that that this will allow patients, who currently have no access to an active treatment for their condition, to have timely access to regorafenib.

3.3 Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include details of the list price and the proposed percentage discount/fixed price.

This submission proposes a new simple discount scheme where upon publication of a positive FAD for TA515 regorafenib for previously treated advanced HCC, there would be a reduction to the confidential price regorafenib. The discount would reduce the price from [redacted] to [redacted] per pack. This discount represents a [redacted] reduction to the price previously considered by the Appraisal Committee and a [redacted]% discount to the list price of £3,744.

3.4 Please provide specific details of the patient population to which the Patient Access Scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?

- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The simple discount scheme applies to the full licensed population.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

Not applicable. The simple discount scheme applies to the full licensed population.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

Not applicable. The simple discount scheme applies to the full licensed population.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

Not applicable. The new PAS is a simple discount scheme and does not require a rebate.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

No additional information will be required.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Not applicable. The new PAS is a simple discount scheme and is applied at the point of purchase.

3.10 Please provide details of the duration of the scheme.

The new PAS price for regorafenib will be in place from the date of a positive FAD publication for TA514, until the time that NICE next reviews the guidance for regorafenib and a final decision has been published on the NICE website.

Please note, the review date specified in the technology appraisal guidance indicates the date that the guidance is eligible for review.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No equity or equality issues are foreseeable.

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix A.

Not applicable.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Company evidence submission template'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

The scheme applies to the full licensed population.

4.2 If you are submitting the Patient Access Scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the appraisal committee considered to be most plausible. No other changes should be made to the model.

Following the FAD Bayer were unable to replicate the plausible ICERs used by the Committee for decision making. Upon request NICE supplied Bayer with two economic models, detailing the following scenarios:

- Model A1: Outlining the upper bound ICER
- Model A4: Outlining the lower bound ICER.

A programming error was identified in the sheet added by the ERG to calculate time-on-treatment in Model A1. Model A4 does not use this sheet for calculation.

The company informed NICE upon identification of the error, and were instructed to document this error (section 4.3) and present both corrected and un-corrected cost-effectiveness results (section 4.7).

An updated version of model A1 (as provided by NICE on 20th December 2017) and an unchanged version of model A4 (except from PAS price) are attached to this submission.

4.3 Please provide details of how the Patient Access Scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the appraisal committee considered most plausible.

Implementation of the new PAS price

The new PAS pack price can be entered directly into cell F21 in the sheet (costs).

Identification of error in ERG model (model A1)

Following the Final Appraisal Determination Bayer were unable to replicate the plausible ICERs used by the Committee for decision making.

Bayer requested the economic model used by ERG/NICE and received two models, one informing the 'most pessimistic scenario' (model A1) leading to an ICER £68,137/QALY and one informing the 'most optimistic scenario' (model A4) leading to an ICER £55,829/QALY.

Incorrect implementation of discount rate in model A1

Bayer identified an error in Model A1.

Model A1 calculates treatment costs in sheet 'ERG-TTD'. On this sheet treatment costs (discounted/undiscounted) are presented in cells T2:U3 (Table 1 below), and show a small difference between the total discounted and undiscounted treatment costs.

Table 1: Total discounted/undiscounted regorafenib treatment costs (original price)

Total cost (undiscounted)	£[redacted]

Total cost (discounted)	£[redacted]

Daily time to treatment discontinuation (TTD) data extrapolated using the log-logistic distribution is presented in Column E (ERG_TTD) and is converted into monthly TTD cycles in column L (ERG_TTD) via a VLOOKUP formula.

Total discounted costs are calculated in column R (ERG_TTD) and use the converted monthly TTD (described above) when the committee basecase log-logistic is selected.

A discount rate is applied in column R based on the annual discount rate in cell D3 and the proportion or number of discount year(s) that has passed in Column B (ERG_TTD).

Column B presents the proportion of the discount year based on the number of days in Column D. For example in cell B19 12 days is equal or converted to 0.03 years.

The calculation in Column R wrongly treats the data in column B as a monthly period i.e. assuming at the start of cycle 12 (after 11 months) that 0.03 years have passed. This leads to an overestimation of the discounted treatment costs.

Correction

This programming error can be corrected by editing the formula in Column B to /12 instead of /365. This reduces the 'most pessimistic scenario' ICER to £66,250/QALY a reduction of £2,000 per QALY.

Table 2: Corrected total discounted/undiscounted treatment costs (original price)

Total cost (undiscounted)	£[redacted]
Total cost (discounted)	£[redacted]

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme.

There is no change to the clinical effectiveness data used for the revised PAS.

4.5 Please list any costs associated with the implementation and operation of the Patient Access Scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 3.5 of the 'User guide for company evidence submission template'.

There are no costs associated with the implementation and operation of the Patient Access Scheme. The proposed simple discount scheme replaces a previous simple discount scheme.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the Patient Access Scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the Patient Access Scheme. Please give the reference source of these costs.

There are no additional costs associated with the implementation and operation of the Patient Access Scheme. The proposed simple discount scheme replaces a previous simple discount scheme.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

A suggested format is shown below (table 3).

Please find below three sets of cost-effectiveness results:

a) Uncorrected models at original price
b) Uncorrected models at proposed PAS price
c) Corrected models at proposed PAS price

1. Upper and lower bound cost-effectiveness analyses using original submission price (£[redacted])

Table 3: Upper bound (ERG model A1)

	Regorafenib + BSC	Placebo + BSC	Incremental
Intervention costs	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]
Life Years	1.234	0.832	0.402
Total QALYs	0.968	0.648	0.320
ICER			£68,137

Table 4: Lower bound (ERG model A4)

	Regorafenib + BSC	Placebo + BSC	Incremental
Intervention costs	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]
Life Years	1.234	0.832	0.402
Total QALYs	0.968	0.648	0.320
ICER			£55,829

2. Upper and lower bound cost-effectiveness analyses using new submission price (£[redacted])

Table 5: Upper bound (ERG model A1)

	Regorafenib + BSC	Placebo + BSC	Incremental
Intervention costs	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]
Life Years	1.234	0.832	0.402
Total QALYs	0.968	0.648	0.320
ICER			£53,112

Table 6: Lower bound (ERG model A4)

	Regorafenib + BSC	Placebo + BSC	Incremental
Intervention costs	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]

Life Years	1.234	0.832	0.402
Intervention costs	0.968	0.648	0.320
Other costs			£44,296

3. Corrected upper and lower bound cost-effectiveness analyses using new submission price (£[redacted])

Table 7: Upper bound (ERG model A1)

	Regorafenib + BSC	Placebo + BSC	Incremental
Intervention costs	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]
Life Years	1.234	0.832	0.402
Total QALYs	0.968	0.648	0.320
ICER			£51,760

Table 8: Lower bound (ERG model A4)

	Regorafenib + BSC	Placebo + BSC	Incremental
Intervention costs	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]
Life Years	1.234	0.832	0.402
Intervention costs	0.968	0.648	0.320
Other costs			£44,296

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

dominance and extended dominance. A suggested format is presented in table 4.

There is only one relevant comparator (BSC). All incremental results are presented in section 4.7.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main company submission of evidence for the technology appraisal. Consider using tornado diagrams.

Deterministic sensitivity analyses are presented for the following scenarios:

a) Proposed PAS price using the original model A1 (upper bound) and A4 (lower bound).

b) Proposed PAS the corrected model A1 (upper bound) and the unmodified model as above A4 (lower bound).

Table 9: Original ERG model: Upper bound (model A1)

	Incremental cost				Incremental QALY				ICER			
Base case	[redacted]				**0.3198**				**£53,112**			
Parameter	**Lower Value**	**Result**	**Upper value**	**Result**	**Lower Value**	**Result**	**Upper value**	**Result**	**Lower Value**	**Result**	**Upper value**	**Result**
Percentage off treatment (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.32	[redacted]	0.32	[redacted]	£53,087	[redacted]	£53,137
Percentage on treatment (Progressed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.32	[redacted]	0.32	[redacted]	£53,271	[redacted]	£52,953
Hazard ratio - PFS	2.49	[redacted]	1.71	[redacted]	2.49	0.32	1.71	0.32	2.49	£53,112	1.71	£53,112
Hazard ratio - OS	1.28	[redacted]	1.88	[redacted]	1.28	0.32	1.88	0.32	1.28	£53,112	1.88	£53,112
Utility - PFS	0.80	[redacted]	0.82	[redacted]	0.80	0.3175	0.82	0.3222	0.80	£53,506	0.82	£52,724
Utility - Progressed	0.75	[redacted]	0.78	[redacted]	0.75	0.3179	0.78	0.3217	0.75	£53,428	0.78	£52,800
Adverse event												
- Monthly rate - Regorafenib + BSC	4.3%	[redacted]	6.7%	[redacted]	4.3%	0.319912	6.7%	0.32	4.3%	£52,730	6.7%	£53,452
- Monthly rate - BSC	3.3%	[redacted]	5.4%	[redacted]	3.3%	0.31974	5.4%	0.31982	3.3%	£53,399	5.4%	£53,062
- AE Monthly cost regorafenib	£829	[redacted]	£1,539	[redacted]	£829	0.31981	£1,539	0.31981	£829	£52,638	£1,539	£53,586
- AE Monthly cost - BSC	£1,045	[redacted]	£1,940	[redacted]	£1,045	0.31981	£1,940	0.31981	£1,045	£53,295	£1,940	£52,784
- disutility	-0.03	[redacted]	-0.00028	[redacted]	-0.03	0.31955	0.00	0.32006	-0.03	£53,155	0.00	£53,069
Resource use costs - regorafenib + BSC												
Progression free												
Hospitalisations	£160	[redacted]	£297	[redacted]	£160	0.31981	£297	0.31981	£160	£51,729	£297	£54,495
Medical staff visits	£318	[redacted]	£591	[redacted]	£318	0.31981	£591	0.31981	£318	£50,363	£591	£55,861
Lab tests	£13	[redacted]	£24	[redacted]	£13	0.31981	£24	0.31981	£13	£53,001	£24	£53,223
Radiological tests	£28	[redacted]	£53	[redacted]	£28	0.31981	£53	0.31981	£28	£52,866	£53	£53,358
Progressed												
Hospitalisations	£567	[redacted]	£1,053	[redacted]	£567	0.32	£1,053	0.32	£567	£52,529	£1,053	£53,695
Medical staff visits	£418	[redacted]	£776	[redacted]	£418	0.32	£776	0.32	£418	£52,682	£776	£53,542
Lab tests	£3	[redacted]	£5	[redacted]	£3	0.32	£5	0.32	£3	£53,109	£5	£53,115

Radiological tests	£27	[redacted]	£50	[redacted]	£27	0.32	£50	0.32	£27	£53,087	£50	£53,137
Resource use costs - Placebo + BSC												
Progression free												
Hospitalisations	£347	[redacted]	£644	[redacted]	£347	0.32	£644	0.32	£347	£54,560	£644	£51,664
Medical staff visits	£311	[redacted]	£577	[redacted]	£311	0.32	£577	0.32	£311	£54,435	£577	£51,789
Lab tests	£15	[redacted]	£28	[redacted]	£15	0.32	£28	0.32	£15	£53,174	£28	£53,050
Radiological tests	£28	[redacted]	£42	[redacted]	£28	0.32	£42	0.32	£28	£53,206	£42	£53,018
Progressed												
Hospitalisations	£724	[redacted]	£1,344	[redacted]	£724	0.32	£1,344	0.32	£724	£52,116	£1,344	£54,108
Medical staff visits	£479	[redacted]	£889	[redacted]	£479	0.32	£889	0.32	£479	£52,453	£889	£53,771
Lab tests	£4	[redacted]	£7	[redacted]	£4	0.32	£7	0.32	£4	£53,106	£7	£53,118
Radiological tests	£23	[redacted]	£43	[redacted]	£23	0.32	£43	0.32	£23	£53,080	£43	£53,144
Regorafenib dose												
- Average Dose PFS (mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.31981	[redacted]	0.31981	[redacted]	£53,112	[redacted]	£53,112
- Average Dose Progressed (mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.31981	[redacted]	0.31981	[redacted]	£53,112	[redacted]	£53,112

Table 10 Original ERG model: Lower bound (A4)

	Incremental cost				Incremental QALY				ICER			
Base case	[redacted]				**0.312**				**£44,296**			
Parameter	**Lower Value**	**Result**	**Upper value**	**Result**	**Lower Value**	**Result**	**Upper value**	**Result**	**Lower Value**	**Result**	**Upper value**	**Result**
Percentage off treatment (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.32	[redacted]	£44,271	[redacted]	£44,321
Percentage on treatment (Progressed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.32	[redacted]	£44,455	[redacted]	£44,137
Hazard ratio - PFS	2.49	[redacted]	1.71	[redacted]	2.49	0.32	1.71	0.32	2.49	£44,296	1.71	£44,296
Hazard ratio - OS	1.28	[redacted]	1.88	[redacted]	1.28	0.32	1.88	0.32	1.28	£44,296	1.88	£44,296
Utility - PFS	0.80	[redacted]	0.82	[redacted]	0.80	0.3175	0.82	0.3222	0.80	£44,624	0.82	£43,972
Utility - Progressed	0.75	[redacted]	0.78	[redacted]	0.75	0.3179	0.78	0.3217	0.75	£44,560	0.78	£44,035
Adverse events												
- Monthly rate - Regorafenib + BSC	4.3%	[redacted]	6.7%	[redacted]	4.3%	0.319912	6.7%	0.32	4.3%	£43,917	6.7%	£44,634
- Monthly rate - BSC	3.3%	[redacted]	5.4%	[redacted]	3.3%	0.31974	5.4%	0.31982	3.3%	£44,582	5.4%	£44,247
- AE Monthly cost regorafenib	£829	[redacted]	£1,539	[redacted]	£829	0.31981	£1,539	0.31981	£829	£43,822	£1,539	£44,770
- AE Monthly cost - BSC	£1,045	[redacted]	£1,940	[redacted]	£1,045	0.31981	£1,940	0.31981	£1,045	£44,479	£1,940	£43,968
- disutility	-0.03	[redacted]	-0.00028	[redacted]	-0.03	0.31955	0.00	0.32006	-0.03	£44,332	0.00	£44,260
Resource use costs - regorafenib + BSC												
Progression free												
Hospitalisations	£160	[redacted]	£297	[redacted]	£160	0.31981	£297	0.31981	£160	£42,913	£297	£45,679
Medical staff visits	£318	[redacted]	£591	[redacted]	£318	0.31981	£591	0.31981	£318	£41,547	£591	£47,045
Lab tests	£13	[redacted]	£24	[redacted]	£13	0.31981	£24	0.31981	£13	£44,185	£24	£44,407
Radiological tests	£28	[redacted]	£53	[redacted]	£28	0.31981	£53	0.31981	£28	£44,050	£53	£44,542
Progressed												
Hospitalisations	£567	[redacted]	£1,053	[redacted]	£567	0.32	£1,053	0.32	£567	£43,713	£1,053	£44,879
Medical staff visits	£418	[redacted]	£776	[redacted]	£418	0.32	£776	0.32	£418	£43,866	£776	£44,725
Lab tests	£3	[redacted]	£5	[redacted]	£3	0.32	£5	0.32	£3	£44,293	£5	£44,299

Radiological tests	£27	[redacted]	£50	[redacted]	£27	0.32	£50	0.32	£27	£44,271	£50	£44,321
Resource use costs - Placebo + BSC												
Progression free												
Hospitalisations	£347	[redacted]	£644	[redacted]	£347	0.32	£644	0.32	£347	£45,744	£644	£42,848
Medical staff visits	£311	[redacted]	£577	[redacted]	£311	0.32	£577	0.32	£311	£45,619	£577	£42,973
Lab tests	£15	[redacted]	£28	[redacted]	£15	0.32	£28	0.32	£15	£44,358	£28	£44,234
Radiological tests	£28	[redacted]	£42	[redacted]	£28	0.32	£42	0.32	£28	£44,390	£42	£44,202
Progressed												
Hospitalisations	£724	[redacted]	£1,344	[redacted]	£724	0.32	£1,344	0.32	£724	£43,300	£1,344	£45,292
Medical staff visits	£479	[redacted]	£889	[redacted]	£479	0.32	£889	0.32	£479	£43,637	£889	£44,955
Lab tests	£4	[redacted]	£7	[redacted]	£4	0.32	£7	0.32	£4	£44,290	£7	£44,301
Radiological tests	£23	[redacted]	£43	[redacted]	£23	0.32	£43	0.32	£23	£44,264	£43	£44,328
Regorafenib dose												
- Average Dose PFS (mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.31981	[redacted]	0.31981	[redacted]	£44,296	[redacted]	£44,296
- Average Dose Progressed (mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.31981	[redacted]	0.31981	[redacted]	£44,296	[redacted]	£44,296

Table 11 Corrected model: Upper bound (model A1)

	Incremental cost				Incremental QALY				ICER			
Base case	[redacted]				**0.319806**				**£51,760**			
Parameter	**Lower Value**	**Result**	**Upper value**	**Result**	**Lower Value**	**Result**	**Upper value**	**Result**	**Lower Value**	**Result**	**Upper value**	**Result**
Percentage off treatment (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.32	[redacted]	0.32	[redacted]	£51,736	[redacted]	£51,786
Percentage on treatment (Progressed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.32	[redacted]	0.32	[redacted]	£51,919	[redacted]	£51,602
Hazard ratio - PFS	2.49	[redacted]	1.71	[redacted]	2.49	0.32	1.71	0.32	2.49	£51,760	1.71	£51,760
Hazard ratio - OS	1.28	[redacted]	1.88	[redacted]	1.28	0.32	1.88	0.32	1.28	£51,760	1.88	£51,760
Utility - PFS	0.80	[redacted]	0.82	[redacted]	0.80	0.3175	0.82	0.3222	0.80	£52,144	0.82	£51,382
Utility - Progressed	0.75	[redacted]	0.78	[redacted]	0.75	0.3179	0.78	0.3217	0.75	£52,068	0.78	£51,456
Adverse events												
- Monthly rate - Regorafenib + BSC	4.3%	[redacted]	6.7%	[redacted]	4.3%	0.319912	6.7%	0.32	4.3%	£51,379	6.7%	£52,100
- Monthly rate - BSC	3.3%	[redacted]	5.4%	[redacted]	3.3%	0.31974	5.4%	0.31982	3.3%	£52,048	5.4%	£51,711
- AE Monthly cost regorafenib	£829	[redacted]	£1,539	[redacted]	£829	0.31981	£1,539	0.31981	£829	£51,286	£1,539	£52,235
- AE Monthly cost - BSC	£1,045	[redacted]	£1,940	[redacted]	£1,045	0.31981	£1,940	0.31981	£1,045	£51,943	£1,940	£51,432
- disutility	-0.03	[redacted]	-0.00028	[redacted]	-0.03	0.31955	0.00	0.32006	-0.03	£51,802	0.00	£51,719
Resource use costs - regorafenib + BSC												
Progression free												
Hospitalisations	£160	[redacted]	£297	[redacted]	£160	0.31981	£297	0.31981	£160	£50,377	£297	£53,144
Medical staff visits	£318	[redacted]	£591	[redacted]	£318	0.31981	£591	0.31981	£318	£49,011	£591	£54,510
Lab tests	£13	[redacted]	£24	[redacted]	£13	0.31981	£24	0.31981	£13	£51,649	£24	£51,872
Radiological tests	£28	[redacted]	£53	[redacted]	£28	0.31981	£53	0.31981	£28	£51,514	£53	£52,006
Progressed												
Hospitalisations	£567	[redacted]	£1,053	[redacted]	£567	0.32	£1,053	0.32	£567	£51,177	£1,053	£52,343
Medical staff visits	£418	[redacted]	£776	[redacted]	£418	0.32	£776	0.32	£418	£51,331	£776	£52,190
Lab tests	£3	[redacted]	£5	[redacted]	£3	0.32	£5	0.32	£3	£51,758	£5	£51,763

Radiological tests	£27	[redacted]	£50	[redacted]	£27	0.32	£50	0.32	£27	£51,735	£50	£51,786
Resource use costs - Placebo + BSC												
Progression free												
Hospitalisations	£347	[redacted]	£644	[redacted]	£347	0.32	£644	0.32	£347	£53,208	£644	£50,312
Medical staff visits	£311	[redacted]	£577	[redacted]	£311	0.32	£577	0.32	£311	£53,083	£577	£50,438
Lab tests	£15	[redacted]	£28	[redacted]	£15	0.32	£28	0.32	£15	£51,822	£28	£51,698
Radiological tests	£28	[redacted]	£42	[redacted]	£28	0.32	£42	0.32	£28	£51,854	£42	£51,667
Progressed												
Hospitalisations	£724	[redacted]	£1,344	[redacted]	£724	0.32	£1,344	0.32	£724	£50,764	£1,344	£52,757
Medical staff visits	£479	[redacted]	£889	[redacted]	£479	0.32	£889	0.32	£479	£51,101	£889	£52,419
Lab tests	£4	[redacted]	£7	[redacted]	£4	0.32	£7	0.32	£4	£51,755	£7	£51,766
Radiological tests	£23	[redacted]	£43	[redacted]	£23	0.32	£43	0.32	£23	£51,728	£43	£51,792
Regorafenib dose												
- Average Dose PFS (mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.31981	[redacted]	0.31981	[redacted]	£51,760	[redacted]	£51,760
- Average Dose Progressed (mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.31981	[redacted]	0.31981	[redacted]	£51,760	[redacted]	£51,760

Table 12: Original ERG model: Lower bound (A4)

	Incremental cost				Incremental QALY				ICER			
Base case	[redacted]				**0.312**				**£44,296**			
Parameter	**Lower Value**	**Result**	**Upper value**	**Result**	**Lower Value**	**Result**	**Upper value**	**Result**	**Lower Value**	**Result**	**Upper value**	**Result**
Percentage off treatment (PFS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.32	[redacted]	£44,271	[redacted]	£44,321
Percentage on treatment (Progressed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.32	[redacted]	£44,455	[redacted]	£44,137
Hazard ratio - PFS	2.49	[redacted]	1.71	[redacted]	2.49	0.32	1.71	0.32	2.49	£44,296	1.71	£44,296
Hazard ratio - OS	1.28	[redacted]	1.88	[redacted]	1.28	0.32	1.88	0.32	1.28	£44,296	1.88	£44,296
Utility - PFS	0.80	[redacted]	0.82	[redacted]	0.80	0.3175	0.82	0.3222	0.80	£44,624	0.82	£43,972
Utility - Progressed	0.75	[redacted]	0.78	[redacted]	0.75	0.3179	0.78	0.3217	0.75	£44,560	0.78	£44,035
Adverse events												
- Monthly rate - Regorafenib + BSC	4.3%	[redacted]	6.7%	[redacted]	4.3%	0.319912	6.7%	0.32	4.3%	£43,917	6.7%	£44,634
- Monthly rate - BSC	3.3%	[redacted]	5.4%	[redacted]	3.3%	0.31974	5.4%	0.31982	3.3%	£44,582	5.4%	£44,247
- AE Monthly cost regorafenib	£829	[redacted]	£1,539	[redacted]	£829	0.31981	£1,539	0.31981	£829	£43,822	£1,539	£44,770
- AE Monthly cost - BSC	£1,045	[redacted]	£1,940	[redacted]	£1,045	0.31981	£1,940	0.31981	£1,045	£44,479	£1,940	£43,968
- disutility	-0.03	[redacted]	-0.00028	[redacted]	-0.03	0.31955	0.00	0.32006	-0.03	£44,332	0.00	£44,260
Resource use costs - regorafenib + BSC												
Progression free												
Hospitalisations	£160	[redacted]	£297	[redacted]	£160	0.31981	£297	0.31981	£160	£42,913	£297	£45,679
Medical staff visits	£318	[redacted]	£591	[redacted]	£318	0.31981	£591	0.31981	£318	£41,547	£591	£47,045
Lab tests	£13	[redacted]	£24	[redacted]	£13	0.31981	£24	0.31981	£13	£44,185	£24	£44,407
Radiological tests	£28	[redacted]	£53	[redacted]	£28	0.31981	£53	0.31981	£28	£44,050	£53	£44,542
Progressed												
Hospitalisations	£567	[redacted]	£1,053	[redacted]	£567	0.32	£1,053	0.32	£567	£43,713	£1,053	£44,879
Medical staff visits	£418	[redacted]	£776	[redacted]	£418	0.32	£776	0.32	£418	£43,866	£776	£44,725
Lab tests	£3	[redacted]	£5	[redacted]	£3	0.32	£5	0.32	£3	£44,293	£5	£44,299

Radiological tests	£27	[redacted]	£50	[redacted]	£27	0.32	£50	0.32	£27	£44,271	£50	£44,321
Resource use costs - Placebo + BSC												
Progression free												
Hospitalisations	£347	[redacted]	£644	[redacted]	£347	0.32	£644	0.32	£347	£45,744	£644	£42,848
Medical staff visits	£311	[redacted]	£577	[redacted]	£311	0.32	£577	0.32	£311	£45,619	£577	£42,973
Lab tests	£15	[redacted]	£28	[redacted]	£15	0.32	£28	0.32	£15	£44,358	£28	£44,234
Radiological tests	£28	[redacted]	£42	[redacted]	£28	0.32	£42	0.32	£28	£44,390	£42	£44,202
Progressed												
Hospitalisations	£724	[redacted]	£1,344	[redacted]	£724	0.32	£1,344	0.32	£724	£43,300	£1,344	£45,292
Medical staff visits	£479	[redacted]	£889	[redacted]	£479	0.32	£889	0.32	£479	£43,637	£889	£44,955
Lab tests	£4	[redacted]	£7	[redacted]	£4	0.32	£7	0.32	£4	£44,290	£7	£44,301
Radiological tests	£23	[redacted]	£43	[redacted]	£23	0.32	£43	0.32	£23	£44,264	£43	£44,328
Regorafenib dose												
- Average Dose PFS (mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.31981	[redacted]	0.31981	[redacted]	£44,296	[redacted]	£44,296
- Average Dose Progressed (mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.31981	[redacted]	0.31981	[redacted]	£44,296	[redacted]	£44,296

4.10 Present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

PSA was not functional in the models provided by ERG. This is likely a result of changes made to the model during the appraisal process. In the interest of transparency and to avoid wholesale changes to the models no further amendments have been made.

4.11 Please present scenario analysis results as described for the main company submission of evidence for the technology appraisal.

Scenario analyses are presented using:

a) Proposed PAS price using the original model A1 (upper bound) and A4 (lower bound).

b) Proposed PAS the corrected model A1 (upper bound) and the unmodified model as above A4 (lower bound). .

Table 13: Original ERG model: Upper bound (model A1)

	Incr costs (£)	Incr QALYs	ICER (£/QALYs)
Base case	[redacted]	0.320	£53,112
PFS – different extrapolations			
Lognormal	[redacted]	0.317	£57,015
Loglogistic	[redacted]	0.317	£56,621
Weibull	[redacted]	0.317	£56,471
Exponential	[redacted]	0.318	£55,322
Gamma	[redacted]	0.318	£55,870
Gompertz	[redacted]	0.319	£54,668
OS – different extrapolations			
Loglogistic	[redacted]	0.413	£51,032
Log-normal	[redacted]	0.411	£51,056
Exponential	[redacted]	0.349	£46,608
Gamma	[redacted]	0.409	£51,134
Gompertz	[redacted]	0.344	£46,086
Time horizon			
3 years	[redacted]	0.273	£57,053
5 years	[redacted]	0.314	£53,556
10 years	[redacted]	0.320	£53,113

Table 14: Original ERG model: Lower bound (model A4)

	Incr costs (£)	Incr QALYs	ICER (£/QALYs)
Base case	[redacted]	0.320	£44,296
PFS – different extrapolations			
Lognormal	[redacted]	0.408	£45,169
Loglogistic	[redacted]	0.317	£47,729
Weibull	[redacted]	0.317	£47,576
Exponential	[redacted]	0.337	£47,465
Gamma	[redacted]	0.406	£45,231
Gompertz	[redacted]	0.319	£45,828
OS – different extrapolations			
Loglogistic	[redacted]	0.413	£43,020
Log-normal	[redacted]	0.411	£43,008
Exponential	[redacted]	0.349	£37,986
Gamma	[redacted]	0.409	£43,068
Gompertz	[redacted]	0.411	£43,008
Time horizon			
3 years	[redacted]	0.273	£46,738
5 years	[redacted]	0.314	£44,571
10 years	[redacted]	0.320	£44,297

Table 15: Corrected model: Upper bound (ERG model A1):

	Incr costs (£)	Incr QALYs	ICER (£/QALYs)
Base case	[redacted]	0.320	£51,760
PFS – different extrapolations			
Lognormal	[redacted]	0.317	£55,649
Loglogistic	[redacted]	0.317	£55,258
Weibull	[redacted]	0.317	£55,107
Exponential	[redacted]	0.318	£53,964
Gamma	[redacted]	0.318	£54,510
Gompertz	[redacted]	0.319	£53,313
OS – different extrapolations			
Loglogistic	[redacted]	0.413	£49,360
Log-normal	[redacted]	0.411	£49,376
Exponential	[redacted]	0.349	£45,111
Gamma	[redacted]	0.409	£49,461
Gompertz	[redacted]	0.344	£44,717
Time horizon			
3 years	[redacted]	0.273	£55,471
5 years	[redacted]	0.314	£52,179
10 years	[redacted]	0.320	£51,762

Table 16: Original ERG model: Lower bound (A4)

	Incr costs (£)	Incr QALYs	ICER (£/QALYs)
Base case	[redacted]	0.320	£44,296
PFS – different extrapolations			
Lognormal	[redacted]	0.408	£45,169
Loglogistic	[redacted]	0.317	£47,729
Weibull	[redacted]	0.317	£47,576
Exponential	[redacted]	0.337	£47,465
Gamma	[redacted]	0.406	£45,231
Gompertz	[redacted]	0.319	£45,828
OS – different extrapolations			
Loglogistic	[redacted]	0.413	£43,020
Log-normal	[redacted]	0.411	£43,008
Exponential	[redacted]	0.349	£37,986
Gamma	[redacted]	0.409	£43,068
Gompertz	[redacted]	0.411	£43,008
Time horizon			
3 years	[redacted]	0.273	£46,738
5 years	[redacted]	0.314	£44,571
10 years	[redacted]	0.320	£44,297

4.12 If any of the criteria on which the Patient Access Scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the appraisal committee can determine which criteria are the most appropriate to use.

Not applicable

Impact of Patient Access Scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the Patient Access Scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the Patient Access Scheme at the end of the appraisal process, you must include the

scenario with the assumptions that the appraisal committee considered to be most plausible.

Table 17: Results showing the impact of Patient Access Scheme on ICERs

		Versus BSC	
	List price	**Original submission**	**New PAS**
Scenario 1: Model A1 Upper Bound	[redacted]	£66,250	£51,760
Scenario 2: Model B1 Lower Bound	[redacted]	£55,829	£44,296

PAS: Patient Access Scheme.

5 Appendix A: Details for outcome-based schemes only

5.1 If you are submitting an outcome based scheme which is expected to result in a price increase, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.2 If you are submitting an outcome based scheme which is expected to result in a price reduction or rebate, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.3 Provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study

- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable.

5.4 Please specify the period between the time points when the additional evidence will be considered.

Not applicable.

5.5 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered.

Not applicable.

5.6 Please provide the other data used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

5.7 Please present the cost-effectiveness results as follows.

- For a scheme that is expected to result in a price increase, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For a scheme that is expected to result in a price reduction or rebate, please summarise in separate tables:

- the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
- the results based on the current evidence and the lower price (if the new evidence is not forthcoming).

A suggested format is shown in table 3, section 4.7.

5.8 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

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7.National Institute of Health and Care Excellence. Ceritinib for untreated ALK-positive non-small-cell lung cancer (TA500). 2018.

8.National Institute of Health and Care Excellence. Lenvatinib with everolimus for previously treated advanced renal cell carcinoma (TA498). 2018.

9.National Institute of Health and Care Excellence. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA495). 2017.

10.National Institute of Health and Care Excellence. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (TA496). 2017.

11. National Institute of Health and Care Excellence. Vismodegib for treating locally advanced or metastatic basal cell carcinoma (TA489). 2017.

12. National Institute of Health and Care Excellence. Venetoclax for treating chronic lymphocytic leukaemia (TA487). 2017.

13. National Institute of Health and Care Excellence. Sorafenib for treating advanced hepatocellular carcinoma (TA474 CDF reconsideration of TA189) 2017.

14. National Insitute of Health and Care Excellence. Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease (TA449) 2017.

15. National Institute of Health and Care Excellence. Trifluridine–tipiracil for previously treated metastatic colorectal cancer (TA405). 2016.

16. National Institute of Health and Care Excellence. Everolimus for advanced renal cell carcinoma after previous treatment (TA432). 2017.

17. National Institute of Health and Care Excellence. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation (TA429). 2017.

18. National Institute of Health and Care Excellence. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma (TA396). 2016.

19. National Institute of Health and Care Excellence. Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer (TA395). 2016.

20. National Institute of Health and Care Excellence. Ibrutinib for treating relapsed or refractory mantle cell lymphoma (TA502). 2018.

21. National Institute of Health and Care Excellence. Cabozantinib for previously treated advanced renal cell carcinoma (TA463). 2017.

22. National Institute of Health and Care Excellence. Pomalidomide with dexamethasone for treating relapsed and refractory multiple myeloma after at least two regimens including lenalidomide and bortezomib (TA427 review of TA338). 2017.

23. National Institute of Health and Care Excellence. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (TA406). 2016.

24. National Institute of Health and Care Excellence. Bosutinib for previously treated chronic myeloid leukaemia (TA401). 2016.

25.National Insitute of Health and Care Excellence. Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (TA535),. 2018.

26. National Insitute of Health and Care Excellence. Lenvatinib for advanced, unresectable, untreated hepatocellular carcinoma [ID1089],. 2018.

Regorafenib for previously treated unresectable hepatocellular carcinoma: A Single Technology Appraisal – Rapid Review

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Introduction

NICE undertook an appraisal of regorafenib for previously treated unresectable hepatocellular carcinoma (Technology Appraisal 514) which culminated in a Final Appraisal Determination (FAD) published in March 2018 which contained a negative recommendation.

Following the Rapid Review process, Bayer have agreed a Patient Access Scheme (PAS) which reduces the acquisition costs of regorafenib to the NHS; the previous PAS discount was [redacted]- the new PAS discount is [redacted] resulting in a post-PAS cost of [redacted] per pack. This PAS forms the basis for the reduced incremental cost-effective ratios (ICERs) reported by the company, although Bayer also identified a discounting error made by the Evidence Review Group (ERG) in amending the company model and additionally provide results from a review of 20 technology appraisals of oral oncology treatments. The ERG has been asked to critique Bayer's Rapid Review submission.

Results provided by the company

Based on new analyses which include the updated PAS and the correction of the ERG's error, the company estimate that the upper and lower bounds on the ICER, as detailed in the FAD, are £51,760 and £44,296, respectively. These results are shown in Table 1 and Table 2.

Table 1: Upper bound presented by the company

	Regorafenib + BSC	Placebo + BSC	Incremental
Total Costs	[redacted]	[redacted]	[redacted][†]
Life Years	1.234	0.832	0.402
Total QALYs	0.968	0.648	0.320
ICER			£51,760

[†]A typographical error has been corrected.

Table 2: Lower bound presented by the company

	Regorafenib + BSC	Placebo + BSC	Incremental
Total Costs	[redacted]	[redacted]	[redacted]
Life Years	1.234	0.832	0.402
Intervention costs	0.968	0.648	0.320
Other costs			£44,296

Critique of the results by the ERG

The ERG acknowledges that it had made an error which was identified by the company. However, the ERG believes that the correction made by the company is not correct as it assumes that there are 12 cycles of 28 days in a year, rather than 13.04 (365.25/28). Amending this value, within cells B8:B3658 in the 'ERG_TTD' worksheet, increases the upper bound ICER slightly to £51,868 per QALY gained as shown in Table 3. Due to the small change in the ICER, the ERG has not re-run all the sensitivity analyses on the upper bound presented by the company.

Table 3: Upper bound corrected by the ERG

	Regorafenib + BSC	Placebo + BSC	Incremental
Total Costs	[redacted]	[redacted]	[redacted]
Life Years	1.234	0.832	0.402
Total QALYs	0.968	0.648	0.320
ICER			£51,868

Discussion of the results of the review undertaken by the company

The company have undertaken a review to support a preference for the lower, rather than the upper, bound. The company state that in 16 of 20 appraisals, the manufacturer used the relative dose intensity (RDI) observed in the clinical study and that this was accepted in 15 of the 16 cases. This implies that in 4 of 20 cases the manufacturers did not use the RDI observed in the trial. The ERG has no reason to dispute these figures and comments that it appears that the correct approach may be decision-specific.

The company also state that the application of half-cycle correction is not consistent, with respect to whether patients who discontinue in a cycle should incur the full costs of a cycle's treatment. Less detail is provided on this review by the company, but the ERG believes that the correct approach is likely to be decision-specific.