ERRATUM

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

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None of the authors have any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Ruth Wong critiqued the company's search strategy. Chris Carroll summarised and critiqued the clinical effectiveness data reported within the company's submission. Paul Tappenden, Andrew Rawdin and Matt Stevenson critiqued the health economic analysis submitted by the company and performed the ERG exploratory analyses. Dr Darby and Professor Heneghan provided clinical advice to the ERG. All authors were involved in drafting and commenting on the final report.

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1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's submission (CS) adequately describes the decision problem. The CS assesses the clinical and cost-effectiveness of regorafenib (Stivarga®), within its licensed indication for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. The positioning of regorafenib within the treatment pathway was appropriately reserved for patients who have received sorafenib treatment, and the comparator of best supportive care (BSC) was appropriate. Evidence relating to all outcomes listed in the final scope produced by the National Institute for Health and Care Excellence (NICE) was included within the CS.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS identified a single, relevant study: the RESORCE trial. This was an international, placebo-controlled Phase III trial which evaluated the efficacy and safety of regorafenib 160mg per day in adult patients with HCC who have previously progressed on sorafenib. In terms of the primary outcome, the RESORCE study found that patients on regorafenib had increased survival: the median overall survival (OS) was reported to be 10.6 months (95% CI 9.1-12.1 months) in patients randomised to regorafenib compared with 7.8 months (95% CI 6.3-8.8 months) in patients randomised to placebo. The estimated hazard ratio (HR) for OS for regorafenib compared with placebo was 0.63 (95% confidence interval [CI] 0.50-0.79, one-sided p=0.000020).

The CS also reported the secondary and tertiary outcomes of the RESORCE trial. Median progression-free survival (PFS), as measured by modified response evaluation criteria in solid tumors (mRECIST), was significantly better for regorafenib (3.1 months, 95% CI 2.8–4.2 months) than for placebo (1.5 months, 95% CI 1.4–1.6 months): HR, 0.46, 95% CI 0.37-0.56; p<0.0001. The median time to progression (TTP) as measured by mRECIST was also significantly better for regorafenib (3.2 months, 95% CI 2.9–4.2 months) than for placebo (1.5 months, 95% CI 1.4–1.6 months): HR, 0.46, 95% CI 0.36-0.55; p<0.0001. The objective response rate (ORR), which aggregates complete response (CR) and partial response (PR) according to mRECIST, was also significantly higher in the regorafenib group than the placebo group (11% compared with 4%; p=0.0047). Similar findings were reported across all outcomes when using the slightly different RECIST 1.1 criteria. Subgroup analyses demonstrated consistent benefit for patients treated with regorafenib, although an additional pre-specified analysis found that those who develop a new extrahepatic lesion when they progressed on sorafenib had a considerably worse survival rate compared with those who did not. The RESORCE trial also found that health-related quality of life (HRQoL) was similar between the groups, but was consistently worse for regorafenib than placebo across different measures. These differences were found to be statistically significant in the case of the Functional Assessment of Cancer Therapy –

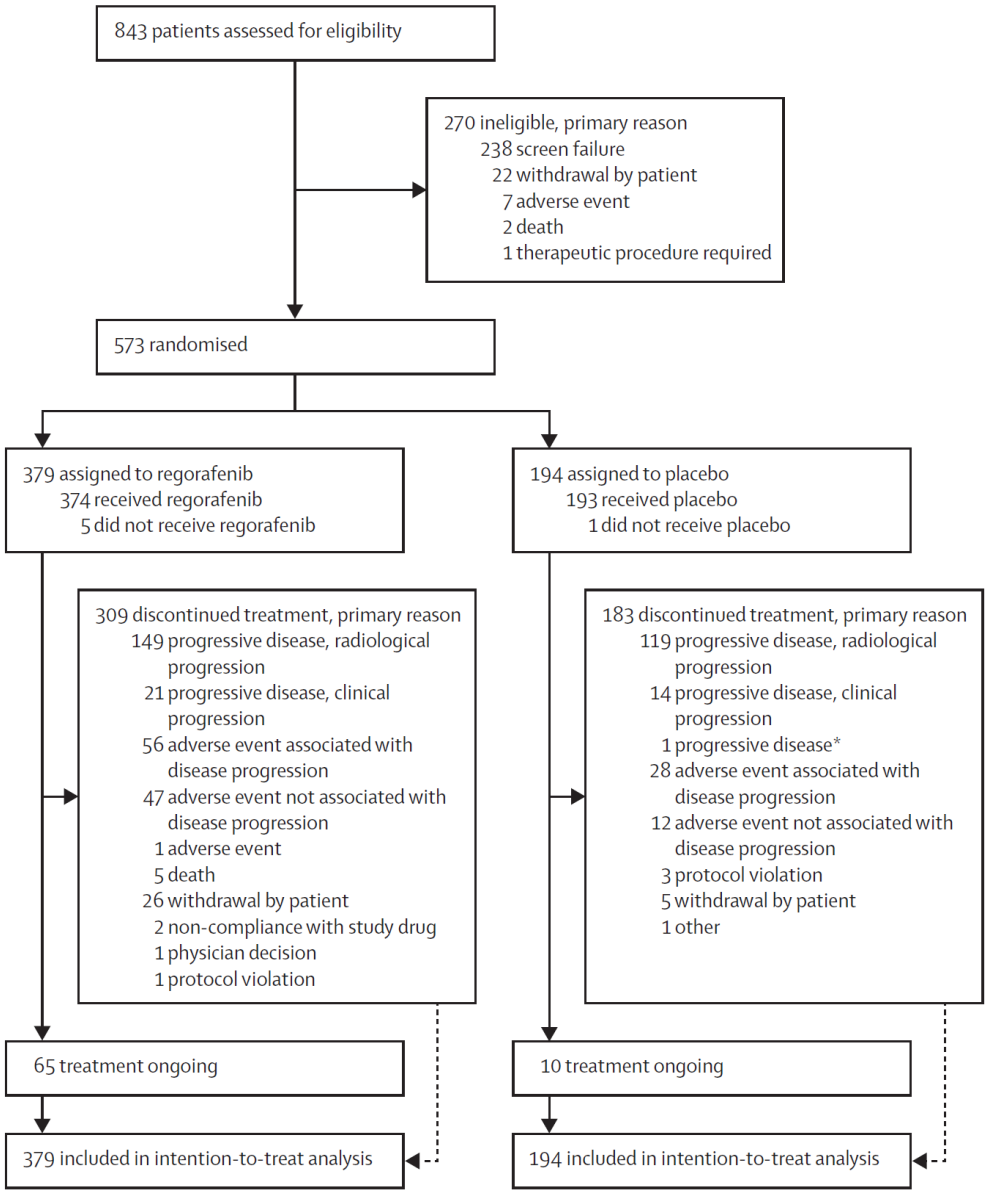
sorafenib for HCC); (6) the use of independent Weibull functions to model OS, and (7) the use of a fully extrapolated log logistic time to treatment discontinuation curve (with full pack dosing). These exploratory analyses were then combined to form the ERG's preferred base case (analysis 8).

The results of the ERG's exploratory analyses are presented in **Table 1**. The ERG's preferred base case deterministic ICER for regorafenib versus BSC is £81,081 per QALY gained. The ERG notes that the ICER would increase slightly if a greater disutility for progression disease is assumed. The ERG also notes that where a reduction in dose is planned and the lower dose is to be maintained over the long-term, the ERG's assumption of indefinite full pack dosing for all patients will lead to an overestimation of the ICER for regorafenib. Additional sensitivity analyses undertaken by the ERG indicate that even under the highly optimistic assumption that all patients have indefinite dose reductions to [redacted] from the start of treatment, the ICER for regorafenib versus BSC remains above [redacted] per QALY gained.

Table 1: Exploratory analyses undertaken by the ERG and the ERG-preferred base case

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's base case (revised base case model, deterministic)					
Regorafenib	1.073	[redacted]	0.406	£14,625	**£36,050**
BSC	0.668	[redacted]	-	-	-
Exploratory analysis 1: Correction of unequivocal model errors and use of alternative unit costs					
Regorafenib	1.048	[redacted]	0.368	£12,659	**£34,406**
BSC	0.680	[redacted]	-	-	-
*Exploratory analysis 2: Inclusion of more appropriate general ward bed day cost**					
Regorafenib	1.048	[redacted]	0.368	£12,647	**£34,376**
BSC	0.680	[redacted]	-	-	-
*Exploratory analysis 3: Use of full pack dosing**					
Regorafenib	1.048	[redacted]	0.368	£15,508	**£42,151**
BSC	0.680	[redacted]	-	-	-
*Exploratory analysis 4: Removal of half-cycle correction for drug acquisition costs**					
Regorafenib	1.048	[redacted]	0.368	£13,332	**£36,235**
BSC	0.680	[redacted]	-	-	-
*Exploratory analysis 5: Use of combined 2007 and 2015 survey costs**					
Regorafenib	1.048	[redacted]	0.368	£20,297	**£55,166**
BSC	0.680	[redacted]	-	-	-
*Exploratory analysis 6: Use of independent Weibull functions to model OS**					
Regorafenib	0.896	[redacted]	0.265	£10,242	**£38,683**
BSC	0.632	[redacted]	-	-	-
*Exploratory analysis 7: Use of a fully extrapolated log logistic time to discontinuation curve (patients on treatment at 29th February 2016 censored, with full pack dosing)**					
Regorafenib	1.048	[redacted]	0.368	£21,751	**£59,120**
BSC	0.680	[redacted]	-	-	-
*Exploratory analysis 8: ERG's preferred base case (including all individual amendments)**					
Regorafenib	0.896	[redacted]	0.265	£21,468	**£81,081**
BSC	0.632	[redacted]	-	-	-

Figure 1: Participant flow in the RESORCE trial[6]



Primary outcome

4.2.2.1 Overall survival

In the RESORCE trial, median OS was reported to be 10.6 months (95% confidence interval (CI) 9.1-12.1 months) in patients randomised to regorafenib compared with 7.8 months (95% CI 6.3-8.8 months) in patients randomised to placebo. The estimated hazard ratio (HR) for OS for regorafenib compared with placebo was 0.63, 95% CI 0.50-0.79, one-sided p=0.000020 (previously published as 0.62, 95% CI 0.50-0.78, p<0.001[13]). This represents a statistically significant reduced risk of death of 37% in the regorafenib group compared with the placebo group. This satisfies the primary objective of the trial in terms of an HR of 0.7 or better, but not the targeted improvement of 43% increase in

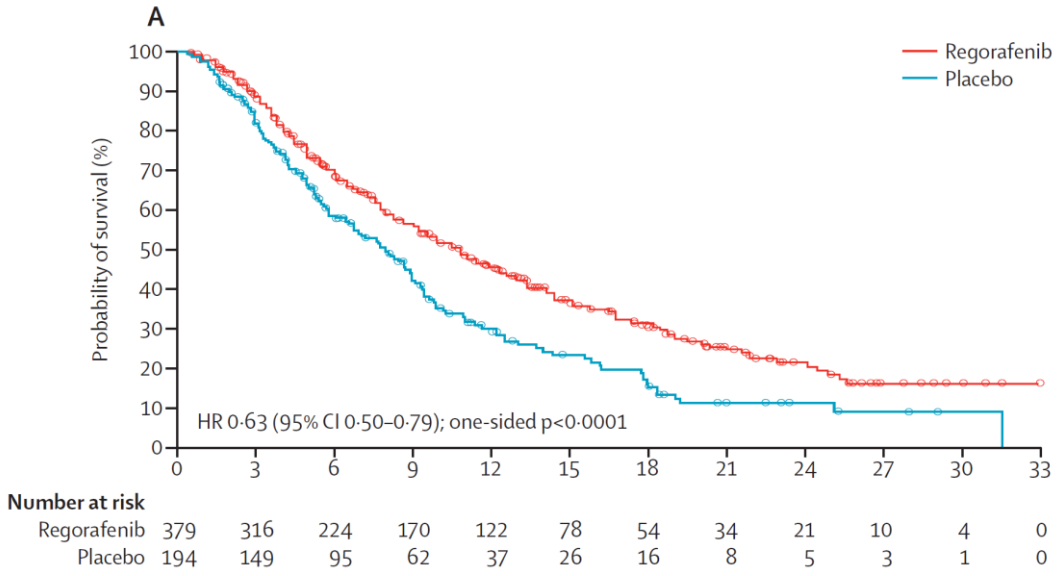
median OS compared to placebo ([redacted]) (see CS,[1] Table 17, page 51). Details are presented in **Error! Reference source not found.** and the Kaplan-Meier curve is reproduced in Error! Reference source not found..

Table 2: Analyses of overall survival in the RESORCE study (FAS; mRECIST) (reproduced from CS, Table 19)

	Regorafenib (N=379)	**Placebo (N=194)**
Number of patients (%) with event	[redacted]	[redacted]
Number of patients (%) censored	[redacted]	[redacted]
Median overall survival, days (95% CI), Range (without censored values)	[redacted]	[redacted]
Median overall survival, months (95% CI), Range (without censored values)	10.6 (9.1, 12.1) [redacted]	7.8 (6.3, 8.8) [redacted]
Primary analysis		
Hazard ratio[a]: Stratified IVRS	[redacted]	
95% CI for hazard ratio:	[redacted]	
p-value (one-sided) from log-rank test)	0.000020	

CI - confidence interval; FAS - full analysis set; IVRS - interactive voice response system
[a] An HR <1 indicates superiority of regorafenib 160mg over placebo.
Median, percentile and other 95% CIs computed using Kaplan-Meier estimates. HR and its 95% CI based on a stratified (IVRS) Cox regression model.
Durations were manually converted from days to months (1 month=30.44 days)

Figure 2: Kaplan-Meier Curve for OS (FAS; mRECIST) (reproduced from Bruix *et al*, 2017, Figure 2A[6])



As measured by RECIST 1.1, median PFS was [redacted] months (95% CI [redacted] months) for regorafenib compared with [redacted] months (95% CI [redacted] months) for placebo: HR 0.43, 95% CI 0.35–0.52; one-sided $p<0{\cdot}0001$.[6]

4.2.2.3 Time to progression (TTP)

In the RESORCE trial, median TTP as measured by mRECIST was statistically significantly better for regorafenib (3.2 months, 95% CI 2.9–4.2 months) than for placebo (1.5 months, 95% CI 1.4–1.6 months): HR, 0.44, 95% CI 0.36-0.55; $p<0.0001$. This represents a 56% reduced risk in TTP in the regorafenib group compared with the placebo group. Details are presented in Table 3 and **Error! Reference source not found.**.

As measured by RECIST 1.1, median TTP (95% CI) was 3.9 months for regorafenib (95% CI 2.9–4.2 months) compared with 1.5 months for placebo (95% CI 1.4–1.6 months): HR, 0.41, 95% CI 0.34-0.51; $p<0.0001$.[6]

Table 3: Analyses of TTP in the RESORCE study (FAS; mRECIST) (reproduced from CS, Table 21)

	Regorafenib (N=379)	**Placebo (N=194)**
Number of patients (%) with event	[redacted]	[redacted]
Number of patients (%) censored	[redacted]	[redacted]
Median TTP, days (95% CI), Range (without censored values)	[redacted]	[redacted]
Median TTP, months (95% CI), Range (without censored values)	3.2 (2.9, 4.2) [redacted]	1.5 (1.4, 1.6) [redacted]
Primary analysis		
Hazard ratio [a]: Stratified IVRS	[redacted]	
95% CI for hazard ratio:	[redacted]	
p-value (one-sided) from log-rank test) [b]:	<0.0001	

CI - confidence interval; FAS - full analysis set; IVRS - interactive voice response system

[a] An HR <1 indicates superiority of regorafenib 160mg over placebo.

Median, percentile and other 95% CIs computed using Kaplan-Meier estimates. HR and its 95% CI based on a stratified (IVRS) Cox regression model.

Durations had been manually converted from days to months (1 month=30.44 days)

were relatively low in both groups, but higher in regorafenib-treated patients compared with those receiving placebo (10% vs. 3%).

Sixty-eight percent of regorafenib patients had dose interruptions or reductions due to AEs compared with 31% of placebo patients, and dose interruptions or reductions due to drug-related AEs occurred in 54% of regorafenib patients and 10% of placebo patients. According to the CS, dose reductions (not including interruptions) due to AEs occurred in [redacted]% of the patients in the regorafenib group and [redacted]% of the placebo group. The AE profile of regorafenib in the RESORCE trial is generally similar to that of regorafenib in trials in colorectal cancer[29, 30] and there does not appear to be a statistically significant relationship between exposure and treatment-emergent AEs.[15] Deaths assessed as related to the study drug were reported for seven (2%) regorafenib patients and two (1%) placebo patients. There are no relevant ongoing studies of regorafenib.

The principal issue with the evidence concerns the limits of the trial population and how far they reflect the population seen in clinical practice in the UK. The RESORCE trial only included meaningful data on patients who were found not to be intolerant to sorafenib, who were ECOG PS 0 or 1, and who were categorised as Child-Pugh class A. The patients included in the RESORCE trial have been described as being relatively 'well'.[31, 32] A recent audit of sorafenib use in the UK[26] found that sorafenib is also used in patients who are ECOG PS 2 and Child-Pugh class B (21% and 16% of the audit population, respectively). These patients have a poorer prognosis and are more unwell. The RESORCE patients also appear to have had a substantial level of tolerance for sorafenib (at least 400mg per day for at least 20 of the last 28 days of treatment), despite rates of dose reduction/interruption and discontinuation with sorafenib being known to be relatively high.[33] The RESORCE trial patients therefore represent a particular group of adult patients with HCC who can tolerate tyrosine kinase inhibitors (TKIs) and have a relatively good prognosis.[31, 32] The licence currently includes all adult patients with HCC who have been previously treated with sorafenib. It therefore does not exclude patients who are ECOG PS 2, Child-Pugh class B, or who are intolerant to sorafenib. The CS acknowledges that there is no meaningful clinical evidence for the efficacy and safety of regorafenib in any of these groups. The sorafenib audit found that ECOG PS $\geq$2 was an independent predictor of mortality (confirming the findings of a sub-analysis of the pivotal SHARP trial[34]) and OS was substantially worse for patients who were Child-Pugh class B (4.6 months) than for those who were Child-Pugh class A (9.5 months).[26] RESORCE subgroup analyses found that patients who were PS 0 and Child-Pugh A5 experienced better efficacy than those who were PS1 and Child-Pugh A6.[6] The sorafenib audit also reported that liver dysfunction was much more common as an AE in Child-Pugh class B patients (40%) compared with Child-Pugh class A patients (18%), as was deterioration in performance status (47% vs 32%).[26] It should be noted that the number of Child-Pugh class B patients was smaller than Child-Pugh class A patients (n=43 vs n=181).[26]

notes that this aspect of the model is not well explained in the CS and the approach taken is overly complex and makes unnecessary assumptions where observed data could have been used instead (see Section 5.3).

Table 4: Post-progression treatment rate (applied to those progressing patients who receive post-progression regorafenib treatment, reproduced from CS Table 40)

Cycle after progressing	Proportion of patients receiving *n* cycles post-progression	
	Regorafenib	BSC*
1	[redacted]	[redacted]
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		

** Post-progression regorafenib use is included within the BSC group in order to estimate impacts of AEs on costs and HRQoL. The ERG does not consider this to be appropriate, however its impact on the ICER is negligible*

Adverse event frequency

The company's model includes the following AEs: anaemia; ascites; AST increase; blood bilirubin increase; fatigue; hypertension; hypophosphataemia and palmar-plantar erythrodysaesthesia syndrome. The model assumes that AEs may be experienced during any cycle and that these impact upon both costs and HRQoL. AE rates were derived from an analysis of IPD from the RESORCE trial.[6] The model assumes per cycle probabilities of AEs of 5.55% for regorafenib and 5.06% for BSC. The distribution of AEs within each group are summarised in **Error! Reference source not found.**.

regorafenib is identical to that for patients receiving sorafenib (see Table 5). This assumption was not raised as a major concern by the clinical advisors to the ERG, but the robustness of the survey was questioned. The full survey is provided in CS Appendix O.[9]

Table 5: Resource use for patients receiving regorafenib or BSC in both the progression-free and post-progression states

Description	Unit cost	Progression-free		Post progression	
		Regorafenib*	BSC	Regorafenib*	BSC
Hospitalisation					
General ward	£801	0.07	0.25	0.08	0.25
Duration of stay (days)	-	5.83	7.00	5.25	7.00
Cost of hospitalisation [1]	-	£4,670	£5,607	£4,205	£5,607
A&E admission	£138	0.37	0.25	0.08	0.25
Hospital outpatient appointments					
Oncologist	£163	1.07	0.75	1.00	0.75
Hepatologist	£253	0.33	0.00	0.00	0.00
Gastroenterologist	£132	0.00	0.00	0.00	0.00
Clinical nurse specialist	£130	0.67	0.50	0.50	0.50
Palliative care team	£131	0.00	2.17	0.00	0.00
Macmillan nurse	£73	0.00	0.00	0.00	0.00
Follow up visits					
GP visit	£36	0.00	0.00	0.00	0.00
Nurse visit	£36	0.00	0.00	0.00	0.00
Specialist visit	£151	0.84	0.84	0.50	0.84
Tests					
Alpha fetoprotein	£3.03	1.00	0.84	1.84[2]	0.84
Liver function	£2.78	1.00	0.84	1.00[2]	0.84
Biochemistry	£1.34	1.00	0.84	1.84[2]	0.84
Complete blood count	£2.65	1.00	0.84	1.84[2]	0.84
International normalised ratio	£3.43	0.71	0.34	0.67[3]	0.34
Radiological tests					
CT scan of abdomen	£122	0.39	0.17	0.84[3]	0.17
MRI of abdomen	£238	0.00	0.00	0.00	0.00

** Estimates elicited for sorafenib assumed to apply identically to regorafenib; costs of radiology and endoscopy not included in original submitted model but later included in model received post-clarification*

[1] Calculated multiplying the estimated length of stay by the estimated cost of a bed day on a general ward (£801)

[2] 1.00 at progression

[3] 0.67 at progression

Unit costs associated with the majority of resource items included in the company's model were taken from the NHS Reference Costs 2015/2016.[37] Other cost sources included: the Personal Social and Services Research Unit (PSSRU, Curtis and Burns[38]), Akhtar & Chung[39] and other NHS sources (bibliographic details not provided in the CS[1]). Of particular note, the estimated cost of a bed day in a general ward (£801 per day) was obtained from a response to a Freedom of Information Act request;[1] this is discussed in further detail in Section 5.3. Unit costs associated with AEs are summarised in **Error! Reference source not found.**.

and post-progression phases. During the progression-free phase, the probability of receiving treatment is modelled according to the PFS curve and a compound probability of discontinuation (an additional 0.087% patients discontinue during each model cycle). The per-cycle probability of discontinuing regorafenib was estimated by dividing the proportion of patients who discontinued treatment for more than one cycle prior to disease progression (2.7%) by the median PFS duration in the regorafenib group (3.1 months). The probability of having discontinued regorafenib during each cycle whilst progression-free is calculated using the following equation:

Probability of having discontinued treatment at time t

= Probability of having discontinued treatment at time t-1 x (1+ per-cycle discontinuation probability) [i]

The ERG does not believe that this approach is logically correct, but notes that setting this discontinuation rate equal to zero has only a minor impact on the cost-effectiveness of regorafenib (ICER = £33,749 per QALY gained).

During the post-progression phase, the company's model estimates the proportion of patients who have progressed and are still receiving regorafenib treatment. This is calculated using the post-progression treatment probability together with the sumproduct of the probability of being newly progressed in the given cycle and the post-progression treatment continuation rate. This approach assumes that the probability of receiving post-progression treatment and the post-progression treatment continuation rate are independent of the time at which the progression occurs. The ERG notes that this assumption may not be valid and the overall approach to modelling time on treatment is overly complex and makes unnecessary assumptions where data exist.

Given that [redacted] of patients continued to receive regorafenib treatment following disease progression, it is unclear why the company's model divides the total treatment received according to the presence or absence of disease progression. The ERG considers that the most appropriate approach to estimating the amount of drug received would instead involve the direct use of the time to treatment discontinuation (or death) curves observed within the RESORCE trial.6 Such an approach would also render the company's approach to modelling pre-progression discontinuation redundant.

In response to a request for clarification, the company provided an analysis of time to treatment discontinuation within the regorafenib group of the RESORCE trial.6 This analysis involved the consideration of two separate time to treatment discontinuation Kaplan-Meier curves. "Curve A" assumed that patients did not continue treatment beyond the 29th February 2016 DCO (see Figure 15). "Curve B" assumed that patients who were still receiving treatment on the 29th February 2016 were censored (see Figure 16). As indicated in the company's clarification response,8 "Curve A"

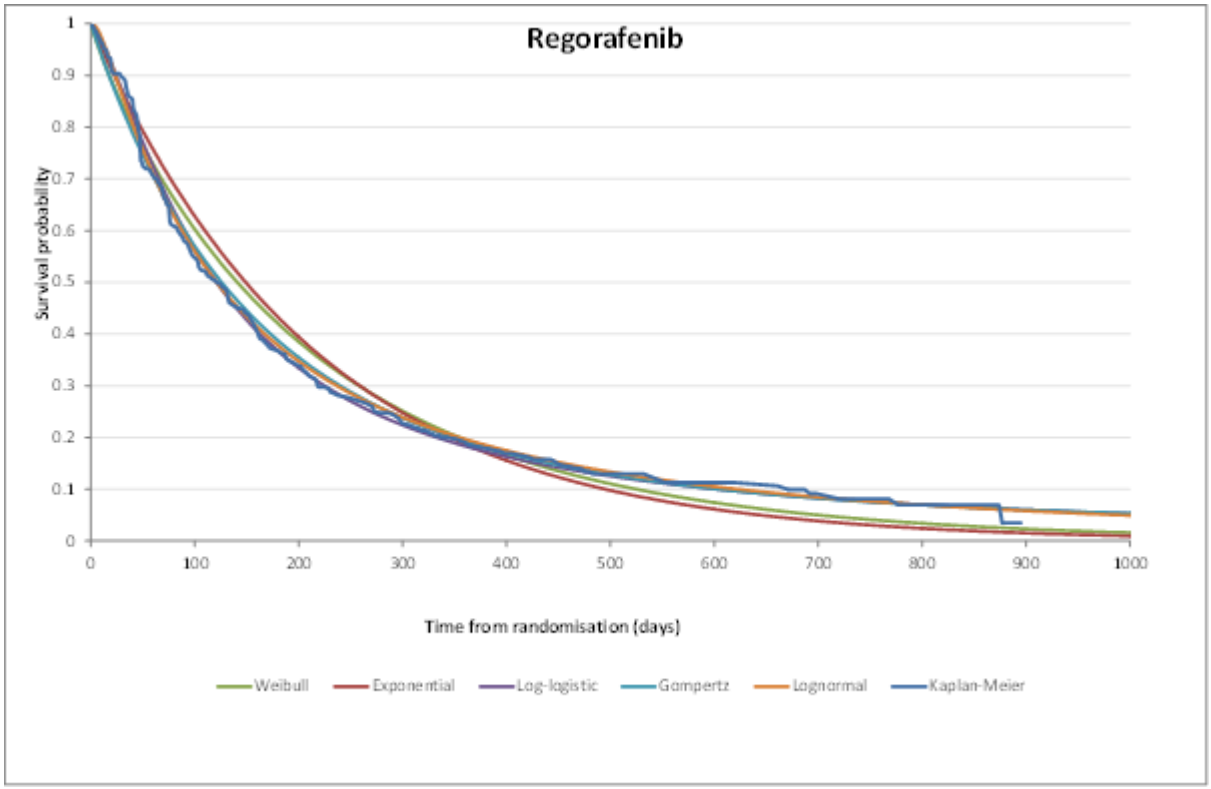


Table 6: Cost-effectiveness results for alternative curves fitted to time to treatment discontinuation, patients on treatment on 29th February 2016 censored (adapted from company's clarification response, question B8)

Time to treatment discontinuation scenario	Incremental costs (regorafenib versus BSC)	ICER (per QALY gained)
Original base case	[redacted]	£33,437
Raw KM treatment data	[redacted]	£38,906
Log normal	[redacted]	£39,207
Log logistic	[redacted]	£38,741
Weibull	[redacted]	£38,985
Exponential	[redacted]	£38,905
Gompertz	[redacted]	£39,060

(4) Inclusion of potentially unrealistic cost savings due to dose reductions/interruptions

The company's model includes cost savings associated with dose reductions and treatment interruptions for regorafenib. One clinical advisor to the ERG stated that should regorafenib be made available on the NHS, it would be prescribed monthly according to a fixed delivery schedule. The clinical advisor also noted that the logistics of current prescribing practices in their centre do not allow for the reduced frequency of individual prescriptions for patients with leftover pills; rather, any pills not taken by the patient would be returned and destroyed. The second clinician stated that 'the unused tablets are essentially lost…the only exception is if a patient develops toxicity in hospital where the remaining stock could be given to another patient in hospital'

Consequently, the ERG does not believe that the cost reductions included in the company's model would be fully realised in clinical practice and instead has costed regorafenib costed at its full maximum dose of 160mg per day for the entire duration of treatment within the exploratory analyses (see Section 5.5). As shown in the company's DSAs, the inclusion of full treatment costs increases the ICER for regorafenib versus BSC considerably (ICER excluding dose reductions = £41,206 per QALY gained, see **Error! Reference source not found.**). The ERG acknowledges that where the reduction in dose is planned and a lower dose is to be maintained in the long-term, the ERG's assumption of 160mg per day for each patient will overestimate the ICER for regorafenib.

(5) Concerns regarding expert clinician survey to inform health state resource use

Within the CS,[1] the company refers to a survey conducted in 2015 with three "*leading clinical experts in the field of oncology in the UK*" that was undertaken to estimate resource use associated with sorafenib and for patients receiving BSC. The company assumed that the sorafenib results were generalisable to regorafenib, although the CS notes that there is currently no experience in the clinical setting with regorafenib in the treatment of HCC. The CS does not make reference to an earlier survey which was conducted in 2007 using four UK clinicians, despite the fact that within the earlier sorafenib appraisal,[5] the NICE Cancer Drugs Fund (CDF) Appraisal Committee preferred the pooled analysis of both the 2007 and 2015 surveys.

For both the CDF appraisal of sorafenib and the clarification questions relating to regorafenib, the company have stated that the 2017 survey is preferable as "*The estimates from 2007 precede the availability of sorafenib and are not based on clinical experience. In contrast the estimates from 2015 are based on clinician experience in the use of sorafenib since its launch in 2008*" (company's clarification response,[8] question B14).

In the sorafenib CDF appraisal, the NICE Decision Support Unit (DSU) expressed a contrary view, stating that: "*The DSU thinks that discarding the results of the original survey is not the best option, especially considering that the original survey involved more clinicians and contained more responses… The estimates of the clinicians that took part in the new survey might have produced better estimates for the sorafenib arm due to the learning curve but the estimates for the BSC arm from the original survey should be equally valid when compared with those of the new survey.*"[43]

Table 7 summarises the completion rates for the 2007 and 2015 surveys.

Table 7: Comparison of the number of responses collected in the 2007 survey compared with the 2015 survey (adapted from DSU report on sorafenib[43])

	2007 survey	2015 survey
Total number of questions	279	247
Questions with no responses (%)	39 (14.0)	16 (6.5)
Questions with one responses (%)	31 (11.1)	35 (14.2)
Questions with two responses (%)	33 (11.8)	100 (40.5)
Questions with three responses (%)	36 (12.9)	96 (38.9)
Questions with four responses (%)	140 (50.2)	0 (0.0)
Total responses	765	523
Average number of responses	2.74	2.12

In the factual accuracy check round for the sorafenib CDF appraisal, the company stated that a preference for the 2015 survey "*on the grounds that health technologies and resource use change over time*" should be made. The DSU (acting as an ERG) responded stating: "*The ERG notes that the difference between the estimates of the physicians taking part in the survey points to uncertainty rather than changes in best supportive care (BSC). For example, in the new survey, the percentage* [redacted] *was estimated to be* [redacted] *by the first physician and* [redacted] *by the second (the third physician's estimate is not available). Similarly, the number* [redacted] *by the first physician was* [redacted] *and* [redacted] *by the second physician (the third physician's estimate is not available). These two parameters are the two main drivers of the difference between the ICERs using the old and new resource use estimates. The ERG believed including the estimates of the 4 physicians that took part in the original survey resulted in more robust estimates."*[43]

The ERG for this appraisal (of regorafenib) notes that there are no new data presented which would alter the judgment of the CDF Appraisal Committee. As such, and noting the arguments put forward by the DSU, the ERG maintains that the pooled estimates are preferable to the 2015 survey responses alone.

For the sake of clarity, the ERG has tabulated the resource use estimates taken from the 2015 survey and the pooled 2007 and 2015 surveys (see **Error! Reference source not found.**). It should be noted that monthly estimates have been assumed to be generalisable to 28-day cycles. These data are conditional on whether a patient is on treatment and whether the patient is in a pre-progression or post-progression state. It is observed that regardless of which survey responses are used, the rates of patients requiring hospitalisation were lower for those on regorafenib as were the assumed durations of hospital stays and thus the cost per hospitalisation is lower. Clinical advice received by the ERG indicates that it is plausible that the use of regorafenib could reduce the number of hospitalisations compared with BSC alone.

It should also be noted that a potential discrepancy was found in the survey data and the way in which these were interpreted and implemented by the company. Further details are provided in Appendix 1 however, briefly, it appears that patients requiring hospitalisation are assumed to have fewer than one hospital visit per month on average, which is not logical. The company states that they had assumed *a priori* that this number would be one or greater, which the ERG believes is logical. Appendix 1 contains a replication of the company's response, which attempts to justify the data used in the CS, and a sensitivity analysis performed by the company in which the number of hospitalisations per month for those requiring hospitalisation is set to one. The ERG does not accept the justification put forward by the company and prefers the assumptions used in the sensitivity analyses performed by the company.

The ERG considers that there are still implementation errors in non-hospital costs within the CS when data from the pooled survey are used, but that the correction of these will have only a minor impact on the ICER and thus have left these at the values used by the company.

The results of the ERG's additional sensitivity analyses indicate that alternative choices of parametric functions to model OS may reduce the ICER for regorafenib (ICER range = £72,642 to £81,081 per QALY gained). The use of alternative parametric functions to model time to treatment discontinuation leads to ICERs in the range £74,122 to £81,703 per QALY gained. The use of the utilities from the SHARP trial increase the ICER for regorafenib versus BSC to £92,719 per QALY gained. Increasing the disutility associated with progressed disease (relative to the progression-free utility score) does not have a substantial impact on the ICER for regorafenib. The exploratory analysis in which the number of hospitalisations per month estimated in the survey was applied to the entire population has only a minor impact on the ICER for regorafenib compared with assuming that the percentage requiring hospitalisation was correct and that patients were hospitalised once per month. The inclusion of dose reductions to [redacted] for all patients from the start of treatment reduces the ICER to [redacted] per QALY gained; the ERG notes that this represents a highly optimistic scenario and that the ICER for regorafenib is likely to be higher than this estimate.

5.6 Discussion

The CS includes a systematic review of published economic evaluations of treatments for HCC together with a *de novo* health economic evaluation of regorafenib (plus BSC) versus BSC alone in patients with HCC. The company's review did not identify any economic evaluations of regorafenib within this indication. Additional searches undertaken by the ERG identified one economic evaluation study which assessed regorafenib versus BSC in patients (Parikh *et al*[35]); this study was published after the company's searches had been carried out. The company and the ERG both agreed that this study is not relevant to the current appraisal due to the use of a short time horizon, the absence of any form of extrapolation of time-to-event outcomes and the use of a US health care system perspective.

Owing to the absence of any relevant existing studies, the company developed a *de novo* partitioned survival model to assess the cost-effectiveness of regorafenib (plus BSC) versus BSC alone in adult patients with unresectable HCC who have been previously treated with sorafenib. Incremental health gains, costs and cost-effectiveness of regorafenib are evaluated over a 15-year time horizon from the perspective of the NHS and PSS. The company's model includes three health states: (1) progression-free; (2) progressed disease, and (3) dead. The model parameters were mostly informed by analyses of time-to-event data (PFS, OS and time on treatment) collected within the RESORCE trial[6] (January 29th 2016 DCO). PFS was modelled using the observed PFS estimates, OS was modelled using a log normal distribution with a treatment effect covariate (an HR) and time to treatment discontinuation was modelled using a "cycle-cohort simulation" approach. Resource use was informed by a survey of three clinical experts undertaken in 2015. The model assumes that a small proportion of patients treated with regorafenib will discontinue prior to disease progression and that a proportion of patients continue regorafenib treatment following progression. The model includes a mean daily dose of