NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]

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

Contains AIC, CIC

Pre-meeting briefing

Regorafenib for previously treated unresectable hepatocellular carcinoma

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

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Abbreviations

BCLC	Barcelona-Clinic Liver Cancer	ORR	Objective response rate
BSC	Best supportive care	OS	Overall survival
CDF	Cancer Drugs Fund	PD	Progressed disease
CR	Complete Response	PFS	Progression free survival
DCR	Disease control rate	PR	Partial response
DOR	Duration of response	PSA	Probabilistic sensitivity analyses
ECOG	Eastern Cooperative Oncology Group	ORR	Objective response rate
EASL-EORTC	European Association for Study of the Liver / European Organisation for the Research and Treatment of Cancer	SD	Stable disease
EQ-5D	EuroQol-5 Dimension	TACE	Transarterial chemoembolisation
HCC	Hepatocellular carcinoma	TEAE	Treatment emergent adverse event
HRQoL	Health related quality of life	TTP	Time to progression
KM	Kaplan-Meir	TKI	Tyrosine kinase inhibitors

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Key issues-Clinical effectiveness

- Does the clinical effectiveness observed in RESORCE relate to the total population in the marketing authorisation and in England with advanced HCC considering the:
  - Absence of people with Child-Pugh B liver impairment
  - Absence of people with ECOG performance status of ≥2
  - Absence of people who could not tolerate sorafenib

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Key issues-cost effectiveness

- Is the model population representative of the population in RESORCE which excluded people intolerant to sorafenib?
- Modelling OS: the company dependent lognormal curve and the ERG independent Weibull curve
- Time to treatment discontinuation: is fitting fully extrapolated parametric curves to the available Kaplan-Meier data the appropriate approach to estimating the amount of regorafenib received in the model?
- Is it appropriate to assume full treatment costs without dose reduction savings as representative of prescribing practice in the NHS?
- The resource use estimate the company derived from 2015 survey or ERG pooled estimates from both 2015 and 2007 surveys?
- What are the most plausible ICERs?
- Are the end of life criteria met?
- Potential equality issues

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Hepatocellular carcinoma

- Hepatocellular carcinoma (HCC) is primary malignancy of the liver and is 17th most common cancer in the UK accounting for 53% of primary liver cancer diagnoses. Worldwide, it is the sixth most frequently diagnosed cancer
- HCC occurs predominantly in patients with underlying chronic liver disease and cirrhosis. Cirrhosis is the primary risk factor for HCC, commonly caused by hepatitis B, hepatitis C, fatty liver disease or alcohol
- Incidence of HCC is rising in western countries including the UK, probably due to hepatitis C virus epidemic and increased alcohol consumption
- HCC often diagnosed at latter stages of disease when limited treatment options are available and patients typically have short life expectancy. Symptoms including fatigue, jaundice, pruritus, encephalopathy, weight loss, ascites, abdominal pain / distension and the presence of a mass

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Details of the technology

Technology	Regorafenib (Stivarga, Bayer)
Mechanism of action	Tyrosine kinase inhibitor (TKI) which inhibits multiple protein kinases involved in oncogenesis, tumour cell proliferation and tumour vasculature. Also inhibits angiogenic kinase receptors which play a central role in angiogenesis thereby preventing the proliferation of cancer cells
Marketing authorisation	"Regorafenib is indicated as monotherapy for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib" Restrictions: not recommended for patients with severe hepatic impairment (Child-Pugh C) as not studied in this population
Administration and dose	Oral, 160 mg once daily for 3 weeks followed by 1 week off therapy. 4-week period considered a treatment cycle
Cost	List price per treatment cycle: £3,744 PAS price per treatment cycle: [redacted]
Average cost of course of treatment	Based on average number of packs received in RESORCE trial: List price : [redacted] (based on average number of packs received in RESORCE) PAS price: [redacted]

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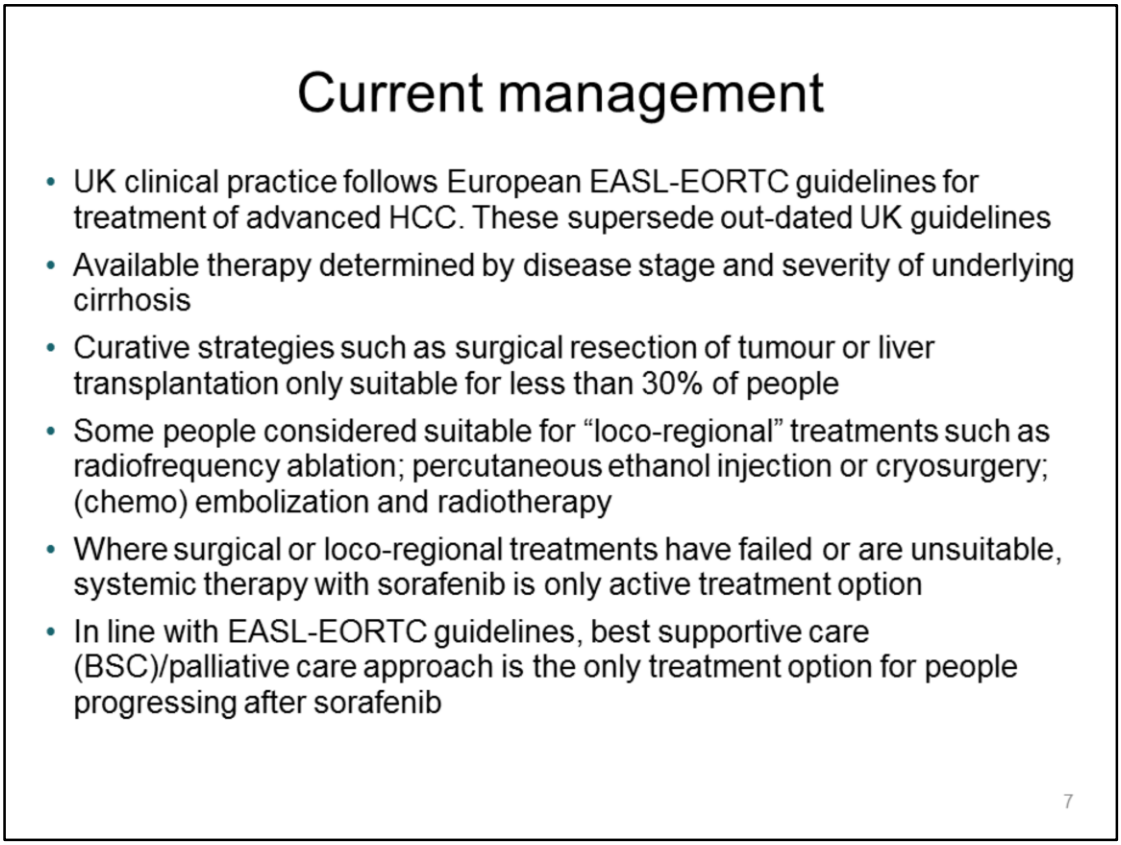

BSC covers a wide range of treatment options intended to maximise quality of life without a specific antineoplastic regimen. Examples of BSC includes herbs, acupuncture, vitamins and mineral supplements, antibiotics, bisphosphonates for bone metastases, chronic erythropoietin, analgesics, radiation therapy for pain control (limited to bone metastases), nutritional support, corticosteroids, transfusions, psychotherapy, and palliative surgery.

Previous appraisals

- NICE TA474
  - Sorafenib has been available through the Cancer Drugs Fund since 2007 and has recently been recommended for routine commissioning through the Cancer Drugs Fund rapid reconsideration process
  - Sorafenib is recommended as an option for treating advanced hepatocellular carcinoma only for people with Child-Pugh grade A liver impairment, only if the company provides sorafenib within the agreed commercial access arrangement.

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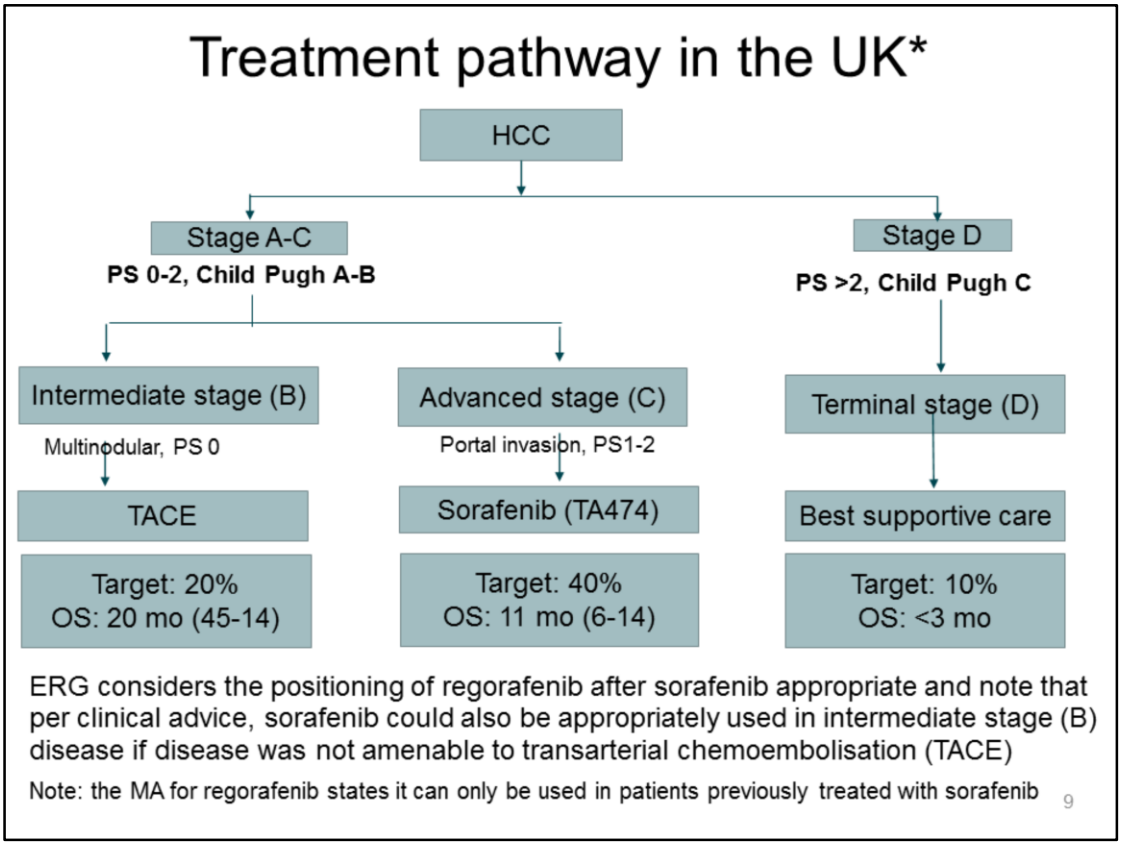

Redrawn using figure 2 (company submission page 22)

*Early stage treatment pathway not included as it is not relevant to this appraisal

Treatment pathway according to EASL EORTC guidelines which are followed in England.

Staging of HCC

- Barcelona-Clinic Liver Cancer (BCLC) classification divides HCC patients into 5 stages (0, A, B, C and D) per pre-established prognostic variables
- Prognosis defined by variables related to tumour status (size, number, vascular invasion), liver function (Child–Pugh's), Eastern Cooperative Oncology Group (ECOG) and health performance status

BCLC Stage	Tumour status	ECOG PS	Liver Function (Child-Pugh)
0 (Very early HCC)	Single tumour < 2cm in diameter without vascular invasion	0	Child-Pugh A
A (Early HCC)	Single tumours >2 cm or 3 nodules <3 cm of diameter	0	Child–Pugh A or B
B (Intermediate HCC)	Multinodular asymptomatic tumours without invasive pattern	0	Child-Pugh A-C
C (Advanced HCC)	Symptomatic tumours; macrovascular invasion or extrahepatic spread (lymph node involvement or metastases)	1–2	Child-Pugh A-C
D (End stage HCC)	Tumours leading to very poor performance status reflecting severe tumour-related disability	3-4	Child-Pugh C

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Source: Table 3 (company submission page 21)

Pre-established prognosis variables as outlined in the joint European Association for Study of the Liver / European Organisation for the Research and Treatment of Cancer (EASL-EORTC) clinical practice guidelines.

Child-Pugh classification

The Child-Pugh score is an accepted classification of liver function, with higher numbers indicating more impaired liver function and lower numbers (e.g. class A) indicating better preserved liver function

	Score		
Measure	**1 point**	**2 points**	**3 points**
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged)	<4	4-6	>6
Encephalopathy grade	None	1–2	3–4 *

Individual scores are summed and then grouped as:

- Child–Pugh A: 5 or 6 points
- Child–Pugh B: 7–9 points
- Child–Pugh C: >9 points

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Decision problem

	NICE scope	Company submission
Population	Adults with previously treated unresectable hepatocellular carcinoma	Adult patients with advanced hepatocellular carcinoma who have been previously treated with sorafenib *
Intervention	Regorafenib	Regorafenib
Comparator	Best supportive care	Best supportive care
Outcomes	Overall survival Progression free survival Response rates Adverse effects of treatment Health-related quality of life	Overall survival Progression free survival Response rates Adverse effects of treatment Health-related quality of life

*Rationale for deviation from NICE scope: MA for regorafenib is restricted to patients who have been previously treated with sorafenib

The ERG in agreement that the company submission adequately describes the decision problem.

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Clinical expert comments

- Current first line treatment for advanced HCC is sorafenib for people with good performance status and well preserved liver function. Sorafenib (and now regorafenib) are the only therapies approved for advanced HCC in the last 10 years
- There is significant unmet need for patients who progress or are intolerant to sorafenib. Only options are best supportive care or clinical trials
- For a selected population of people with HCC who are tolerant but progress on sorafenib, have preserved liver function and good performance status, regorafenib offers an additional second line treatment option which has evidence demonstrating improvement in survival
- Regorafenib will be used in specialist clinics experienced in management of systemic therapy for advanced HCC and use of sorafenib in first line setting. Thus, clinical expertise and infrastructure should already be in place although monitoring the effects of regorafenib would require additional testing/scanning
- The toxicity of regorafenib is similar to other multikinase inhibitors. A patient's quality of life is affected by the presence of underlying malignancy and chronic liver disease. Quality of life expected to be maintained rather than increased

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Patient perspective

- Most people with advanced HCC are diagnosed too late for surgical treatments to be an option
- Regorafenib provides both improved quality of life and increased survival: important for a condition where outcomes are poor
- Side effects are generally manageable
- As an oral treatment, it is more convenient than intravenous therapy
- The eligible population will be only 25-30% of the approx. 3,287 with the condition

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Clinical effectiveness
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Company's clinical evidence-RESORCE

Trial name	RESORCE
Population	People with advanced HCC who have been previously treated with sorafenib
Intervention	Regorafenib + BSC (n=379),160mg (4 x40mg tablets) orally once daily for weeks 1-3 of each 4-week cycle
Comparator	Placebo + BSC (n=194)
Trial design	Randomised, double-blind, placebo-controlled, phase III
Location	152 international study sites in 21 countries from North America, South America, Europe and Asia. 20 UK patients randomised to study treatment at 4 study sites
Subgroups	Pre-planned subgroup analysis for overall survival (OS), progression free survival (PFS), time to progression (TTP) and safety parameters by age include (<65 years, ≥ 65 years), sex, geographical region(Asia versus non-Asia), baseline ECOG performance status(0,1), baseline Child-Pugh status (A5,A6), aetiology (hepatitis B, hepatitis C, alcohol use)
Duration of study and follow-up	Primary endpoint reached in February 2016. During double-blind period, median treatment duration was 3.6 months (range 1.6-7.6) in the regorafenib arm and 1.9 months (range 1.4-3.9) in placebo arm. All patients followed up monthly for survival until documented death

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After the primary endpoint of study was reached and study results supported a positive benefit / risk assessment for regorafenib in the trial, patients who were currently on placebo at that time were offered the opportunity to receive regorafenib through open-label treatment whereas patients randomized to regorafenib continued open-label regorafenib.

RESORCE trial contd.

Key eligibility criteria for participants	• Histologically or cytologically confirmed HCC with confirmed diagnosis of cirrhosis • Failure to prior treatment with sorafenib • BCLC stage Category B or C that could not benefit from treatments of established efficacy such as resection, local ablation, chemoembolisation, or systemic sorafenib. • Child-Pugh status A • ECOG PS of 0 or 1 • Life expectancy ≥ 3 months • Age ≥ 18 years old
Baseline characteristics	Over 96% with Child-Pugh score of A. Mean age 61 years, predominantly male (88%). 65% in regorafenib group and 67% in placebo group had ECOG performance status of 0. 85.8% of people in regorafenib group and 88.7% in placebo group had BCLC stage C disease. Alcohol use reported as aetiology for 28.4% in placebo and 23.8% in regorafenib group. Median time since progression on sorafenib until start of study treatment was identical (1.4 months) for both treatment groups Median time since initial diagnosis of HCC to start of study treatment lower in placebo group (20 months) compared with regorafenib group (21 months)

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RESORCE trial outcomes

Primary outcomes	• Overall survival (OS)
Secondary outcomes	• Progression-free survival (PFS) • Time to progression (TTP) • Objective response rate (ORR) • Disease control rate (DCR)
Tertiary endpoints	• Duration of response (DOR) • Duration of stable disease

Exploratory endpoints	• OS measured from the start of prior sorafenib therapy
	• Maximum percentage reduction in size of target lesions
	• Maximum percentage change from baseline in size of target lesions, per RECIST 1.1 and mRECIST criteria
	• Health related quality of life (HRQoL)
	  ◦ EuroQol-5 Dimension (EQ-5D)
	  ◦ FACT-Hep (version 4)

Other endpoints	• Safety

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Company submission
Generalisability of RESORCE population to UK clinical setting (1)

- An audit of sorafenib-treated patients, identified by the Cancer Drugs Fund and local databases by King et al. (2017) provides baseline characteristics of patients treated with sorafenib from 2007-2013 (see table 30 in the company submission). Data obtained for 448 sorafenib-treated patients from 15 hospitals.
- Comparison with trial population from RESORCE demonstrates that the two populations are generally comparable
- However, patients in the audit are older (mean age of 68 vs 61/62), less likely to have HCC caused by hepatitis B and less likely to have extrahepatic disease. A minority of English people treated in a clinical setting had a ECOG performance status>=2 and Child-Pugh B liver impairment whereas people meeting this criteria were excluded from RESORCE.

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Please see page 85-89 of the company submission for more information

Company submission
Generalisability of RESORCE population to UK clinical setting (1)

ECOG status and Child-Pugh Class:

- People in England can receive sorafenib only if they have Child-Pugh A status with regorafenib expected to be used after sorafenib treatment. At this advanced stage of disease, liver impairment and performance status could have deteriorated further and use of further chemotherapy is usually reserved for 'fitter' patients.
- Due to evidence of reduced benefit for TKIs in such people with poor capacity to benefit, company anticipates use of regorafenib would be low.

Hepatitis B:

- Analysis by King at al. indicates that hepatitis B is not significantly correlated with survival and a significant difference in efficacy for those with/without hepatitis B was also not demonstrated in RESORCE.

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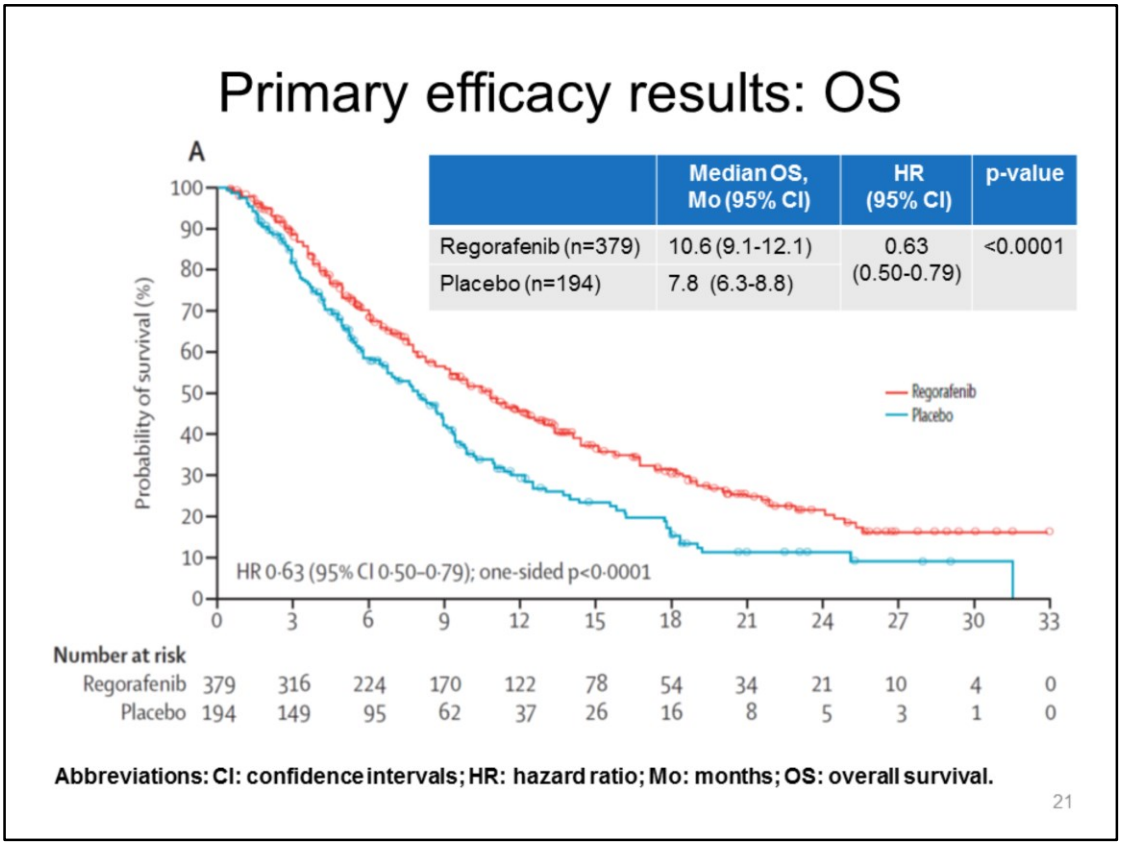
Please see page 85-89 of the company submission for more information



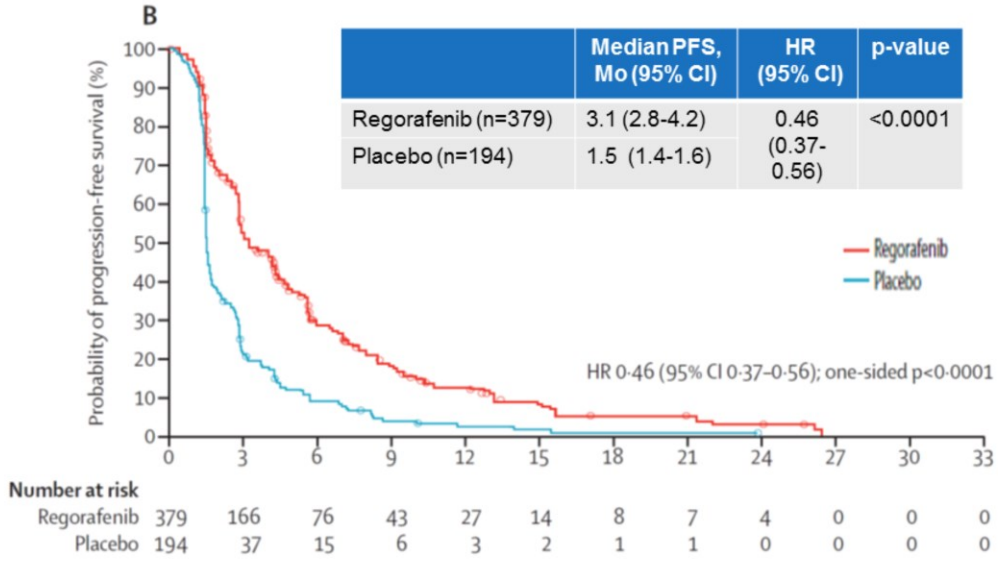
Source: Figure 4, company submission page 56.

Based on the Full Analysis Set (FAS) which was the intention to treat (ITT) population

Please see table 19, company submission page 57, for a breakdown of analyses of OS in the RESORCE trial. Sensitivity analyses confirmed robustness of primary analysis of OS.

Median, percentile and other 95% CIs computed using Kaplan-Meier estimates. Hazard ratio and its 95% CI was based on either a stratified interactive voice response system (IVRS), stratified validated electronic system for data collection (RAVE), or non-stratified Cox Regression Model. Additionally, durations manually converted from days to months (1 month=30.44 days)

Secondary efficacy results: PFS



	Median PFS, Mo (95% CI)	HR (95% CI)	p-value
Regorafenib (n=379)	3.1 (2.8-4.2)	0.46 (0.37-0.56)	<0.0001
Placebo (n=194)	1.5 (1.4-1.6)		

Abbreviations: CI: confidence intervals; HR: hazard ratio; Mo: months; OS: overall survival.

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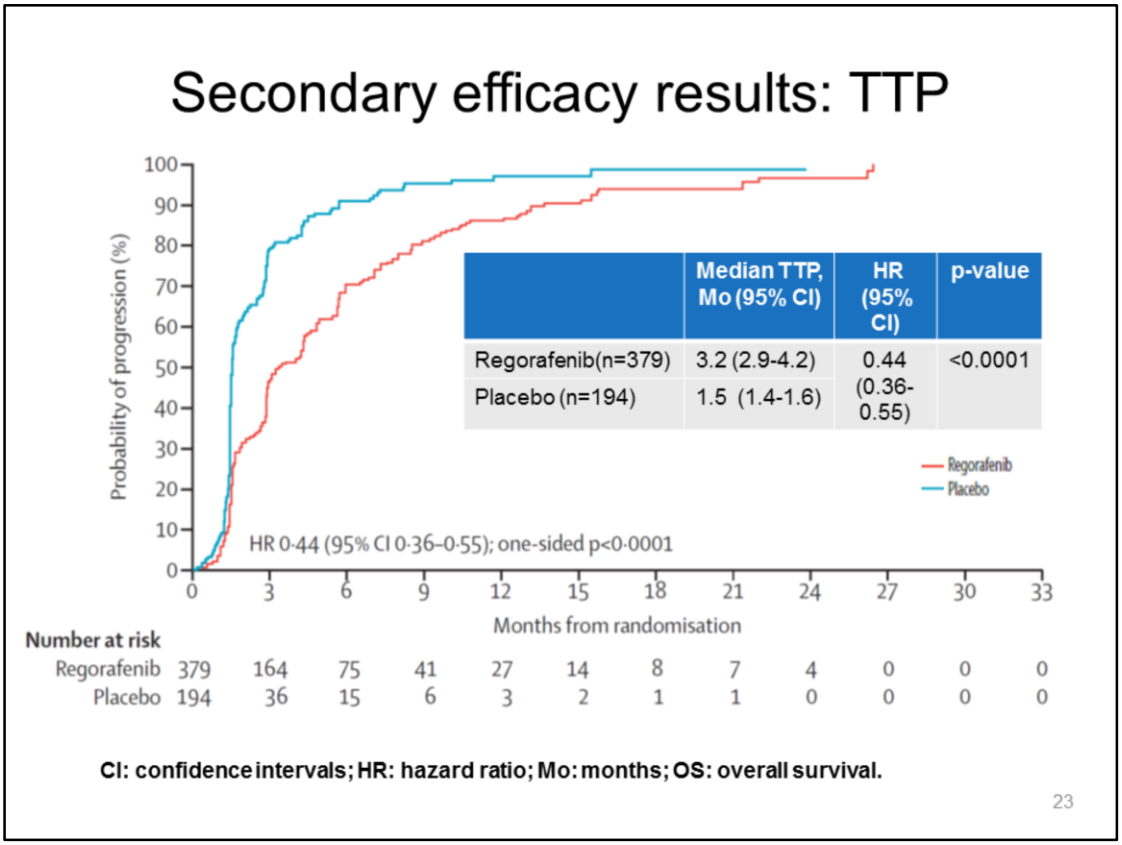
Source: Figure 5, company submission page 58

Please see table 20, company submission page 59, for a breakdown of analyses of PFS in the RESORCE trial. Sensitivity analyses confirmed robustness of primary analysis of PFS.



Source: Figure 6, company submission page 60

At the cut-off date for the final analysis (29th February 2016), there had been 447 events. The percentage of patients with disease progression was 89.2% (n=173) in the placebo group and 72.3% (n=274) in the regorafenib group.

Please see table 21, company submission page 61, for a breakdown of analyses of TTP in the RESORCE trial. Sensitivity analyses confirmed robustness of primary analysis of TTP.

Analyses of response to therapy in RESORCE

Best overall response	Regorafenib N=379 (100%) [95% CI]	Placebo N=194 (100%) [95% CI]
Complete response (CR)	2 (1%) [<1%; 2%]	0
Partial response (PR)	38 (10.0%) [7%; 14%]	8 (4%) [2%; 8%]
Stable disease (SD)	206 (54%) [49%; 59%]	62 (32%) [26%; 39%]
Progressive disease (PD)	86 (23%) [19%; 27%]	108 (56%) [48%; 63%]
Not evaluable (NE)	19 (5%) [3%; 8%]	8 (4%) [2%; 8%]
Not assessed (NA)	27 (7%) [5%; 10%]	8 (4%) [2%; 8%]
Clinical progression	86 (23%) [19%; 27%]	40 (21%) [15%; 27%]
Objective Response Rate	**40 (11%)**	**8 (4%)**
Disease Control Rate	**247 (65%)**	**70 (36%)**

Comparison of treatments – Inferential Statistics			
Regorafenib versus placebo	**Difference**	**[95% CI]**	**p-value**
Response rate	-6.61	[-10.84, -2.39]	0.0047
Disease control rate	-29.31	[-37.52, -21.11]	<0.0001

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Source: Table 22, company submission page 63

As HCC is a highly vascularised tumour, modified RECIST (mRECIST) allows more accurate assessment when evaluating agents that reduce tumour vascularity, cell proliferation and response to treatment with TKIs

Per mRECIST evaluation:
Complete response (CR) defined as the absence of arterially enhanced areas in all target lesions
Partial response (PR) and progressive disease (PD) defined as greater than 30% decrease and a greater than 20 % increase, respectively, in the sum of diameters of arterial enhanced areas in all target lesions
Stable disease (SD) defined as neither PR nor PD
Patients with no enhanced lesions were classified as non-measurable
Objective response rate (ORR) defined as CR+PR
Disease control rate (DCR) defined as CR+PR+SD (stable disease had to be maintained for at least 6 weeks)

Health related quality of life: summary of patient reported outcomes

Least squares Mean (LSM) time-adjusted AUC [95% CI]	Regorafenib	Placebo	Difference	P-value	MID
EQ-5D index	0.76 (0.75, 0.78)	0.77 (0.75, 0.79)	-0.01 (-0.03, 0.02)	0.4695	0.1
EQ-5D VAS	71.68 (70.46, 72.90)	73.45 (71.84, 75.06)	-1.77 (-3.58, 0.04)	0.0558	10
FACT-G	75.14 (74.12, 76.16)	76.55 (75.20, 77.90)	-1.41 (-2.93, 0.11)	0.0698	6-7
FACT-Hep total	129.31 (127.84, 130.79)	133.17 (131.21, 135.12)	-3.85 (-6.06, -1.65)	0.0006	8-9
Trial outcome index	91.47 (90.30, 92.64)	95.52 (93.98, 97.07)	-4.05 (-5.79, -2.31)	<0.0001	7-8

AUC=area under curve; FACT=Functional Assessment of Cancer Therapy; FACT-G=FACT-General; FACT-Hep=FACT-hepatobiliary; LSM=Least squares mean; MID=minimally important difference; VAS=visual analogue scale;

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Source: Table 27, page 68 of company submission

FACT-Hep is a disease-specific module of the FACT questionnaire developed to measure the quality of life HRQoL in patients with hepatobiliary cancers. Higher scores on all scales of the FACT-Hep questionnaire reflect better quality of life or fewer symptoms.
Please see refer to pages 67-71 of the company submission for more information.

Adverse events and dose modification

- Population for safety analysis in RESORCE included people receiving at least one dose of study medication (n=567; placebo n=193 and regorafenib n=374)
- At least one treatment emergent adverse event (TEAE) was experienced by all participants during double-blind period of RESORCE (regorafenib, n=374 [100%]; placebo, n= 179 [92.7%]). High rate in both groups expected for pre-treated HCC patient population
- Commonly reported adverse events with regorafenib include: hand-foot skin reaction, asthenia / fatigue, diarrhoea, decreased appetite, and hypotension
- Incidence of TEAEs leading to permanent treatment discontinuation in RESORCE: 25% in the regorafenib versus 19% in placebo group
- Most serious adverse drug reactions in patients receiving regorafenib are severe liver injury, haemorrhage, and gastrointestinal perforation and hypotension
- Dose reductions due to adverse events occurred in 47.9% of the patients in the regorafenib group and 7.8% of the placebo group
- Study drug could be delayed or reduced per pre-specified schedule in the case of transaminase elevation, unacceptable toxic effects, hand-foot skin reaction and hypertension
- Up to two regorafenib dose-reductions due to toxicity were allowed (from 160 mg to 120 mg to 80 mg)

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See company submission, pages 73-81 for more information on adverse events and specific Grade 3 and TEAEs for each treatment arm

Please see slide 37 for modelling of time on treatment in the company economic model

ERG critique

Overview and generalisability of trial population to clinical practice in England

- Company systematic review generally well-conducted
- RESORCE is a high quality RCT, with a low risk of selection, performance, detection, attrition and reporting bias
- The marketing authorisation is broader than the trial population
- There is absence of trial evidence from RESORCE on some patient groups who would be eligible to receive regorafenib:
  - adults with HCC who are sorafenib intolerant (having been unable to receive sorafenib at ≥400mg/day for ≥20 of the last 28 days of treatment)
  - who are Child-Pugh class B or
  - who have ECOG performance status ≥ 2
- ERG note that people in RESORCE 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

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ERG critique
Generalisability of trial population to UK clinical practice

- Recent audit of sorafenib use in the UK found sorafenib is also used in patients who are ECOG performance status ≥ 2 and Child-Pugh class B (21% and 16% of the audit population, respectively).
- The audit also shows that ECOG performance status ≥ 2 was an independent predictor of mortality and OS was worse for patients who were Child-Pugh class B (4.6 months) than for those who were Child-Pugh class A (9.5 months)
- It also reported that liver dysfunction was more common as an adverse event in Child-Pugh class B patients (40%) compared with Child-Pugh class A patients (18%), as was deterioration in performance status (47% vs 32%)
- Trial participants from RESORCE represent people with HCC who can tolerate tyrosine kinase inhibitors (TKIs) and have a relatively good prognosis
- Given the adverse event profile of regorafenib, there is a probability that people who do not match trial population will experience less efficacy and more adverse events (as many are hepatic) than people who match RESORCE profile
- Substantial uncertainty around benefits of regorafenib in people who do not satisfy the inclusion criteria of the RESORCE trial

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Please refer to pages 40-43 of ERG report


Cost effectiveness
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Published economic evaluations

- The company identified 19 economic evaluations. Most of the included studies related to sorafenib for HCC. No cost-effectiveness studies which assessed use of regorafenib in patients with advanced HCC were identified
- An update search on 27th July 2017 conducted by ERG identified an economic evaluation comparing regorafenib with BSC for treatment of advanced HCC (Parikh *et al.*) This was not identified by the company's search strategy as it was published in after the company's searches
- The ERG agreed with the company that this study cannot address the decision problem set out in the final scope of this appraisal

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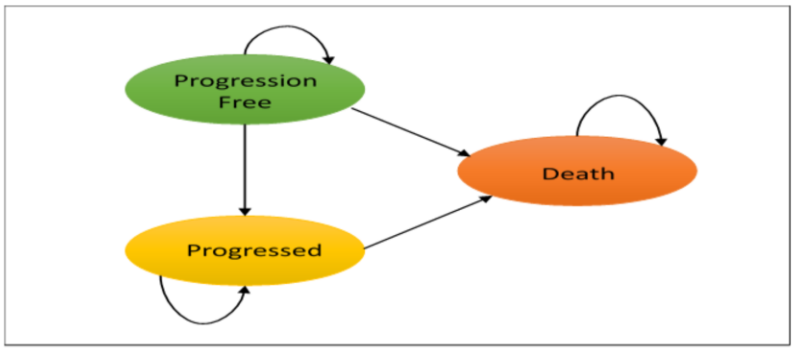
Company model

Partitioned survival model – 3 states



Factor	Chosen values
Time horizon	15 years
Perspective	NHS and PSS
Discount rate	3.5% per year
Cycle length	28 day cycle length (in line with regorafenib dosing schedule: one 3 week cycle followed by one week off treatment).

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Company model
Clinical inputs

- Efficacy and clinical data inputs used in the model were derived using patient-level data from RESORCE including:
  - Overall survival
  - Progression free survival
  - Discontinuation from treatment (discontinuation rates differ in the progression free and progressed disease health states)
  - Dose modifications
  - Adverse events
- PFS data from RESORCE represents full pattern of progression, therefore PFS curve taken directly from the observed Kaplan-Meier data from trial.
- For OS, standard parametric curve fitting was performed using patient-level data from RESORCE

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Company model

4 different models submitted, 3 post-clarification

Model	Description
Original company base-case	Reported in the company submission • dependent survival curves with a Cox derived HR. • original data cut of 29th February 2016 from RESORCE
Post-clarification model 1	Revised model submitted after ERG clarification requests • additional functionality including allowing for independent OS curves • 29th February 2016 data cut • no base-case provided for this model
Post-clarification model 2	Second revised model based submitted after ERG clarification requests • model functionality is restricted to only allow for the modelling of dependent OS curves • latest data-cut (23rd January 2017) • following the identification of a programming error, the company submitted a corrected version of this model. • Base case provided - this document will refer to this revised company base-case model throughout unless otherwise stated.
Post-clarification model 3	Third revised model on which ERG exploratory analyses and additional sensitivity analyses is based on: • additional functionality including allowing for independent OS curves • 23rd January 2017 data-cut • Base case remains the same as post-clarification model 2

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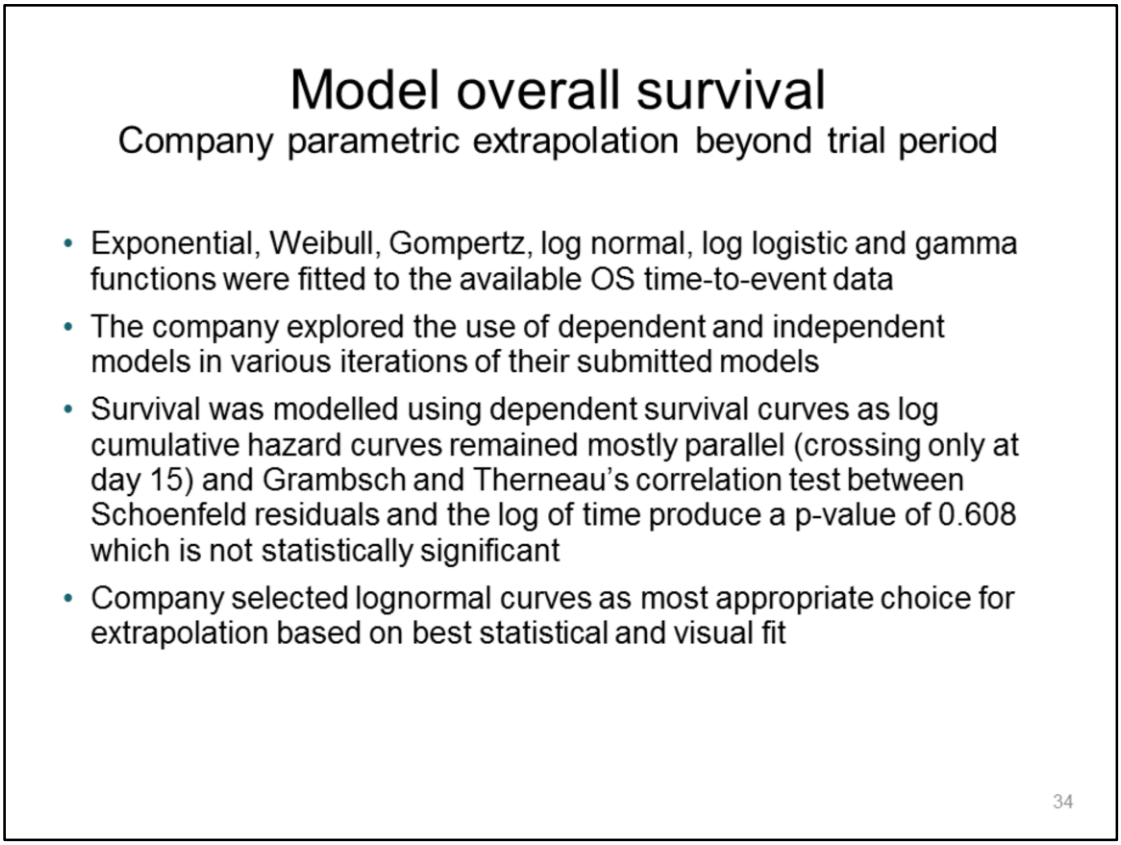
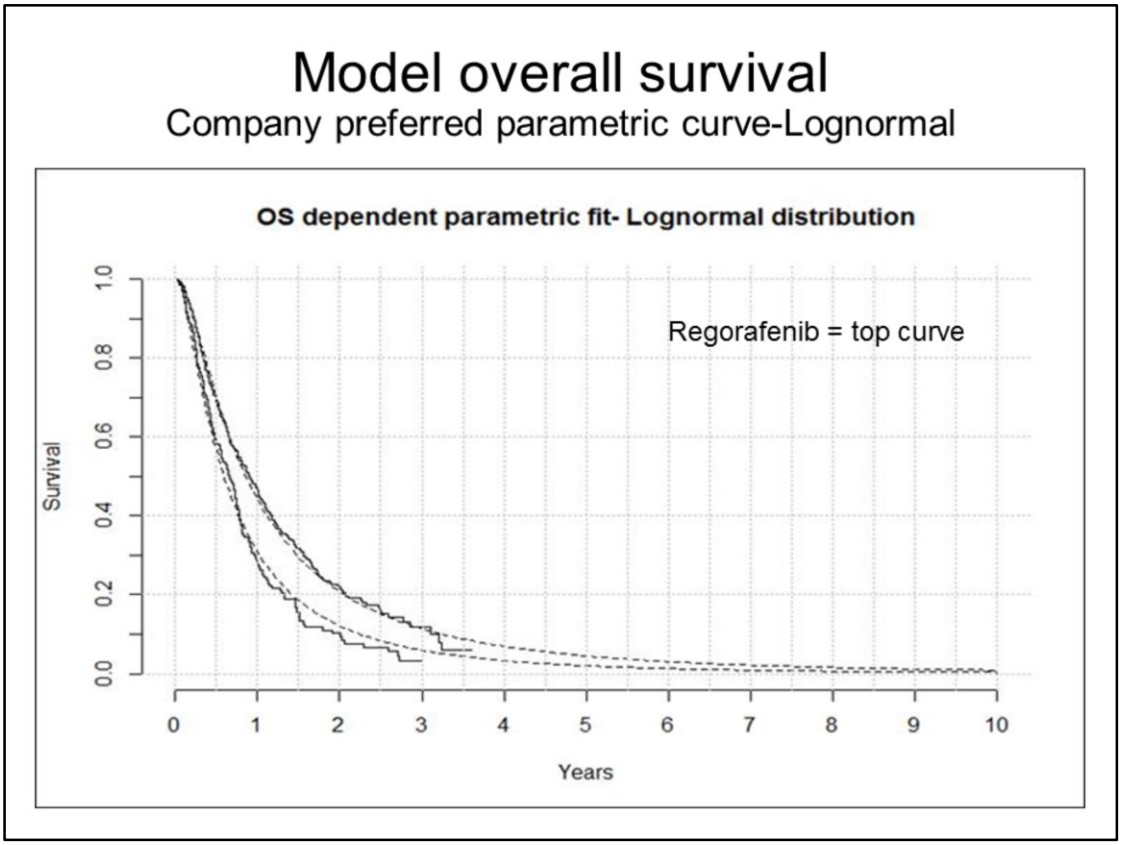


Company note that support for use of the lognormal curve also comes from NICE appraisals of sorafenib where the lognormal curve was also found to be the best fit. Being in a comparable population the best fitting curve for sorafenib also provides some support for the choice of curve for regorafenib.



Source: Figure 4 (page 6 in company response to question B1). Please see pages 5-8 for graphs of other functions provided separately.

Company model
Time on treatment

- Kaplan-Meier time to treatment discontinuation (or death) curves observed within RESORCE were directly used to determine the amount of regorafenib received in the model
- Patients still on treatment at 23rd January 2017 cut-off were censored
- Parametric curves (log normal, log logistic, Weibull, exponential and Gompertz) were fitted to the available data on time to treatment discontinuation. Statistical goodness-of-fit of the parametric models was considered through the use of AIC and BIC statistics
- Company selected the loglogistic curve to model time on treatment as it fit data best statistically.

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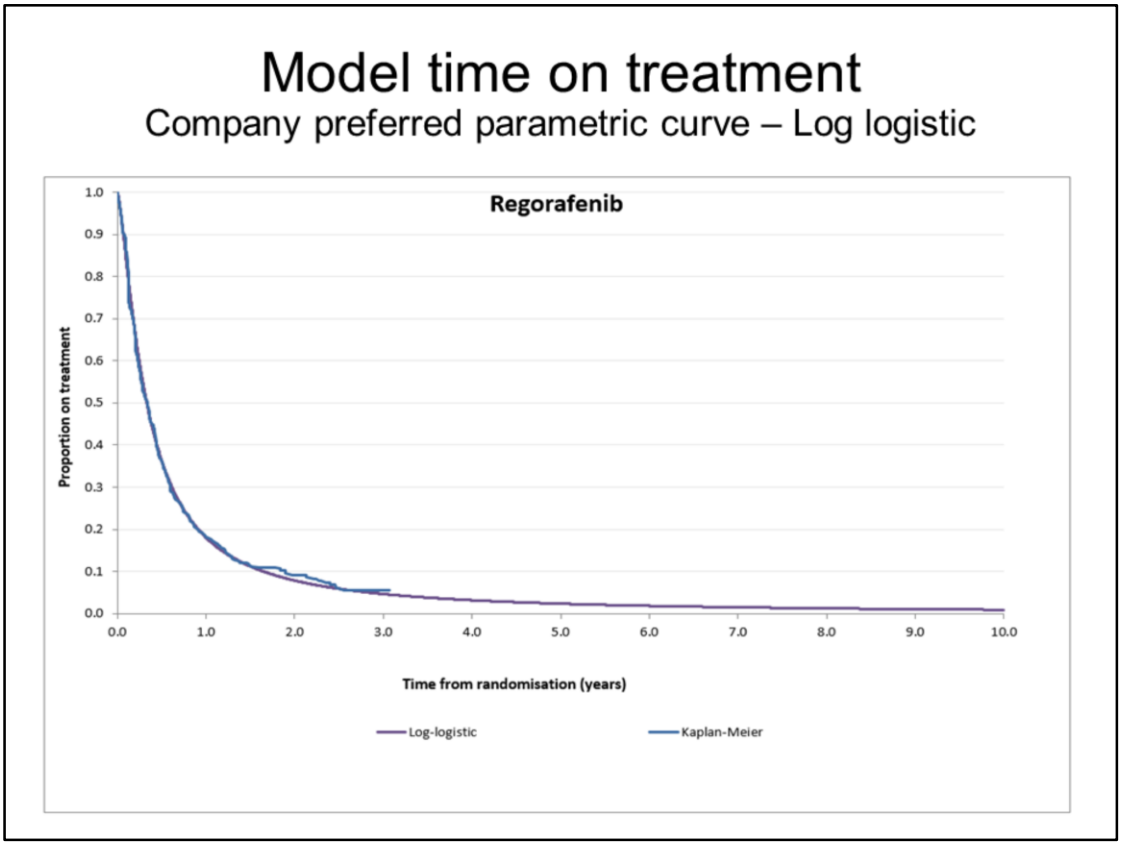
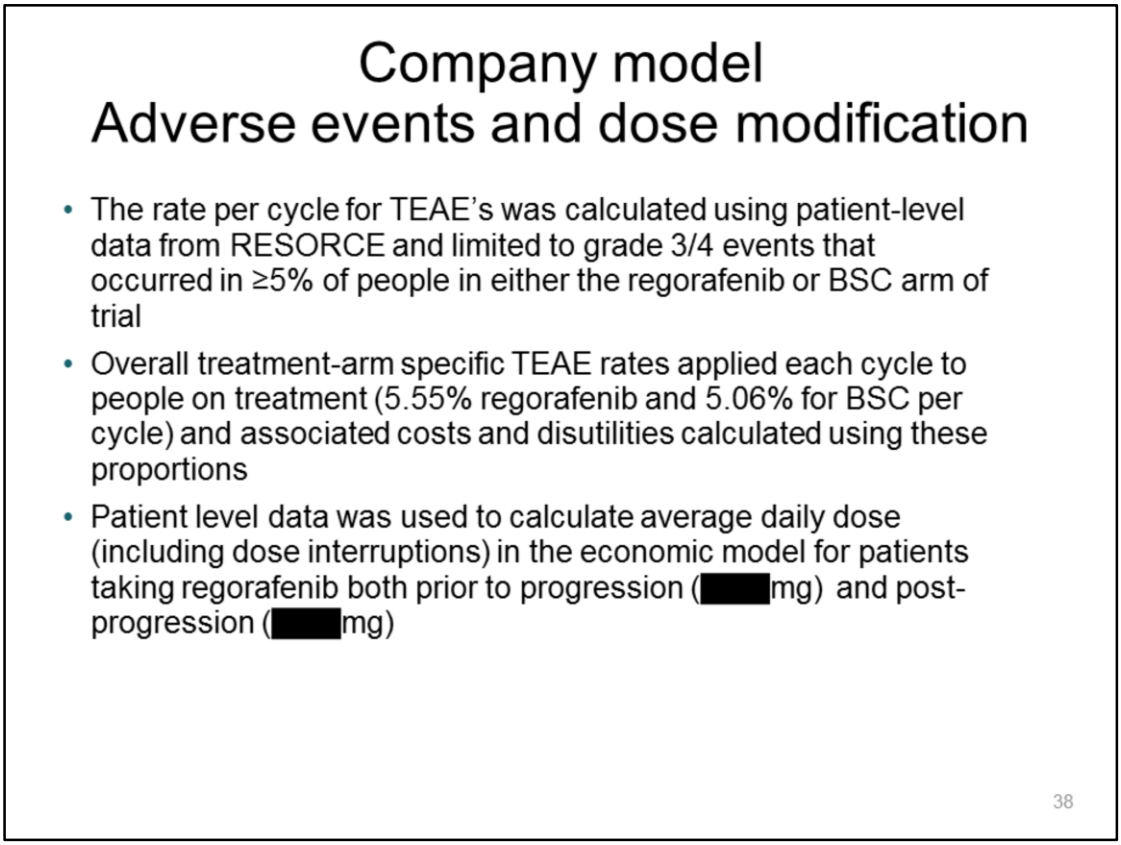


Source: Figure 6 (page 13 in company response to clarification question B1)



TEAEs included in the model are:
- Anaemia
- Ascites
- Aspartate aminotransferase increase
- Blood bilirubin increase
- Fatigue
- Hypertension
- Hypophosphatemia
- Palmar-plantar erythrodysaesthesia syndrome (Hand Foot Skin reaction – HFSR)

Company model
Quality of life data and utility values

- The company literature search for health related quality of life (HRQoL) data in HCC identified only one relevant published study: placebo-controlled SHARP trial of sorafenib for HCC. As the reported post-progression state utility was higher than the progression-free state, these were disregarded by the company
- Instead, utility values in the economic model were calculated from EQ-5D data collected during the RESORCE trial
- Mean EQ-5D utility at most of the assessment points was high (progression-free utility range = 0.76 to 1.0; post-progression utility range = 0.56 to 0.90)
- The following utility values included in the cost-effectiveness model:

Patient group	Utility estimates
Pre-progression, no TEAE	0.811 (based on average of all observations in this analysis in this patient group)
Post-progression, no TEAE	0.763
Pre-progression, TEAE	0.797 (TEAE-associated disutility = 0.014)
Post-progression, TEAE	0.749 (TEAE-associated disutility = 0.014)

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As EQ-5D questionnaire was completed for people receiving blinded treatment only, company noted that this could introduce a bias into post-progression utility values if people who continued treatment post-progression were less-ill compared to those who stopped treatment at progression. However, the questionnaire was completed at the end of treatment visits meaning that post-treatment utility was included.
Potential for bias was investigated by comparing health parameters at the point of progression for people who continue blinded treatment after progression, with people who stop their treatment at the point of progression. No significant differences were noted and results of the EQ-5D analyses were considered appropriate for use in the economic model.

Please see company submission pages (138-139 for more information)

Company model
Resource use and cost

- Company's model includes resource costs associated with: (i) drug acquisition for regorafenib; (ii) health state resource use, and (iii) the management of adverse events
- Health state resource use estimates based on a physician survey of three leading UK experts in HCC (conducted in 2015) carried out for sorafenib (TA474). Resource units previously used for sorafenib were assumed to be directly transferable to regorafenib because the burden of disease experienced by people on the two drugs is similar, they are from the same drug class and the economic model structure in appraisals for both drug are similar
- Unit costs associated with the majority of resource items included in model were taken from NHS Reference Costs 2015/2016. Other cost sources (such as response to Freedom of Information Act request and Personal Social Services Research Unit) also used

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Please see pages 60-61 of the ERG report for more information

Company base case

Updated deterministic base case with PAS (post-clarification model 2) included the following changes:

- Use of 23rd January 2017 data cut off
- PFS modelled using observed Kaplan-Meier curves
- OS modelled using dependent log normal functions using a revised treatment effect covariate
- Time to treatment discontinuation modelled using log logistic function
- Correction of minor errors *

Technologies	Total costs	Total QALYs	Incr costs	Incr QALYs	ICER (£/QALY)
Regorafenib	[redacted]	1.073	£14,625	0.406	**£36,050**
BSC	[redacted]	0.668	-	-	-

*Probabilistic results not provided by the company for the revised base-case

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*Correction to errors included correction of the costs of palliative care team visits, the number of cycles per year and the BSC adverse event rate programming error (see clarification response questions B16, B22 and B24)

Original company probabilistic base case ICER for regorafenib versus BSC is £33,335 per QALY gained (probabilistic ICER not provided for revised base case submitted after clarification). Regorafenib associated with 100% probability of being cost-effective at a willingness to pay (WTP) threshold of £50,000 per QALY and a 21% probability of being cost-effective at a WTP of £30,000.

A deterministic sensitivity analyses was carried out by the company for the original base-case reported as tornado plot is based on a willingness to pay of £50,000 per QALY. The ERG were unable to reproduce these results from the executable model provided. Deterministic sensitivity analyses were not presented for the updated base-case model provided after clarification.

ERG critique

Company analysis generally in line with NICE reference case

- The ERG focused their critique on the original model reported in the company submission
- Exploratory analyses undertaken by the ERG were based on post-clarification model 3 which included the 23rd January 2017 data-cut and independent survival models
- Company's economic evaluation was generally in line with NICE Reference Case.
- Main uncertainty relates to people included in the marketing authorisation for regorafenib who were excluded from the RESORCE trial.
- ERG identified anomalies in company modelled costs and incorporated alternative unit costs in ERG base-case analysis. Minor programming errors were also corrected (see pages 68-70 of ERG report)

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The marketing authorisation for regorafenib is broad including all adults with HCC who have been previously been treated with sorafenib (model population) whereas RESORCE excluded people who had discontinued sorafenib treatment on account of toxicity

ERG critique
Modelling of OS using dependent survival curves

- The ERG note that not all parametric distributions belong to the family of parametric proportional hazards models and make assumptions of proportional hazards (such as the lognormal and log-logistic). Additionally, validity of proportional hazards should be assessed in the extrapolation period as an assumption holding in the observed period does not necessarily mean that it will hold in the unobserved
- Independent models do not require a treatment effect covariate to be estimated and do not impose restrictive assumptions about proportional hazards/odds between competing treatment groups
- The ICER generated using log normal survival functions fitted independently to the OS data for each treatment group is similar to the ICER in the company's original base case.
- However, in the revised company base-case (post-clarification model 2), the company models OS using dependent log normal functions using a revised treatment effect covariate. The ERG note that it is unclear whether this is a revised HR (used incorrectly by company before clarification) or the dependent model treatment effect covariate

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ERG critique

Extrapolation of OS using lognormal function in company model

- ERG notes that no formal assessment of clinical plausibility of the extrapolated survival times was provided by company
- Discussion of clinical validity by the company relates only to differences between the observed and predicted OS estimates
- One clinical advisor to the ERG did not consider the log normal OS distribution in the company base case to be clinically plausible as the model-predicted sustained gap in OS between the regorafenib and BSC groups beyond 35-cycles produced by the log normal function was unrealistic within a progressed HCC population.
- The advisor's preferred curve was Weibull function, although it was noted that both the exponential and Gompertz functions were also potentially plausible. ERG's second clinical advisor did not state a preference.
- ERG's preferred model is the independent Weibull function based on clinical opinion on plausibility of the extrapolated curves, the goodness-of-fit to the observed data and also the empirical hazards provided by the company within the clarification period
- Alternative functions are explored in the ERG sensitivity analyses

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ERG critique

Modelling of time to treatment discontinuation to estimate regorafenib acquisition costs

- The ERG disagreed with the company approach of estimating time on treatment separately during the progression-free and post-progression phases in the original company base case and considered fitting a parametric curve to Kaplan-Meier time to treatment discontinuation (TTD) curves observed within RESORCE to be the most appropriate approach
- Company revised their updated base-case to include time on treatment modelled using the log-logistic parametric curve
- The ERG accepted TTD Kaplan-Meier curve which assumed that all people who were still receiving treatment at data cut off were censored
- It was noted by the ERG that the company incorrectly truncated the total treatment costs at 29 cycles, thereby ignoring additional costs incurred due to the tail of the curve. This was rectified in ERG exploratory analysis 7 and incorporated in the ERG preferred base case

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ERG critique

Cost savings due to dose reductions included in company model

- Company's model includes cost saving associated with dose reductions and treatment interruptions for regorafenib
- Both clinical advisors to ERG noted that current prescribing practices in the NHS do not account for reduced frequency of individual prescriptions for patients with leftover pills. Instead, any pills not taken by the patient would be essentially lost or destroyed. It was noted that the only exception would be if a patient developed toxicity in hospital where the remaining pills could be given to another patient. Cost reductions included in the company's model would therefore not be fully realised in clinical practice
- ERG costed regorafenib at its full maximum dose of 160mg per day for the entire duration of treatment within exploratory analyses. This inclusion of full treatment costs increases ICER for regorafenib versus BSC considerably
- 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
- A highly optimistic scenario in which dose reductions for all patients from the start of treatment is included in the ERGs sensitivity analyses

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Company response to factual accuracy check of ERG report

Average dose from RESORCE included as the base-case

- The company argue that the approach of assuming full dose for the entire duration of treatment is not representative of the management of high cost medicines or best practice and not representative of clinical practice in England
- During the sorafenib CDF reappraisal (TA474), Bayer sought to understand how avoiding medicines wastage for oral cancer medicines is managed in two of the largest tertiary centres in the UK and were advised that medicines supply is actively managed
- Evidence from pharmacists from two hospitals are provided supporting pack splitting to minimise wastage
- The company maintain that regorafenib (also an oral medicine) can reasonably be expected to be managed in the same way

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ERG critique
Expert elicitation survey to inform health state resource use

- The company use a survey conducted in 2015 to inform resource use
- The ERG note that the company does not reference an earlier survey conducted in 2007 using four UK clinicians, despite the NICE Cancer Drugs Fund (CDF) Appraisal Committee for sorafenib preferring the pooled analysis of both the 2007 and 2015 surveys
- Company reiterated preference for the 2015 survey at clarification as the estimates from 2007 precede the availability of sorafenib and are not based on clinical experience.
- TA474 sorafenib reappraisal
  - The committee preferred to pool the 2007 and 2015 surveys
- ERG also note a potential discrepancy in the survey in that it appears that patients requiring hospitalisation are assumed to have fewer than one hospital visit per month on average, which is not logical (see additional clarification response)
- The ERG prefer the pooled 2007 and 2015 surveys and the company sensitivity analysis in which the number of hospitalisation is set to 1

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Please see page 77-78 of ERG report for more information on the DSU response to the company on their preference for 2015 resource use survey in the sorafenib appraisal. Also refer to Table 36 in the ERG report (page 79) which compares assumed resource use and costs per 28-day treatment cycle for the pooled 2007 and 2015 survey with the 2015 survey alone

Please refer to Appendix I and additional clarification response received on the 1st of September which details the company's original assumptions and contains a replication of the company's response, which attempts to justify the data used in the company submission, 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

ERG critique
Costs included in the model and uncertainty in parameters

- Company model included overestimation of the cost of a general ward bed day. Unclear why current NHS Reference Costs were not used
- Other potentially inappropriate NHS Reference costs included in company model were identified and amended by ERG in exploratory analyses
- Company's probabilistic sensitivity analyses (PSA) included parameters that were held fixed such as time-to-event curves (OS and time to treatment discontinuation). PSA therefore underestimates the uncertainty surrounding the incremental costs and effects of regorafenib.
- ERG note this may be important as use of log normal distributions (as used to model OS) tend to increase probabilistic ICERs. Due to time constraints, ERG did not modify the company's uncertainty analysis.

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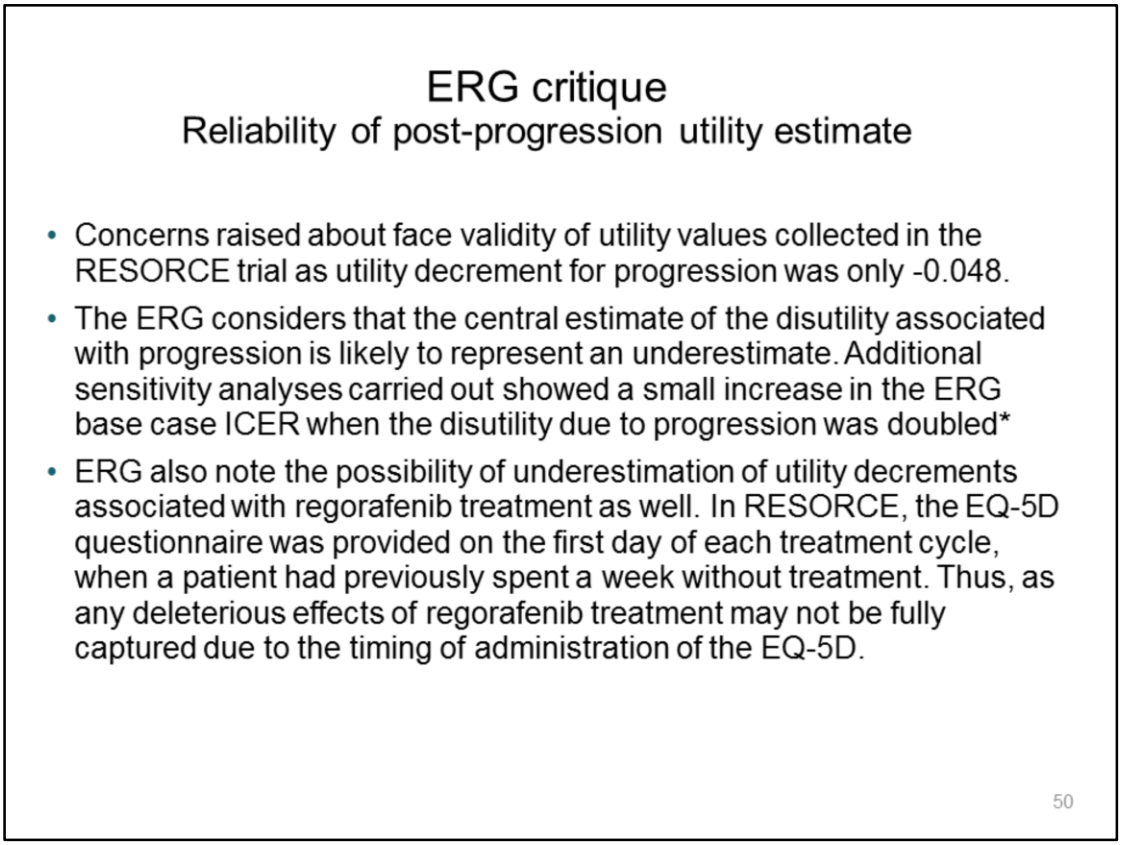

*As shown in Table 2 (page 57 of ERG report) , the EQ-5D response rate for patients in the pre-progression state was high (typically greater than 90%) and the ERG notes that the estimated pre-progression EQ-5D score of 0.811 appears high for a population with advanced HCC who have previously progressed on sorafenib.
The percentage of patients in the post-progression state completing the EQ-5D was much lower, typically between 20% and 30%, which raises the possibility that only the patients in the best health at that time point completed the EQ-5D questionnaire

ERG exploratory analyses

All exploratory and additional sensitivity analyses conducted by the ERG were based on post-clarification model 3. The analyses also include corrections of programming errors and unit cost corrections (exploratory analysis 1)

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
Company's base case (revised base case model, deterministic)					
Regorafenib	1.073	[redacted]	0.405	£14,625	**£36,050**
BSC	0.668	[redacted]	-	-	-
Exploratory analysis 1: Correction of unequivocal model errors and use of alternative unit costs					
Regorafenib	1.072	[redacted]	0.405	£13,637	**£33,703**
BSC	0.668	[redacted]	-	-	-
Exploratory analysis 2: Inclusion of more appropriate general ward bed day cost					
Regorafenib	1.072	[redacted]	0.405	£13,536	**£33,456**
BSC	0.668	[redacted]	-	-	-
Exploratory analysis 3: Use of full pack dosing					
Regorafenib	1.072	[redacted]	0.405	£16,594	**£41,012**
BSC	0.668	[redacted]	-	-	-

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Source: Table 2, page 3 of ERG addendum

Exploratory analyses 2-8 also include corrections and amendments made in exploratory analysis 1

ERG exploratory analyses (2)

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
Exploratory analysis 4: Removal of half-cycle correction for drug acquisition costs					
Regorafenib	1.072	[redacted]	0.405	£14,309	**£35,365**
BSC	0.668	[redacted]	-	-	-
Exploratory analysis 5: Use of combined 2007 and 2015 surveys and hospitalisations set to 1					
Regorafenib	1.072	[redacted]	0.405	£22,099	**£54,619**
BSC	0.668	[redacted]	-	-	-
Exploratory analysis 6: Use of independent Weibull functions to model OS					
Regorafenib	0.967	[redacted]	0.319	£11,553	**£36,241**
BSC	0.648	[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	1.072	[redacted]	0.405	£22,305	**£55,128**
BSC	0.668	[redacted]	-	-	-
Exploratory analysis 8: ERG's preferred base case (including all individual amendments)					
Regorafenib	0.967	[redacted]	0.319	£23,768	**£74,559**

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Source: Table 2, page 3 of ERG addendum

*Probabilistic analyses for ERG preferred base case not provided not provided by the ERG

Exploratory analyses 2-8 also include corrections and amendments made in exploratory analysis 1

ERG additional sensitivity analyses

Scenario	Inc. QALY	Inc. costs	ICER (regorafenib vs BSC)
ERG base case	0.319	£23,768	**£74,559**
Alternative OS functions			
OS – log normal	0.410	£28,851	**£70,409**
OS - exponential	0.348	£23,836	**£68,462**
OS – Gompertz	0.343	£23,296	**£67,835**
Alternative time to treatment discontinuation functions			
TTTD - exponential	0.319	£21,461	**£67,320**
TTTD – Weibull	0.319	£22,832	**£71,622**
TTTD – log normal	0.319	£23,977	**£75,214**
TTTD – Gompertz	0.319	£24,192	**£75,888**
Alternative utility values			
Utilities from SHARP trial	0.281	£23,768	**£84,597**
Disutility due to progression doubled (state utility=0.715)	0.311	£23,768	**£76,441**
Alternative interpretation of company's resource use survey			
Number of hospitalisations per month estimated per month assumed to apply to the entire population.	0.319	£24,481	**£76,793**
Inclusion of dose reductions			
Indefinite dose reduction to 120mg/day	[redacted]	[redacted]	[redacted] 53

Source: amended from Table 3, page 4 of ERG addendum – see this table for further OS functions and disutility values

ERG's additional sensitivity analyses indicate that alternative choices of parametric functions to model OS may reduce the ICER for regorafenib (ICER range = £67,835 to £70,551 per QALY gained) and alternative parametric functions to model time to treatment discontinuation leads to ICERs in the range £67,320 to £75,888 per QALY gained.

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.

CDF clinical lead comments (1)

- No biological reason why regorafenib would not be as efficacious in people intolerant of sorafenib, as long as both performance status and liver function remain satisfactory. NHS England would wish to extend access to patients intolerant of sorafenib provided all other relevant treatment criteria are met
- As time to treatment discontinuation is greater than PFS, it is important that the model uses the actual treatment times and not the PFS times
- Mature follow up data for sorafenib (plus other treatments) in specialist centres show 5 year survival figures of 5-8% (published in Liver Cancer 2017). 5 year survival of patients without further therapies after sorafenib is not zero, some patients have indolent disease
- Important to model the doses of medication that patients are given in practice rather than an average dose in an economic model. Patients are given whole month supplies of regorafenib and any unused drug cannot be re-used by other patients. Therefore, whole months of drug supply should be modelled.
- Utility values are high for people with progressed disease who have recently been treated with sorafenib (utility 0.81) even with performance status of 0 or 1 at entry. The utility of 0.76 also seems high for progression after 2nd line therapy

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CDF clinical lead comments (2)

- Generalisability issues will be mitigated by NHS England only commissioning regorafenib (subject to a NICE recommendation) to reflect the population of patients assessed by NICE in this appraisal
- Should NICE recommend regorafenib for the second line systemic therapy of HCC, NHS England would wish to commission regorafenib in patients and satisfying the following criteria:
  - histologically or cytologically confirmed diagnosis of hepatocellular carcinoma
  - metastatic disease or advanced local disease that is ineligible for or failed surgical or loco-regional therapies
  - previous systemic therapy for HCC with sorafenib, either treated to disease progression with sorafenib or intolerant of sorafenib despite appropriate dose reductions
  - Child-Pugh liver function class A
  - ECOG performance status of 0 or 1
  - regorafenib to be otherwise used in its SPC

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End of life

NICE End of life Criterion	Data available from cost-effectiveness analysis (company base case)	Data available from RESORCE
The treatment is indicated for patients with a short life-expectancy, *normally* less than 24 months	Mean OS predicted in the base-case of the cost-effectiveness analysis was 10.8 months for BSC	Median OS from RESORCE for the BSC arm was 7.8 months.
There is sufficient evidence to indicate that the treatment offers an extension to life, *normally* of at least an additional 3 months, compared with current NHS treatment	Regorafenib treatment was associated with a mean extension of life of 0.52 years (6.24 months)	Median OS extended by 2.8 months in the regorafenib arm from RESORCE

Changes made by the ERG relating to the choice of parametric OS functions do not change the conclusion with respect to the end of life criteria

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Innovation
Company's comments

- With its multi-kinase, inhibitory profile, regorafenib offers an additional treatment option for individuals with un-resectable HCC
- Best supportive care is currently the only treatment option available following disease progression with sorafenib

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Equality considerations

- No equality issues raised by professional groups
- Company noted that in response to the appraisal consultation document for the Cancer Drug's Fund rapid reconsideration topic for sorafenib, a consultee noted that the prevalence of liver cancer deaths is higher in socially deprived areas
- As issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal, this was not considered an equalities issue

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]

Document B

Company evidence submission

File name	Version	Contains confidential information	Date
Regorafenib_ID991_Redacted_AppendixB_11Jul17_Final	1.1	Yes	11 July 2017

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Abbreviations

AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
AFP	Alpha-fetoprotein
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
ANG2	Angiopoietin-2
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under Curve
BCLC	Barcelona Clinic Liver Cancer
BCRP	breast cancer resistant protein
BNF	British National Formulary
BP	Blood Pressure
BSC	Best Supportive Care
CDF	Cancer Drugs Fund
CI	Confidence interval
CMH	Cochrane Mantel Haenszel
CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CYP2C9	Cytochrome P450 2C9
DCR	Disease Control Rate
DNA	Deoxyribonucleic acid
DOR	Duration of Response
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organisation for the Research and Treatment of Cancer
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor receptor
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol five dimensions questionnaire
ESDO	European Society of Digestive Oncology
ESMO	European Society for Medical Oncology

EWB	Emotional Well-being
EU MAA	European Union Marketing Authorisation Application
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-Hep	Functional Assessment of Cancer Therapy - Hepatobiliary
FAS	Full Analysis Set
FWB	Functional well-being
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
GCP	Good Clinical Practice
GCSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GIST	Gastrointestinal stromal tumour
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCS	Hepatobiliary cancer subscale
HCV	Hepatitis C virus
HFSR	Hand-foot skin reaction
HGF	Hepatocyte Growth Factor
HIV	Human Immunodeficiency Virus
HPB	HepatoPancreatoBiliary
HR	Hazard ratio
HRQoL	Health-related quality of life
IACR	International Agency for Research on Cancer
INR	International Normalised Ratio
IPG	Interventional Procedure Guidance
IQR	Inter-quartile range
ITT	Intention to treat
IVRS	Interactive voice response system
KM	Kaplan Meier
LPLV	Las patient last visit
LSM	Least squares mean
MAPK	Mitogen-activated protein kinases
MCN	Managed Clinical Network
mCRC	Metastatic colorectal cancer
MDRD	Modified diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram(s)
MI	Myocardial Infarction
MID	Minimal Clinically Important Difference
mL	Millilitre(s)
mmHG	Millimetres of Mercury
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic Resonance Imaging

NCI	National Cancer Institute
Ng	Nanogram(s)
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NYHA	New York Heart Association
o.d.	*omne in die* (once a day)
ORR	Objective tumour response rate
OS	Overall Survival
PAS	Patient Access Scheme
PD	Progressive disease
PDGFR	Platelet-derived growth factor receptor
PEI	Percutaneous ethanol injection
PFS	Progression-free Survival
PK	Pharmacokinetics
p.o.	*per os* (by mouth)
PR	Partial response
PRO	Patient reported outcomes
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PWB	Physical Well-being
QD	*Quaque Die* (Every day)
RCT	Randomised Clinical Trial
RECIST	Response Evaluation Criteria in Solid Tumors
RET	Rearranged during Transfection
RFA	Radiofrequency ablation
ROW	Rest of World
SAE	Serious Adverse Event
SAF	Safety analysis set
S.D.	Standard deviation
SD	Stable disease
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	System Organ Class
SWB	Social / family well-being
TA	Technology Appraisal
TACE	Transarterial chemoembolisation
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TIE	Tyrosine kinase with immunoglobulin-like and EGF-like domains
TKI	tyrosine kinase inhibitor
TOI	Trial Outcome Index
TTP	Time to progression

UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analogue Scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The CHMP have issued a positive opinion for the following licence:

Regorafenib is indicated as monotherapy for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib

The population defined in the final scope is adults with previously treated unresectable hepatocellular carcinoma. There is no specification in the scope concerning defining previous treatment.

The submission is limited to patients with unresectable (i.e. advanced) hepatocellular carcinoma who have been previously treated with sorafenib.

- This is relevant to NHS clinical practice; it would not be used in a wider population.
- The evidence base for regorafenib is limited to this population.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with previously treated unresectable hepatocellular carcinoma	Adult patients with advanced hepatocellular carcinoma (HCC) who have been previously treated with sorafenib	The licence for regorafenib is restricted to patients who have been previously treated with sorafenib.
Intervention	Regorafenib	Regorafenib	N/A
Comparator(s)	Best supportive care	Best supportive care	N/A
Outcomes	Overall survival Progression free survival Response rates Adverse effects of treatment Health-related quality of life	Overall survival Progression free survival Response rates Adverse effects of treatment Health-related quality of life	N/A

B.1.2 Description of the technology being appraised

Table 2. Technology being appraised

UK approved name and brand name	Regorafenib (Stivarga®)
Mechanism of action	Regorafenib is a novel, oral, bi-aryl urea that potently inhibits multiple protein kinases involved in oncogenesis, tumour cell proliferation/survival and tumour vasculature (neo-angiogenesis), which have been shown to play important roles in hepatocellular carcinoma (HCC) (1-3). In preclinical studies, overexpression of activated mitogen activated protein kinase (MEK)-1 in HCC tumour cell lines enhanced tumor growth and conferred resistance to apoptosis (1). MAPK (mitogen-activated protein kinases) are among protein kinases potently blocked by regorafenib. Regorafenib also inhibits angiogenic kinase receptors, such as vascular endothelial growth factor receptor (VEGFR)-1, -2, -3, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR)-1 and 'tyrosine kinase with immunoglobulin-like and EGF-like domains 2' (TIE-2) receptor, which play a central role in angiogenesis (2). In vitro assays have also demonstrated inhibition of various oncogenic kinases such as RAF, 'rearranged during transfection' RET, RAF-1, BRAF, and $BRAF^{V600E}$ and c-KIT, thereby preventing the proliferation of cancer cells (2). A phase II study in patients with HCC that had progressed following sorafenib treatment, confirmed the antitumour activity of regorafenib found in preclinical studies (4).
Marketing authorisation/CE mark status	Application for the marketing authorisation for regorafenib in this indication was submitted to the European Medicines Agency (EMA) on 3rd October 2016. The marketing authorisation process for the United Kingdom (UK) is centralised through the EMA. Regorafenib has received positive CHMP opinion as a treatment for adult patients with hepatocellular carcinoma who have been previously treated with sorafenib. The marketing authorisation is expected in Jul/August 2017
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Indication: as monotherapy for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib Restrictions: not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as it has not been studied in this population. See Appendix C for (draft) SmPC. A European public assessment report (EPAR) is not available.
Method of administration	Oral administration. 160 mg (4 tablets of 40 mg) to be taken

and dosage	once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle. Dose modifications, which may be required based on individual safety and tolerability, are to be applied in 40 mg (one tablet) steps, with a lowest recommended daily dose of 80 mg and a maximum daily dose of 160 mg. Specific dose modifications and measures exist in case of hand-foot skin reaction (HFSR) / palmar-plantar erythrodysaesthesia syndrome (see Dose modification [starting page 34] and SmPC)
Additional tests or investigations	It is recommended to perform liver function tests (alanine transaminase [ALT], aspartate aminotransferase [AST] and bilirubin) before initiation of regorafenib treatment and to monitor closely (at least every two weeks) during the first 2 months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated. It is also recommended to monitor biochemical and metabolic parameters during regorafenib treatment and to institute appropriate replacement therapy per standard clinical practice if required. This monitoring would likely be carried out as part of the routine management of advanced HCC.
List price and average cost of a course of treatment	£3744.00 per treatment cycle. In the RESORCE trial the average number of packs received was [redacted]. The average cost per course of treatment in the trial was £[redacted] [3,744 x [redacted]].
Patient access scheme (if applicable)	A confidential simple patient access scheme is available. The pack price under this scheme is [redacted] ([redacted]) discount to the list price). Under this scheme the cost of a course of treatment (as received in the RESORCE study) would have been [redacted]. This represents an upper limit as Bayer anticipates less treatment would be received in clinical practice.

B.1.3 Health condition and position of the technology in the treatment pathway

Disease overview

Hepatocellular carcinoma is the most common type of primary liver cancer, accounting for more than 85% of primary liver cancer diagnoses worldwide and occurring mainly in developing regions (5). The prevalence of HCC has a strong geographical distribution, with highest incidence rates in East Asia, the Western Pacific Region and Africa (6). In the UK, HCC is the 17th most common cancer, whereas worldwide it is the sixth most frequently diagnosed cancer (7, 8). HCC affects more men than women and the incidence increases with age (8). Latest information (2014) on the incidence of liver cancer in the UK indicates that, unlike in other regions in the world, HCC accounts for 53% of primary liver cancer diagnoses (8-13). In 2014, liver cancer was the 9th most common cause of cancer death in the UK (compared with it being the 2nd most common cause of death from cancer worldwide, according to the International Agency for Research on Cancer (IARC) in 2012) (7, 8).

The primary risk factor for HCC is cirrhosis. Whilst cirrhosis can have many causes, it is most commonly due to Hepatitis B, Hepatitis C, fatty liver disease or alcohol. The incidence of HCC is rising in Western countries including the UK, probably as a direct result of the Hepatitis C virus epidemic and increased alcohol consumption (14-17).

HCC develops as small nodules, with most growth taking place in the asymptomatic phase. Estimated doubling times of HCC vary between one and 19 months (16). HCC is often diagnosed at a late stage of the disease when patients present with symptoms including fatigue, jaundice, pruritus, encephalopathy, weight loss, ascites, abdominal pain / distension and the presence of a mass. Disease symptoms combined with the poor prognosis and lack of treatment options in advanced disease are likely to have a significant psychological impact on patients, and their families. Social and work life is interrupted due to illness and healthcare appointments and quality of life will inevitably be affected.

Diagnosis is confirmed by blood tests (raised alpha-fetoprotein (AFP) levels), imaging (ultrasound, arteriography, computed tomography [CT] or Magnetic resonance imaging [MRI] scan), and liver biopsy. Often, due to diagnosis being in the latter stages of disease, treatment options are limited and patients typically have a short life-expectancy i.e. <12 months, 5-year survival <5% (14).

The choice of treatment for HCC depends on the location and stage of the cancer and its effect on liver function (see Classification of HCC – page 20). Treatment aims are to slow progression of the disease, improve quality of life and prolong survival. Surgical removal of the tumour, liver transplantation or radio-frequency ablation with the aim of providing a cure may be possible, though unfortunately, as there are often no specific symptoms, less than 30% of patients are diagnosed at the early stages where liver tumours are considered more amenable to curative resection or transplantation (14). Some patients at an intermediate stage of disease may be suitable for “loco-regional” treatments: ablation (radiofrequency ablation (RFA); percutaneous ethanol injection (PEI) or cryosurgery); (chemo) embolisation, and radiotherapy.

The European Clinical Practice Guidelines for HCC (European Society for Medical Oncology [ESMO]-European Society for Digestive Oncology [ESDO] guidelines (18)) document that without treatment, the median survival for stage C HCC is between 4 and 8 months. With treatment, e.g. sorafenib, the median survival for stage C HCC is between 6 and 11 months.

The lack of effective therapies highlights how difficult this disease is to treat and the dire situation that patients are in when they reach the later stages of liver cancer.

Regorafenib provides the opportunity to further extend life following sorafenib.

Classification of HCC

The Barcelona-Clinic Liver Cancer (BCLC) classification divides HCC patients into 5 stages (0, A, B, C and D) per pre-established prognostic variables. Prognosis is defined by variables related to tumour status (size, number, vascular invasion), liver function (Child–Pugh’s) and Eastern Cooperative Oncology Group (ECOG) health performance status and outlined in the joint European Association for Study of the

Liver / European Organisation for the Research and Treatment of Cancer (EASL-EORTC) guidelines in 2012 (14). The classification of HCC is shown in Figure 1 and outlined in Table 3.

Figure 1. Classification of HCC (from EASL-EORTC Clinical Practice Guidelines (14)

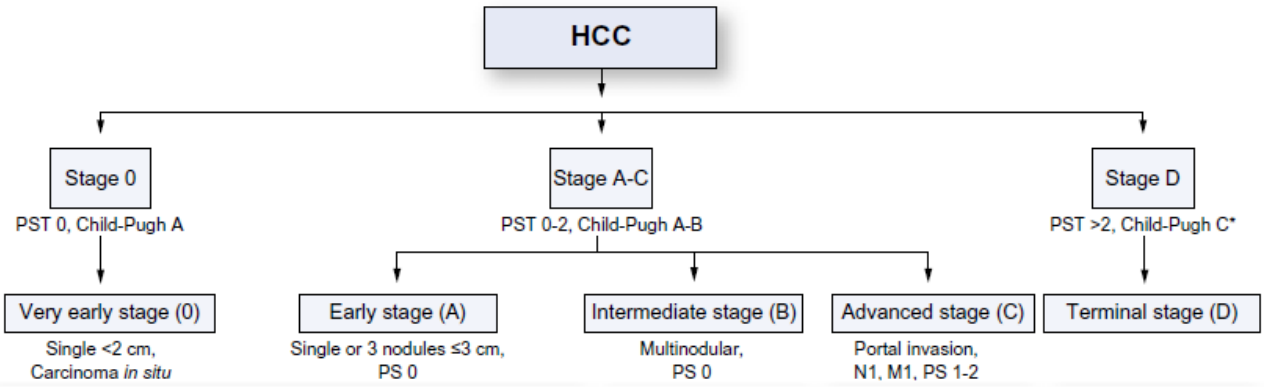


Table 3. Staging of HCC (using BCLC classification)

BCLC Stage	Tumour status	ECOG performance status	Liver Function (Child-Pugh)
0 (Very early HCC)	Single tumour < 2cm in diameter without vascular invasion / satellites	0	Well preserved liver function Child-Pugh A
A (Early HCC)	single tumours >2 cm or 3 nodules <3 cm of diameter	0	Child–Pugh A or B
B (Intermediate HCC)	multinodular asymptomatic tumours without an invasive pattern	0	Child-Pugh A-C
C (Advanced HCC)	symptomatic tumours; macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases)	1–2	Child-Pugh A-C
D (End stage HCC)	Tumours leading to a very poor performance Status which reflects a severe tumour-related disability	3-4	Child-Pugh C

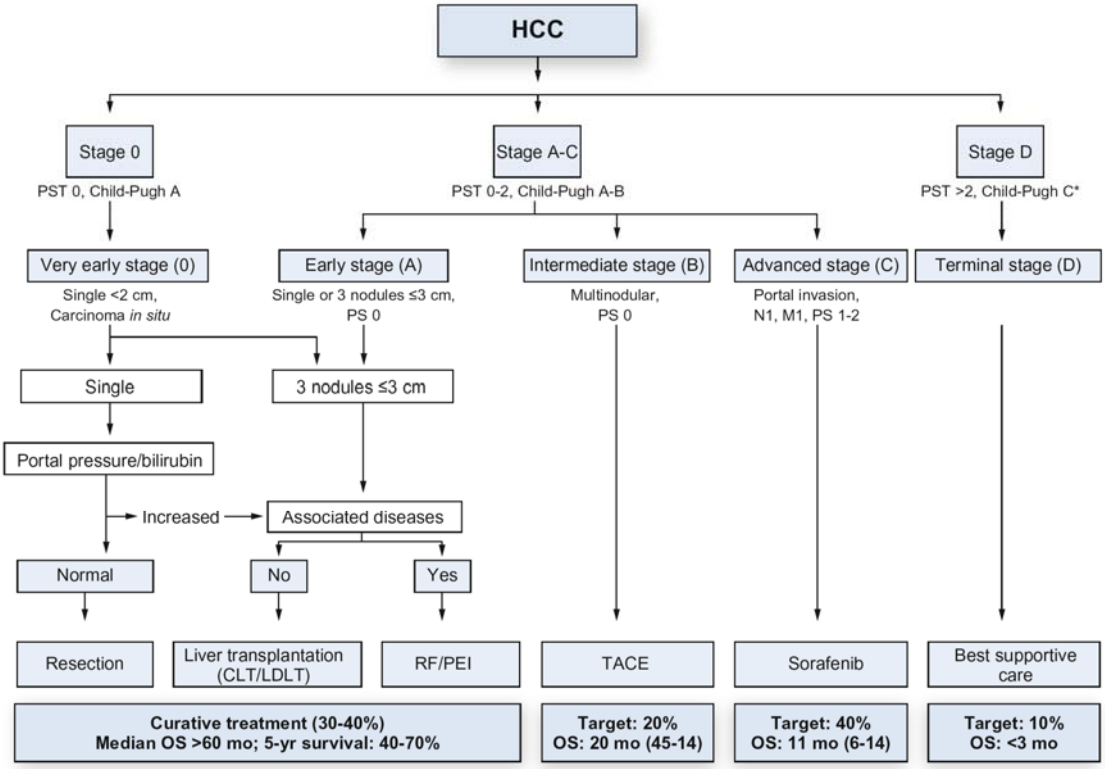
Adapted from EASL-EORTC Clinical Practice Guidelines (14)

Current management pathway

There are several international clinical guidelines for the management of HCC (see Table 4). Most guidelines are based on the BCLC staging system.

Figure 2 shows the treatment strategy as recommended by the EASL / EORTC (14). These are typical of other guidelines. UK guidelines exist but are several years old and have been largely superseded by the development of the EASL-EORTC guidelines. UK clinical practice follows the European (EASL-EORTC) guidelines for the treatment of advanced HCC.

Figure 2. Updated BCLC staging system and treatment strategy (EASL EORTC guidelines)



CLT=cadaveric liver transplant; DLT=domino liver transplant; HCC=Hepatocellular cancer; mo=months; OS=overall survival; PEI=percutaneous ethanol injection; PST=performance status; RF=radio-frequency ablation; TACE=trans-arterial chemoembolisation

As stated previously, the choice of therapy is determined by disease stage, and severity of the underlying cirrhosis. Due to HCC often being diagnosed at intermediate / advanced stages, curative strategies such as surgical resection of the tumour or liver transplantation are only suitable for < 30% of patients (14). Some patients may be candidates for “loco-regional” treatments: ablation (radiofrequency

ablation (RFA); percutaneous ethanol injection (PEI) or cryosurgery); (chemo) embolisation, and radiotherapy.

Since patients with HCC typically present with more advanced disease, there are limited treatment options and the prognosis is poor, with 5-year survival rates of <5%. In patients where surgical or loco-regional treatments have failed or are unsuitable, systemic therapy is the only active treatment option, for which sorafenib is considered the standard of care. Sorafenib is currently under review as part of the Cancer Drugs Fund (CDF) reappraisal.

In line with treatment guidelines (Figure 1), following sorafenib clinicians use a best supportive/palliative care approach. Best supportive care covers a wide range of treatment options intended to maximise quality of life without a specific antineoplastic regimen. Examples of BSC includes herbs, acupuncture, vitamins and mineral supplements, antibiotics, bisphosphonates for bone metastases, chronic erythropoietin, analgesics, radiation therapy for pain control (limited to bone metastases), nutritional support, corticosteroids, transfusions, psychotherapy, and palliative surgery.

Thus, if sorafenib is not available as a treatment option, or HCC has progressed on sorafenib therapy, patients are in a dire situation with no current active treatment option. This submission provides evidence for the use of regorafenib in this difficult to treat patient group. Regorafenib provides an opportunity to further extend lives following sorafenib relapse. A summary of UK and international guidelines is presented in Table 4.

Table 4. Summary of UK and International guidelines in liver cancer

Guideline	Date	Reference
NICE Technology Appraisals		
CDF reappraisal of sorafenib	Under review	
Sorafenib for the treatment of advanced hepatocellular carcinoma (TA189) - *Sorafenib is not recommended for the treatment of advanced hepatocellular carcinoma in patients for whom surgical or locoregional therapies have failed or are not suitable.* Note – sorafenib is currently undergoing further review by NICE in HCC as part of the CDF rapid reconsideration process.	May 2010	NICE TA189
NICE Interventional procedure guidance (IPG) relevant to liver cancer		
IPG488 Chemo saturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer.	May 2014	
IPG460 Selective internal radiation therapy for primary hepatocellular carcinoma.	July 2013	
IPG444 Irreversible electroporation for treating primary liver cancer.	February 2013	
IPG298 Ex-vivo hepatic resection and reimplantation for liver cancer.	April 2009	
IPG214 Microwave ablation of hepatocellular carcinoma.	March 2007	
IPG211 Radiofrequency-assisted liver resection.	February 2007	
IPG135 Laparoscopic liver resection.	July 2005	
IPG2 Radiofrequency ablation of hepatocellular carcinoma.	July 2003	
Related NICE Pathways		
NICE Pathway: Liver cancers http://pathways.nice.org.uk/pathways/liver-cancers	Last updated April 2016	
Other UK Health Technology Appraisal recommendations - Scottish Medicines Consortium		
Sorafenib (Nexavar®) (482/08): *'…sorafenib is accepted for restricted use within NHS Scotland for the treatment of patients with advanced hepatocellular carcinoma who have failed or are unsuitable for surgical or loco-regional therapies. The advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of sorafenib and is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.'*	11th January 2016	
Other UK guidelines		
Scottish HepatoPancreatoBiliary (HPB) Managed Clinical Network (MCN) Guideline for the management of hepatocellular carcinoma (HCC)	June 2010	(19)
UK guidelines for the management of suspected hepatocellular carcinoma (HCC) in adults - commissioned by the British Society of	2003	(16)

Gastroenterology. Published prior to sorafenib or regorafenib becoming available.		
European and US guidelines		
EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma - *Sorafenib is recommended as the standard systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A-B class) and with advanced tumours – BCLC C – or those tumours progressing on loco-regional therapies.*	2012	(14)
European Society for Medical Oncology. Hepatocellular Carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up - *Sorafenib is the standard systemic therapy for patients with advanced HCC and well-preserved liver function (BCLC stage C) and those with intermediate-stage HCC who progress following TACE. In case of progression or intolerance to sorafenib, best supportive care is preferred or patients be included in clinical trials.*	2012	(18)
American Association for the Study of Liver Diseases (AASLD). Management of hepatocellular carcinoma: An Update - *Sorafenib is now considered first-line treatment in patients with HCC who can no longer be treated with potentially more effective therapies.*	2010	(20)

B.1.4 Equality considerations

As noted in the second appraisal committee document for sorafenib (CDF rapid reconsideration) the prevalence of liver cancer deaths is higher in socially deprived areas.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised. A single RCT forms the evidence base for the use of regorafenib in HCC i.e. the RESORCE study. This study is outlined in Table 5.

B.2.2 List of relevant clinical effectiveness evidence

Table 5. Clinical effectiveness evidence

Study	RESORCE				
Study design	Randomised, double-blind, placebo-controlled, phase III				
Population	Advanced HCC patients who had been previously treated with sorafenib				
Intervention(s)	Regorafenib (+best supportive care [BSC]) 160mg o.d. for weeks 1-3 of each four-week cycle N=379				
Comparator(s)	Placebo (+ BSC) N=194				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	This trial provides the only RCT data on the clinical effectiveness of regorafenib in advanced HCC.				
Reported outcomes specified in the decision problem (outcomes included in the model are 'bolded')	**Overall Survival** **Progression-free survival** **Response rates** **Adverse effects of treatment** **Health-related quality of life (FACT-Hep; EQ-5D)**				
All other reported outcomes	Time to progression Disease Control Rate Duration of Response Duration of stable disease Overall survival from the start of prior sorafenib therapy				

BSC=best supportive care; EQ-5D=EuroQol-5 Dimensions questionnaire; FACT-Hep=Functional assessment of cancer therapy-hepatobiliary cancer questionnaire

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

RESORCE: A randomised, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib (Study 15982) (21, 22)

The RESORCE study met its primary endpoint in February 2016 and results were published in The Lancet in January 2017 (21). Some aspects of the study have not been fully published and some data included in this submission is drawn from the Clinical Study Report (CSR) (22) and a poster (23) presented at ESMO (October 2016) .

[redacted]NB. All patients in both arms also received best supportive care (BSC) – in the text the 'regorafenib + BSC' arm is generally written as 'regorafenib' and the 'placebo + BSC' is generally written as 'placebo'.

Trial design and methodology (21, 22)

RESORCE was an international, phase 3, multicentre, randomised, double-blind, placebo-controlled trial.

Settings and locations where the data were collected:

The study took place within the secondary care setting across 152 study centres in 21 countries from:

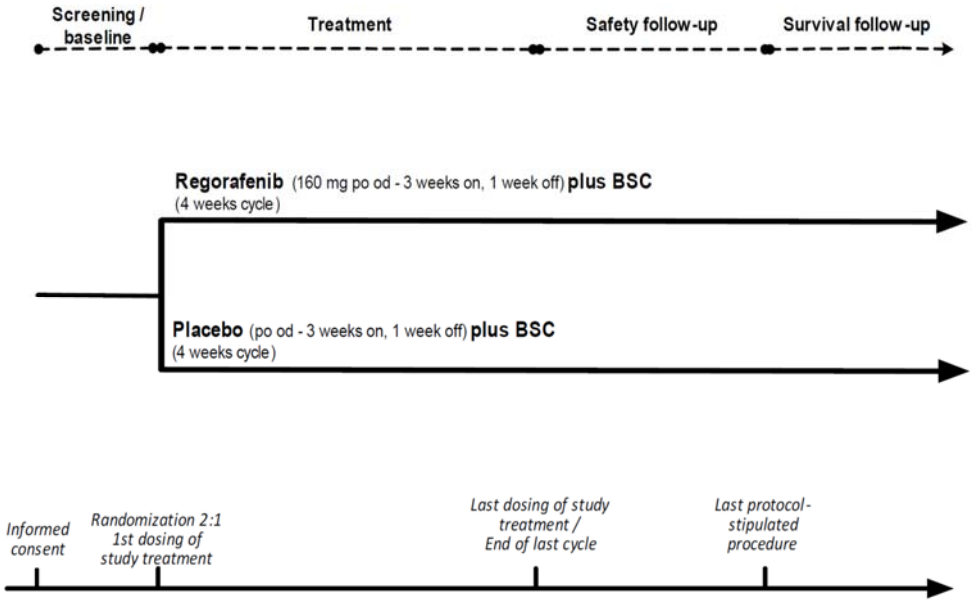
- Europe (Austria, Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Spain, Switzerland, United Kingdom (UK)),
  Russian Federation
- North America (United States (US)),
- South America (Argentina, Brazil)
- Australia and Asia (China, Japan, Singapore, South Korea, Taiwan).

There were 5 clinical trial centres in the UK that enrolled patients – 4 of these centres had a total of 20 patients randomised to treatment. Study enrolment started in May 2013 and was completed in December 2015 during which time a total of 843 patients were screened (see Figure 3). Of these, 573 patients were randomised on a 2:1 basis to receive regorafenib (n=379) or matching placebo (n=194).

Patients continued masked study treatment until disease progression, clinical progression, death, unacceptable toxicity, substantial non-compliance with the protocol or withdrawal of patient from the study (by physician or patient). Patients receiving blinded treatment who experienced disease progression and for whom, in the investigator's opinion, study treatment was providing clinical benefit, were offered the opportunity to continue their treatment. Upon discontinuation of study treatments, all patients entered a follow-up period and, where consent remained, all were followed monthly for survival, until death was documented.

After the primary endpoint of the study was reached (overall survival [OS]; 29th February 2016) and the results supported a positive benefit / risk assessment for regorafenib, patients on placebo at that time were offered the opportunity of receiving regorafenib through open-label treatment and patients randomised to regorafenib could continue open-label regorafenib. Data presented in this submission relates to the double-blind period only.

Figure 3. RESORCE study design



BSC=best supportive care; mg=milligrams; o.d.=once daily;

Method of randomisation

Eligible patients were randomly assigned to regorafenib or matching placebo on a 2:1 basis using a computer-generated randomisation list via an interactive voice response system (IVRS). Each patient was given a unique randomisation code which linked them to a treatment arm and specified the treatment assigned. Randomisation was stratified by geographical region (Asia vs. rest of the world), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1), alpha-fetoprotein (AFP) levels (<400ng/mL vs. ≥400ng/mL), extrahepatic disease (presence vs. absence), and macrovascular invasion (presence vs. absence).

Masking

Patients, investigators, and the study sponsor were masked to treatment assignment using the unique drug pack numbers assigned to the patient via IVRS and preprinted onto each bottle.

Regorafenib and placebo were identical in appearance to preserve blinding and patients assigned to the placebo arm followed the same dosing instructions as those receiving regorafenib.

Investigators were blinded to study treatment for assessment of whether a death was considered related to study drug.

Unblinding was only to be carried out in an emergency, and not routinely on the occurrence of a serious adverse event (SAE).

Eligibility criteria (21):

Table 6. RESORCE inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years old • Histologically or cytologically confirmed HCC or non-invasive diagnosis of HCC as per American Association for the Study of Liver Diseases (AASLD) criteria in patients with a confirmed diagnosis of cirrhosis. • Barcelona Clinic Liver Cancer (BCLC) stage Category B or C that could not benefit from treatments of established efficacy with higher priority such as resection, local ablation, chemoembolisation, or systemic sorafenib. • Failure to prior treatment with sorafenib (defined as documented radiological progression per the radiology charter). Randomisation had to be performed within 10 weeks after the last treatment with sorafenib. • Tolerability of prior treatment with sorafenib defined as not less than 20 days at a minimum daily dose of 400 mg QD (every day) within the last 28 days prior to withdrawal. • ECOG PS of 0 or 1 • Child-Pugh status A • Local or loco-regional therapy of intrahepatic tumour lesions (e.g. surgery, radiation therapy, hepatic arterial embolisation, chemoembolisation, radiofrequency ablation, percutaneous ethanol injection, or cryoablation) must have been completed ≥4 weeks before first dose of study medication. Note: patients who received sole intrahepatic intraarterial chemotherapy, without lipiodol or embolising agents were not eligible. • Life expectancy ≥ 3 months • Written consent • At least one uni-dimensional measurable lesion by computed tomography (CT) scan or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and mRECIST for	• Prior liver transplantation or candidates for liver transplantation. • Prior treatment with regorafenib. • Prior and/or concomitant treatment within a clinical study other than with sorafenib during or within 4 weeks of randomisation. • Sorafenib treatment within 2 weeks of randomisation. • Patients with large oesophageal varices at risk of bleeding that were not being treated with conventional medical intervention: beta blockers or endoscopic treatment. • Prior systemic treatment for HCC, except sorafenib. • Permanent discontinuation of prior sorafenib therapy due to sorafenib related toxicity. • Permanent discontinuation of prior sorafenib therapy due to any cause more than 10 weeks prior to randomisation. • Previous or concurrent cancer distinct from HCC *except* cervical carcinoma in situ, uteri, and/or non-melanoma skin cancer and treated basal cell carcinoma, superficial bladder tumours (Ta, Tis & T1) or any cancer curatively treated > 3 years prior to entry into the study. • Known history or symptomatic metastatic brain or meningeal tumours. • Major surgical procedure or significant traumatic injury within 28 days before randomisation. • Cardiac disease (congestive heart failure > New York Heart Association (NYHA) class 2, cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin). • Unstable angina (angina symptoms at rest, new-onset angina) or myocardial infarction (MI) within the past 6 months prior to randomisation. • Uncontrolled hypertension (systolic blood pressure [BP] >150 mmHg or diastolic pressure >90 mmHg despite optimal medical management). • Phaeochromocytoma.

HCC. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, may have been considered measurable if there had been demonstrated progression in the lesion. • Adequate bone marrow, liver and renal function as defined by: haemoglobin >8.5 g/dL; Absolute neutrophil count (ANC) ≥ 1500/mm^3; platelet count ≥ 60,000/mm^3; total bilirubin ≤ 2 mg/dL. Mildly elevated total bilirubin (<6 mg/dL) was allowed if Gilbert's syndrome was documented; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5 X upper limit of normal (ULN); prothrombin time-international normalised ratio (PT-INR) < 2.3 X ULN and partial prothrombin time (PTT) <1.5 X ULN; serum creatinine ≤ 1.5 X ULN; lipase ≤ 2 X ULN; glomerular filtration rate (GFR) ≥30 mL/min/1.73 m^2 per the Modified diet in renal disease (MDRD) study equation. • Women of childbearing potential and men must have agreed to use adequate contraception until at least 2 months for men and for women after the last study drug administration.	• Uncontrolled ascites (defined as not easily controlled with diuretic or paracentesis treatment). • Pleural effusion or ascites that caused respiratory compromise (National Cancer Institute [NCI]-common terminology criteria for adverse events [CTCAE] Grade ≥2 dyspnoea). • Persistent proteinuria of NCI-CTCAE Grade 3 or higher. Urine dipstick result of 3+ was allowed if protein excretion was < 3.5 g/24 hours. • Ongoing infection > Grade 2 per NCI-CTCAE grading. Hepatitis B was allowed if no active replication was present. Hepatitis C was allowed if no antiviral treatment was required; known history of human immunodeficiency virus (HIV) infection; • Clinically significant bleeding NCI-CTCAE Grade 3 or higher within 30 days before randomisation. • Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischaemic attacks), deep vein thrombosis or pulmonary embolism within 6 months before the start of study medication. • Unresolved toxicity higher than NCI-CTCAE Grade 1 (excluding alopecia or anaemia) attributed to any prior therapy/procedure. • Any illness or medical condition that was unstable or could have jeopardised the safety of the patient and his/her compliance in the study. • Seizure disorder requiring medication • History of organ allograft; substance abuse, medical, psychological or social conditions that may have interfered with the patient's participation or evaluation of study results; • Inability to swallow oral medications; • Pregnancy or breast-feeding • Non-healing wound, ulcer, or bone fracture. • Renal failure requiring haemo- or peritoneal dialysis. • Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation. • Interstitial lung disease with ongoing signs and symptoms at the time of screening. • Any malabsorption condition. • Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person of the investigational site that would have had access to study records and electronic case report form [eCRF] data).

Interventions

Patients were randomised to receive:

- oral regorafenib 160 mg (4 x 40mg tablets orally [p.o.], once daily) plus BSC
- Matching placebo plus BSC

daily for the first 3 weeks of each 4-week cycle. Study treatment was taken in the morning with approximately 240 mL of water, after a low-fat (< 30% fat) breakfast.

Patients continued masked study treatment until disease progression, death, unacceptable toxicity, substantial non-compliance with the protocol or withdrawal of patient from the study (by physician or patient).

Regorafenib 40mg tablets (and matching placebo) were supplied as coated, immediate-release, non-divisible, grey-orange-red, oval tablets.

Best supportive care included any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumour agents or antineoplastic chemo / hormonal / immunotherapy.

After the primary endpoint of the study was reached and the study results supported a positive benefit / risk assessment for regorafenib in the trial, those patients who were currently on placebo at that time were offered the opportunity to receive regorafenib through open-label treatment on this study.

Dose modification

Study drug could be delayed or reduced as per a pre-specified schedule (Table 7); in the case of transaminase elevation (Table 8), unacceptable toxic effects (Table 9), hand-foot skin reaction (HFSR)(Table 10) and hypertension (Table 11). Toxicities were graded using the NCI CTCAE version 4.03, except for hand foot skin reaction (HFSR) (CTCAE term palmar plantar erythrodysaesthesia syndrome) which was graded per the descriptions in Table 10. Up to two regorafenib dose-reductions due to toxicity were allowed (from 160 mg to 120 mg to 80 mg).

Transaminases were closely monitored during the study with laboratory monitoring and weekly checks of AST, ALT and bilirubin during the first 2 cycles of regorafenib dosing required. After 2 cycles of treatment, AST, ALT and bilirubin monitoring was required on days 1 and 15 of the first 6 cycles.

Blood pressure was to be monitored weekly for the first 6 weeks of study treatment.

Table 7. Regorafenib dose levels (22)

Dose level	Dose	Administration
Dose level 0 (standard dose)	160mg p.o. o.d.	4 tablets of regorafenib, 40mg/tablet, or 4 matching placebo tablets
Dose level -1	120mg p.o. o.d.	3 tablets of regorafenib, 40mg/tablet, or 3 matching placebo tablets
Dose level -2	80mg p.o. o.d.	2 tablets of regorafenib, 40mg/tablet, or 2 matching placebo tablets

p.o. = per oral; o.d. = daily

Table 8. Dose modifications / interruption for ALT and/or AST increases related to study drug (21)

NCI-CTCAE v 4.03	1st occurrence	2nd occurrence	3rd occurrence
≤ Grade 2	Treat on time and check AST, ALT and bilirubin weekly for at least 4 weeks.		
Grade 3	Interrupt treatment. Check AST, ALT, bilirubin until ≤ G2 or baseline. Reduce 1 dose level and check AST, ALT, bilirubin weekly for at least 4 weeks. [a]	Interrupt treatment. Check AST, ALT, bilirubin until ≤ G2 or baseline. Reduce 1 further dose level and check AST, ALT, bilirubin weekly for at least 4 weeks. [a]	Discontinue b
Grade 3 with ALT or AST >8 x ULN and a concomitant rise in bilirubin (of any degree) compared to previous bilirubin values	As above. In case of negative risk-benefit assessment, consider permanent discontinuation at the first occurrence [b,c].	Discontinue [b]	
≥ Grade 4	Discontinue [b]		

ALT=alanine aminotransferase; AST=aspartate aminotransferase; G=Grade; NCI CTCAE = National Cancer Institute Common Toxicity Criteria; ULN=upper limit of normal
a: If all values remain stable for 2 full cycles, dose re-escalation may be considered at the discretion of the investigator. After re-escalation AST, ALT, bilirubin should be checked weekly for at least 4 weeks.
b: In case of discontinuation, check AST, ALT, bilirubin weekly until recovery to baseline or stabilisation.
c: Patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the above outlined recommendations for the respective observed elevation of ALT and/or AST.

Table 9. Dose modification / delay for toxicities related to study drug (except hand-foot skin reaction and hypertension)[a] (21)

NCI-CTCAE v4.03	Dose Interruption	Dose Modification	Dose for Subsequent Cycles
Grade 0-2	Treat on time	No change	No change
Grade 3[b]	Delay until < grade 2[b]	Reduce 1 dose level	If toxicity remains <grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (≥ grade 3) recurs, institute permanent dose reduction
Grade 4	Delay until < grade 2[b]	Reduce by 1 dose level. Permanent discontinuation can be considered at treating investigator's discretion.	

[a] excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and asymptomatic laboratory abnormalities

[b] If no recovery after a 4-week delay, treatment will be permanently discontinued

Table 10. Dose Modifications and Toxicity Grading for Hand-Foot Skin Reaction (per CTCAE v 4.03 "Palmar-plantar erythrodysaesthesia syndrome") (21)

Skin Toxicity Grade	Occurrence	Suggested Dose Modification[b]
Grade 1[a]: Numbness, dysaesthesia, paraesthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort which affects the patient's normal activities	1st occurrence	Consider decreasing dose by one dose level and immediately institute supportive measures. If there is no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to grade 1[a].
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to grade 1[a]. When resume treatment, treat at reduced dose level.
	3rd occurrence	Interrupt therapy until toxicity resolves to grade 1[a]. When resume treatment, decrease dose by one additional dose level[b] (2 dose levels total)
	4th occurrence	Discontinue therapy.
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st occurrence	Institute support measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to grade 1[a]. When resume treatment, decrease dose by one dose level.
	2nd occurrence	Institute support measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to grade 1[a]. When resume treatment, decrease dose by one additional dose level[b] (2 dose levels total).
	3rd occurrence	Discontinue treatment permanently.

[a] If toxicity returns to grade 1 after dose reduction, dose-escalation was permitted at the investigator's discretion
[b] The lowest recommended dose was 80mg. Patients requiring > 2 dose reductions were to discontinue protocol therapy

Table 11. Management of treatment-emergent hypertension (21)

Event Grade (NCI-CTCAE v4.03)	Definition	Anti-hypertensive therapy	Study drug dosing
Grade 1	Prehypertension (systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg)	None	Continue regorafenib. Consider increased blood pressure (BP) monitoring.
Grade 2	Systolic BP 140-159 mmHg or diastolic BP 90-99 mmHg OR Symptomatic increase by >20 mmHg (diastolic) if previously within normal limits	Treat with the aim to achieve diastolic BP ≤ 90 mmHg: - If BP previously within normal limits, start antihypertensive monotherapy. - If patient already on antihypertensive medication, titrate up the dose.	Continue regorafenib If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤ 90 mm Hg [a]. When regorafenib is restarted, continue at the same dose level.
Grade 3	Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 90 mmHg: - Start antihypertensive Medication AND/OR - Increase current antihypertensive medication AND/OR - Add additional antihypertensive medications.	Hold regorafenib until diastolic BP is ≤90 mmHg, and if symptomatic, until symptoms resolve[a]. When regorafenib is restarted, continue at the same dose level. If BP is not controlled with the addition of new or more intensive therapy reduce 1 dose level[b]. If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level [c]
Grade 4	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis		Discontinue therapy

Abbreviations: BP = blood pressure; NCI-CTCAE=National Cancer Institute-common terminology criteria for adverse events.

[a] Patients requiring a delay of study treatment > 4 weeks should go off regorafenib.

[b] If BP remains controlled for at least one full cycle, dose re-escalation is permitted at the investigator's discretion.

[c] Subjects requiring > 2 dose level reductions (< 80 mg reduction) should go off regorafenib therapy.

Treatment compliance

Designated study personnel were responsible for dispensing the study drug to patients. Patients were evaluated every cycle for treatment compliance by counting tablets dispensed and returned.

During the double-blind period, patients who were assigned to receive regorafenib had a median treatment duration of 3.6 months (IQR 1.6-7.6) (vs. patients assigned to placebo: median 1.9 months (IQR 1.4-3.9).

The median daily dose during the double-blind treatment period was 159.3 mg (regorafenib-treated patients) and 160 mg (placebo patients). The mean daily dose of regorafenib was 144·1 mg (standard deviation [S.D.] 21·3) and of placebo was 157·4 mg (10·3). Excluding treatment delays or interruptions, almost half of the regorafenib group (184 [49%] of 374]) received the full protocol dose (160 mg/day) with no reductions.

Permitted and disallowed concomitant medications

All medication necessary for the patient's welfare, and not expected to interfere with the evaluation of the study drug, could be given at the discretion of the investigator. These included standard therapies for concurrent medical conditions, prophylactic anti-emetics, nucleoside/nucleotide analogues for Hepatitis B virus (HBV), megestrol acetate as supportive care, bisphosphonates and denosumab, and treatment with non-conventional therapies (e.g. herbs or acupuncture) and vitamin/mineral supplements.

Best supportive care included:

- antibiotics,
- analgesics,
- radiation therapy for pain control (limited to bone metastases),
- corticosteroids,
- transfusions,

- psychotherapy,
- growth factors,
- palliative surgery,
- or any other symptomatic therapy necessary to provide BSC,

Enrolled patients could not receive St. John's Wort, tyrosine kinase inhibitors (TKIs), any other drugs that targeted angiogenesis, especially vascular endothelial growth factor (VEGF) and vascular endothelial growth receptor (VEGFR), antiviral treatment for Hepatitis C virus, bone marrow transplant or stem cell rescue, or systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors, investigational anti-tumour agents or anti-neoplastic chemo / hormonal / immunotherapy, and experimental or approved therapies during the trial or within 30 days before starting to receive study medication, except prior therapy with sorafenib as detailed in the protocol.

Prior and concomitant palliative radiation therapy was allowed if the target lesion(s) were not included within the radiation field and no more than 25% of the bone marrow was irradiated.

Patients were also excluded if they had received biological response modifiers, such as granulocyte colony stimulating factor (G-CSF), within 3 weeks of study entry. G-CSF and other hematopoietic growth factors could be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator; however, they could not be substituted for a required dose reduction. Patients taking chronic erythropoietin were permitted.

Patients taking narrow therapeutic index medications (e.g., warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, and cyclosporine) were monitored proactively. Warfarin is metabolised by the cytochrome P450 (CYP) enzyme CYP2C9 and its levels may be especially affected by regorafenib.

Patients taking warfarin, heparin or similar could participate if no prior evidence of underlying abnormality in coagulation parameters existed. Weekly evaluations were

performed until INR and PTT were stable based on a pre-dose measurement as defined by the local standard of care.

As clinical data indicates no effect of regorafenib on digoxin pharmacokinetics, regorafenib may have been given concomitantly with p-glycoprotein substrates, such as digoxin, without a clinically meaningful drug interaction.

The glucuronosyl transferases UGT1A1 and 1A9 were to be avoided, where possible. Likewise, since there was a possibility of increased regorafenib toxicity, chronic co-administration of CYP3A4 inhibitors (e.g. clarithromycin, grapefruit juice, itraconazole, and ketoconazole) with regorafenib should be avoided; and as there was a possibility of decreased regorafenib efficacy upon chronic co-administration of CYP3A4 inducers with regorafenib (e.g. rifampin), chronic co-administration of CYP3A4 inducers with regorafenib was also to be avoided where possible.

The administration of regorafenib (160 mg for 14 days) prior to administration of a single dose of rosuvastatin (5 mg), a breast cancer resistant protein (BCRP) substrate, resulted in a 3.9-fold increase in mean exposure (AUC) of rosuvastatin and a 4.6-fold increase in maximum observed plasma concentration. This indicated that co-administration of regorafenib could increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, fluvastatin, atorvastatin). Therefore, it was recommended to monitor patients closely for signs and symptoms of increased exposure to BCRP substrates.

Concurrent diagnostic and therapeutic procedures

Fifty-nine regorafenib patients (15.6%) and 27 placebo patients (13.9%) underwent diagnostic procedures during the study including, including excision CT scan (n=34), gastroscopy (n=15), and x-ray (n=10).

Concurrent therapeutic procedures (regorafenib: 4.7%; placebo: 4.1%) included paracentesis, radio-frequency ablation, surgery, thoracentesis, and transcatheter arterial embolisation.

Table 12. Concurrent diagnostic and therapeutic procedures (Full analysis set [FAS])

Concurrent anti-cancer	Any procedure	Regorafenib N=379 n (%)	Placebo N=194 n (%)
Any concurrent therapeutic procedure	No	361 (95.3%)	186 (95.9%)
	Yes	18 (4.7%)	8 (4.1%)
Any concurrent diagnostic procedure	No	320 (84.4%)	167 (86.1%)
	Yes	59 (15.6%)	27 (13.9%)

Follow-up diagnostic and therapeutic procedures

During the follow-up period, after the end of the study, 49 patients (8.6%) underwent therapeutic procedures, and 57 patients (9.9%) underwent diagnostic procedures. The most frequent procedures included:

- paracentesis and TACE (therapeutic) and
- CT scan, x-ray, ultrasound and MRI (diagnostic).

In addition, 130 patients used antineoplastic agents (Regorafenib: 20.1%; placebo: 27.8%).

A higher proportion of placebo patients than regorafenib patients underwent therapeutic or diagnostic procedures or received anti-neoplastic drugs during the follow-up period, which may suggest a better control of symptoms in the regorafenib-treated patients.

Table 13. Follow-up diagnostic and therapeutic procedures (FAS)

Follow-up anti-cancer	Regorafenib N=379 n (%)	Placebo N=194 n (%)
Any follow-up therapeutic procedure	22 (5.8%)	27 (13.9%)
Any follow-up diagnostic procedure	35 (9.2%)	22 (11.3%)

Efficacy outcome measures used in the economic model or specified in the scope (21, 22, 24)

Table 14 summarises the relevant RESORCE study endpoints, including details of when / how each were measured. All endpoints described were pre-specified in the

analyses. The primary efficacy outcome measure was overall survival (OS). The efficacy variables (TTP, PFS, ORR and DCR) were evaluated using both mRECIST and RECIST 1.1 criteria. In the main body of this submission mRECIST results are presented. Standard RECIST results are presented in Appendix M.

The HCC-specific mRECIST (25) differs from RECIST 1.1 (26) in that it includes amendments developed for the SHARP trial (27) that require cytopathological confirmation of malignancy to classify pleural effusion or ascites as progression, and that apply more stringent criteria to define progression due to lymph node involvement at the hepatic hilum or new intrahepatic sites (28). It also considers complete tumour necrosis on dynamic imaging studies. Full details of the mRECIST and RECIST criteria used in the RESORCE protocol can be found in Appendix L.

All efficacy and safety parameters assessed in RESORCE, and the methods to measure them are commonly accepted standard variables and methods in clinical studies for HCC. In addition, all evaluations were in accordance with Good Clinical Practice (GCP) to ensure safety of patients participating in research.

Table 14. Relevant endpoints and measures in the RESORCE study

Endpoint	Definition & timing of assessment / measure
Primary Endpoints	
Overall Survival (OS)	Measured from the date of randomisation until the date of death due to any cause. After the last dose of study medication and the 'end of treatment' visit, all patients entered a follow-up period during which information on survival status was collected.
Secondary Endpoints	
Time to Progression (TTP)	Defined as the time (days) from randomisation to radiological or clinical disease progression. Disease progression was based on RECIST 1.1 criteria and the mRECIST criteria for HCC regarding the definition of Progressive Disease (25). Radiological tumor assessment (CT / MRI scans of chest, abdomen and pelvis) using the RECIST Version 1.1 and modified RECIST criteria for HCC was performed at screening, every 6 weeks during treatment for the first 8 cycles, and every 12 weeks thereafter.
Progression-free survival (PFS)	Time (days) from date of randomisation to date of disease progression (radiological or clinical) or death due to any cause, if death occurs before progression is documented.
Objective tumour response rate (ORR)	Tumour response and disease progression were evaluated based on RECIST 1.1 criteria and the mRECIST criteria for HCC regarding the definition of Progressive Disease (25). Radiological tumor assessment (CT / MRI scans of chest, abdomen and pelvis) using the RECIST Version 1.1 and modified RECIST criteria for HCC was performed at screening, every 6 weeks during treatment for the first 8 cycles, and every 12 weeks thereafter. Objective tumour response rate (ORR) was defined as the rate of patients with complete response (CR) or partial response (PR) over all randomised patients. Patients prematurely discontinuing the study without an assessment were considered non-responders for the analysis.
Disease Control Rate (DCR)	The rate of subjects, whose best response was not progressive disease compared to all treated subjects (i.e. complete response, partial response or stable disease). In order to be counted as a responder in DCR stable disease had to be maintained for at least 6 weeks.
Tertiary endpoints	
Duration of response	For CR or PR - Measured from the date of first documented response (CR or PR) to date of disease progression or death (if death occurred before disease progression). Evaluated using both mRECIST and RECIST 1.1 criteria (25).
Duration of stable disease	The time (days) from randomisation to date that disease progression or death (if death occurred before progression) was first documented. Only calculated for patients who failed to achieve a best response of CR or PR. Evaluated using both mRECIST and RECIST 1.1 criteria (25).
Exploratory endpoint	
Overall survival measured from the	Measured from the beginning of prior sorafenib treatment until the date of death due to any cause.

Endpoint	Definition & timing of assessment / measure
start of prior sorafenib therapy	
Health Related Quality of Life (HRQoL): **FACT-Hep (version 4)**	The FACT-Hep and EQ-5D were both self-administrated by the patient before seeing the physician at baseline, day 1 of each cycle, and at end-of-treatment visit. FACT-Hep is a disease-specific module of the FACT questionnaire, used extensively in oncology clinical trials. The FACT-Hep is a 45-item questionnaire developed to measure the quality of life HRQoL in patients with hepatobiliary cancers, including metastatic colorectal cancer, HCC, pancreatic cancer, and cancers of the gallbladder and bile duct (29, 30). FACT-Hep consists of five subscales: (1) physical well-being (PWB); (2) social/family well-being (SWB); (3) emotional well-being (EWB); (4) functional well-being (FWB); and the hepatobiliary cancer subscale (HCS). The HCS includes 18 items that assess specific symptoms of hepatobiliary carcinoma and side-effects of its treatment. Aggregate scores can also be formed. The PWB, FWB, SWB and EWB are summed to form the FACT-General (FACT-G) total score. The FACT-G and HCS score are summed to form the FACT-Hep total score (FACT-Hep = FACT-G + HCS) (range 0 to 180). The Trial Outcome Index (TOI) consists of the summation of the PWB, FWB and HCS subscales. The TOI has been demonstrated to be a sensitive indicator of clinical outcome in other disease types. All FACT items are rated on 5-point scales ranging from 0 = not at all to 4 = very much. Higher scores on all scales of the FACT-Hep reflect better quality of life or fewer symptoms. The MID for the respective scores are: (FACT-G) subscales = 2–3; FACT-G total score = 6–7; HCS = 5–6; FACT-Hep total score = 8–9; TOI = 7–8.
EuroQol – 5 Dimension (EQ-5D)	The EQ-5D is a generic quality of life preference based instrument which has been validated in cancer populations to measure both utility and health status. The EQ-5D contains a descriptive system measuring 5 health dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension contains 3 levels of response: no problem (level 1), some problems (level 2), and extreme problems (level 3). The five health dimensions are summarised into the EQ-5D index score (ranges -0.59 to 1 with higher scores representing better health states). The EQ-5D also contains a visual analog scale (EQ-visual analog scale [VAS]), which records the respondent's self-rated health status on a vertical graduated visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). On average, it took less than 5 minutes to complete the questionnaire.

Endpoint	Definition & timing of assessment / measure
OTHER ENDPOINTS	
Safety	Adverse event (AE) assessment occurred at every visit until 30 days after last study treatment (excluding survival assessment). AEs were classified by seriousness, intensity and causal relationship. Adverse events were classified using NCI-CTCAE version 4.03 guidelines Laboratory, haematology, biochemistry, urinalysis, and PT/PT-INR/PTT measures were assessed at screening, on day 1 and day 15 of every treatment cycle and at the end of treatment visit. Alfa fetoprotein (AFP) was not assessed on day 15 visits. Liver function (ALT, AST, and bilirubin) & blood pressure was monitored every week in cycles 1 and 2. Physical and Vital signs (Body weight/height, temperature, blood pressure (BP), and heart rate) examination occurred at every visit. ECG – measured at screening, day 1 of each cycle and then at 'end of treatment' visit. Adverse event = *any untoward medical occurrence in a patient after providing written informed consent for participation in the study.* Serious adverse event = *an adverse event that results in death, is life threatening, or requires hospitalisation or prolongation of existing hospitalisation, results in a persistent or significant disability or incapacity, or a congenital anomaly or birth defect, or is determined by the investigator to be a medically important event.*

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ECG=Electrocardiogram; PT=prothrombin time; INR=international normalised ratio; PTT=partial thromboplastin time

Exploratory endpoints included follow-up, maximum percentage reduction in the size of target lesions and maximum percentage change from baseline in the size of target lesions, per RECIST 1.1 and mRECIST criteria.

Pre-planned subgroups

The following subgroups were analysed for OS, PFS, TTP and safety parameters:

- Age: < 65 years, ≥ 65 years
- Sex: male, female
- geographical region: Asia vs. rest of world (non-Asia)

- baseline ECOG performance status: 0, 1
- Baseline AFP (< 400 ng/mL, ≥ 400 ng/mL),
- Baseline Child-Pugh status (A5, A6),
- Baseline extrahepatic disease (presence, absence),
- Baseline macrovascular invasion (presence, absence)
- Aetiology (Hepatitis B, Hepatitis C, alcohol use)

Patient Baseline characteristics (21-23)

Demographics and baseline characteristics of patients were well-matched between treatment groups. Of the 573 patients randomised and valid for inclusion in the FAS / ITT population, 504 (88%) were male (n=333 [87.9%] regorafenib; n=171 [88.1%] placebo). Mean age was approximately 61 years, with approximately 60% of patients under the age of 65 years.

Forty percent of patients in both treatment groups were 'Asian', while approximately 36% of patients were 'White'. Some participating countries do not require/allow reporting of race for demographic purposes, hence race was not reported in at least 20% of patients. The treatment groups were also well balanced with respect to geographic region with approximately 38% of patients from Asia and approximately 62% from the 'Rest of the World'.

Most patients had an ECOG performance status of 0 (regorafenib=65%; placebo=67%) and BCLC stage C disease (regorafenib=85.8%; placebo=88.7%).

The median time since initial diagnosis of HCC to start of study treatment was lower in the placebo group with 20 months compared with 21 months in the regorafenib group. The median time since progression on sorafenib until start of study treatment was identical (1.4 months) for both treatment groups. In general, the treatment groups were well-balanced with respect to the characteristics related to progression on sorafenib. The contribution to the aetiology of HCC of hepatitis B or C was similar in both treatment groups with 37.6% vs 37.7% for hepatitis B and 21.1% vs 20.6%

for hepatitis C in the placebo and regorafenib groups, respectively. Alcohol use was reported as an aetiology for 28.4% in the placebo group and 23.8% in the regorafenib group.

Over 96% of the patients in both treatment groups had a Child-Pugh score of A (5 or 6 points). When patients were assessed per mRECIST criteria, a similar percentage in both treatment groups (regorafenib=46%; placebo=45%) had 2 target lesions at baseline. This was similar when patients were assessed per RECIST 1.1 criteria (regorafenib=45.1%; placebo=42.8%). Over half of study patients had 1 or 2 non-target lesions at baseline per mRECIST criteria (regorafenib=57%; placebo=56%); with similar results per RECIST 1.1 criteria (approximately 58% patients in both groups).

Table 15. RESORCE Baseline demographic and disease characteristics (FAS)

	Regorafenib N=379 (100%)	**Placebo N=194 (100%)**
Age (yr) (mean ± S.D.)	61.8 ±12.4	61.1±11.6
Median age (range)	64 (54-71)	62 (55-68)
< 65 years	199 (52.5)	116 (59.8)
≥ 65 years	180 (47.5)	78 (40.2)
Sex – no. (%)		
Male	333 (87.9)	171 (88.1)
Female	46 (12.1)	23 (11.9)
Race		
White	138 (36.4)	68 (35.1)
Black	6 (1.6)	2 (1.0)
Asian	156 (41.2)	78 (40.2)
White / Black	2 (0.5)	1 (0.5)
Not reported	77 (20.3)	45 (23.2)
Region – no. (%)		
Asia	143 (37.7)	73 (37.6)
Rest of World	236 (62.3)	121 (62.4)
Cause of disease (Aetiology)* – no. (%)		
Hepatitis C	78 (20.6)	41 (21.1)
Alcohol use	90 (23.8)	55 (28.4)
Hepatitis B	143 (37.7)	73 (37.6)
Genetic / metabolic	16 (4.2)	6 (3.1)
Non-Alcoholic steatohepatitis	25 (6.6)	13 (6.7)
Unknown	66 (17.4)	32 (16.5)
Other	12 (3.2)	4 (2.1)
ECOG performance status – no. (%)		
0	247 (65)	130 (67)
1	132 (35)	64 (33)
BCLC stage - no. (%)		

	Regorafenib N=379 (100%)	Placebo N=194 (100%)
A (early)	1 (0.3)	0
B (intermediate)	53 (14.0)	22 (11.3)
C (advanced)	325 (85.8)	172 (88.7)
Macroscopic vascular invasion – no. (%)		
Yes	110 (29.0)	54 (27.8)
No	269 (71.0)	140 (72.2)
Extrahepatic disease – no. (%)		
Yes	265 (69.9)	147 (75.8)
No	114 (30.1)	47 (24.2)
Macroscopic vascular invasion and/or extrahepatic disease – no. (%)	304 (80)	162 (84)
Child-Pugh class – no (%)		
A	373 (98.4)	188 (96.9)
B†	5 (1.3)	6 (3.1)
Child-Pugh score – no (%)		
5	244 (64.4)	118 (60.8)
6	129 (34.0)	70 (36.1)
7†	5 (1.3)	5(2.6)
8	0	1 (0.5)
Alpha-fetoprotein(AFP) (ng/ml)		
Mean (± S.D.)	13507.9 (±49056.8)	12621.7 (±38472.3)
median (range)	183.2 (1.0-477591.0)	234 (1.0-310229.1)
<400 ng/mL	217 (57.3)	107 (55.2)
≥400 ng/mL	162 (42.7)	87 (44.9)
Previous therapy – no. (%)		
Local anti-cancer therapy	256 (67.9)	133 (68.6)
Including use of drug given locally	224 (59.1)	115 (59.3)
Radiotherapy	48 (12.7)	37 (19.1)
Systemic anticancer therapy	379 (100)	194 (100)

S.D.=standard deviation

* Patients may have had more than one aetiology of HCC

† The information in this table is based on the last observations on or before the first study drug intake. Changes may have occurred between the screening of patients and their first day of study drug intake. During the study, it was found that 3 patients were on anticoagulant medication which, per the study protocol, led to Child-Pugh classification of B.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence (21, 22, 24)

Analysis sets

The primary population for efficacy analysis was the Full Analysis Set (FAS), which was an intention-to-treat (ITT) population. The population for safety analysis consisted of all patients who received at least one dose of study medication.

Table 16. Definition of all data analysis sets in RESORCE

Analysis set	Definition	Number of valid patients in treatment group	
		Regorafenib	Placebo
Full analysis set (FAS) [intention-to-treat (ITT)]	All randomised patients.	N=379 (100%)	N=194 (100%)
Safety analysis set (SAF)	All randomised patients who received at least one dose of study medication.	N=374* (98.7%)	N=193* (99.5%)

*Five patients in the regorafenib group and one patient in the placebo group were not treated with study drug

Overview of statistical analyses (21, 22, 24)

Table 17. Summary of statistical analyses in RESORCE

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
RESORCE	The null hypothesis was that there was no difference in OS between treatment arms, which is equivalent to a hazard ratio of 1. The alternative hypothesis was that the hazard ratio of regorafenib over placebo is below 1.	**Primary efficacy analysis (conducted on the FAS):** Primary efficacy variable: OS (planned when approximately 370 deaths occurred). The groups were compared using a stratified log-rank test. A Kaplan-Meier (KM) plot displaying the OS curves of the two treatment groups was plotted and HR of regorafenib over placebo and its 95% confidence interval (CI) generated from the Cox model (using one-sided overall alpha of 0.025). **Secondary & tertiary efficacy analyses:** For analyses of time to progression and progression-free survival, groups were compared using a one-sided log-rank test with an alpha of 0.025 stratified by the same factors used in the OS analysis. TTP and PFS results were displayed using both RECIST version 1.1 and modified RECIST. KM plots were presented for each treatment group and the HR (regorafenib over placebo) and its 95% CI generated with the Cox model as for OS. Response rates and disease control rates in the two groups were compared using the Cochran–Mantel–Haenszel test, with adjustment for the stratification factors. Estimates and 95% CI were computed for each treatment group. The differences of ORR between the regorafenib and	The sample size was based on the primary efficacy endpoint (OS). The targeted improvement was a 43% increase in median OS compared to placebo (i.e. assuming a median OS under placebo of 8 months, the median OS under regorafenib was expected to be at least 11.4 months). The associated hazard ratio of regorafenib over placebo was 0.7. Approximately 370 events were required assuming a one-sided α = 0.025, a targeted improvement in median survival of 43%, a power of 90%, and a randomisation ratio of 2:1 between regorafenib and placebo. Approximately 560 patients were planned to be randomised to conduct the study in a reasonable time frame.	**Handling of missing data:** Missing or unevaluable tumour assessments were not used in the calculation of derived efficacy variables related to tumour assessments unless a new lesion occurred or the lesions that were evaluated already showed progressive disease. No imputation was performed for missing lesion assessments and tumour response evaluation e.g. if a patient missed a scan visit and progressive disease (PD) was documented at the next available scan visit, the actual visit date of the first documented PD was used to calculate PFS and TTP. If a date was incomplete, (e.g. only the year and month of the tumour assessment or if the date of death was available), then day 15 of the month was used for the calculation of, for example, OS and PFS. If the actual scan date of the radiological progression was missing and radiological or clinical progression had been documented based on the criteria specified in the protocol, the scheduled scan date was used to calculate the time to progression.

		placebo group and the corresponding 95% CIs were also calculated. Summary statistics were displayed for all best response categories: CR, PR, SD, PD by radiographic imaging, and PD by clinical judgment, including frequency counts and percentages with exact 95% CI. Analysis of DOR was descriptive only (summarised for both RECIST version 1.1 and modified RECIST), with KM estimates and curves displayed for each treatment group. The duration of stable disease was analysed similarly. For HRQoL assessments, an analysis-of-covariance (ANCOVA) model was used to compare the time-adjusted area under the curve (AUC) between groups with covariates for baseline scores and stratification factors. The least-squares mean (LSM) with 95% CI was estimated for each treatment group and for the difference between groups. Descriptive statistics on observed data were presented for the FACT-Hep questionnaire and for the EQ-5D index score (utility value) and visual analog scale score (VAS) at each assessment time and for change from baseline by treatment group. Safety was analysed descriptively. Sensitivity analyses included: -Stratification data collected on the CRF (vs. those collected via IVRS).		OS of patients not known to have died were censored at their last date of being known to be alive or at the database cutoff date, whichever came first. For patients lost to follow-up and without contact after randomisation, the OS was censored at Day 1. TTP and PFS for patients without radiological or clinical tumour progression (or death [PFS only]) at the time of analysis were censored at their last date of tumour evaluation. If a patient has no post-baseline tumour assessment available, i.e. the overall best response assessment is missing, the patient is considered not assessable and not included into numerator, but included into denominator for calculation of objective tumour response rate, disease control rate, and overall best response rates (CR, PR, SD and PD). The same rules as for the analyses of PFS, TTP were applied for censoring, for both duration of stable disease and DOR. Missing Patient Reported Outcomes (PRO) data - subscale scores were prorated. **Handling of dropouts:** Patients withdrawn from study treatment were not replaced.

Interim analyses

An interim efficacy analysis was not performed.

See Appendix D for 'Participant flow in the RESORCE study'.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Table 18 presents a quality assessment of the RESORCE study. RESORCE was completed to the highest standard with adequate randomisation and blinding procedures. Please see in Appendix D for a detailed quality assessment.

Table 18. Quality assessment results for RESORCE

Trial number (acronym)	RESORCE study
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes / Yes / Yes

In England it is anticipated that regorafenib will be used as per its marketing authorisation. Patients will be monitored closely for progression and for any adverse events due to treatment with dose modifications used as necessary. In addition, patients are expected to receive other best supportive care measures as necessary to alleviate symptoms. The RESORCE study is closely aligned to anticipated clinical practice in England. The generalisability of the RESORCE study to England is discussed from page 85.

B.2.6 Clinical effectiveness results of the relevant trials

The primary completion date for RESORCE was 29th February 2016. This submission presents the study results from the clinical database released on 5th August 2016.

Tumour response and disease progression were evaluated based on RECIST 1.1 and mRECIST criteria. Results per mRECIST (the more contemporary criteria) are presented in this section, while, for completeness, matching RECIST results are available in Appendix M. According to the EASL-EORTC guidelines 2012) (14) the assessment of response in HCC should be based on the mRECIST criteria.

Summary of efficacy results

Results from RESORCE, an international, multicentre, randomised, double-blind, placebo-controlled phase III study, demonstrate regorafenib to be an effective treatment in extending survival and delaying further disease progression in patients with hepatocellular carcinoma who have been previously treated with sorafenib.

The study met its primary efficacy objective: The addition of regorafenib to BSC resulted in a significantly better OS as compared to placebo plus BSC with a hazard ratio of 0.627 [95% CI 0.500, 0.785], p=0.000020 stratified log rank test, and a median OS of 10.6 months (95% CI 9.1, 12.1) vs. 7.8 months (95% CI 6.3, 8.8).

Median overall survival was 10.6 months [95%CI 9.1,12.1] in patients randomised to regorafenib compared with 7.8 months [95% CI 6.3, 8.8] in patients randomised to placebo.

PFS was significantly better in patients receiving regorafenib than in patients receiving placebo with a hazard ratio of 0.455 [95% CI 0.371, 0.558], p<0.000001 stratified log rank test, and a median PFS of 3.1 months vs. 1.5 months.

TTP was significantly better in patients receiving regorafenib than in patients receiving placebo with a hazard ratio of 0.442 [95% CI 0.358, 0.545], p<0.000001 stratified log rank test, and a median TTP of 3.2 months vs. 1.5 months.

OS, PFS and TTP advantages were consistent across all subsets analysed.

The response rate (complete response or partial response) was 10.6% for regorafenib and 4.1% for placebo treated patients (p=0.004728). The DCR (complete response, partial response and stable disease maintained for 6 weeks) was significantly higher in patients treated with regorafenib (65.2% vs. 36.1%, p<0.000001). Given that late stage HCC is a difficult cancer to treat, with very few treatments having any beneficial impact on the disease and patient survival, a higher response rate - including 2 reports of complete responses - plus a doubling of the disease control rate is a significant therapeutic achievement. In approximately half (49%; 184/379) of patients receiving regorafenib, there was evidence of tumour shrinkage (vs. 23%; 44/194 placebo patients). Tumour shrinkage and / or disease stabilisation, is likely to translate into clinical benefit, which was confirmed by the results for median overall survival, median PFS and TTP in comparison with placebo treatment.

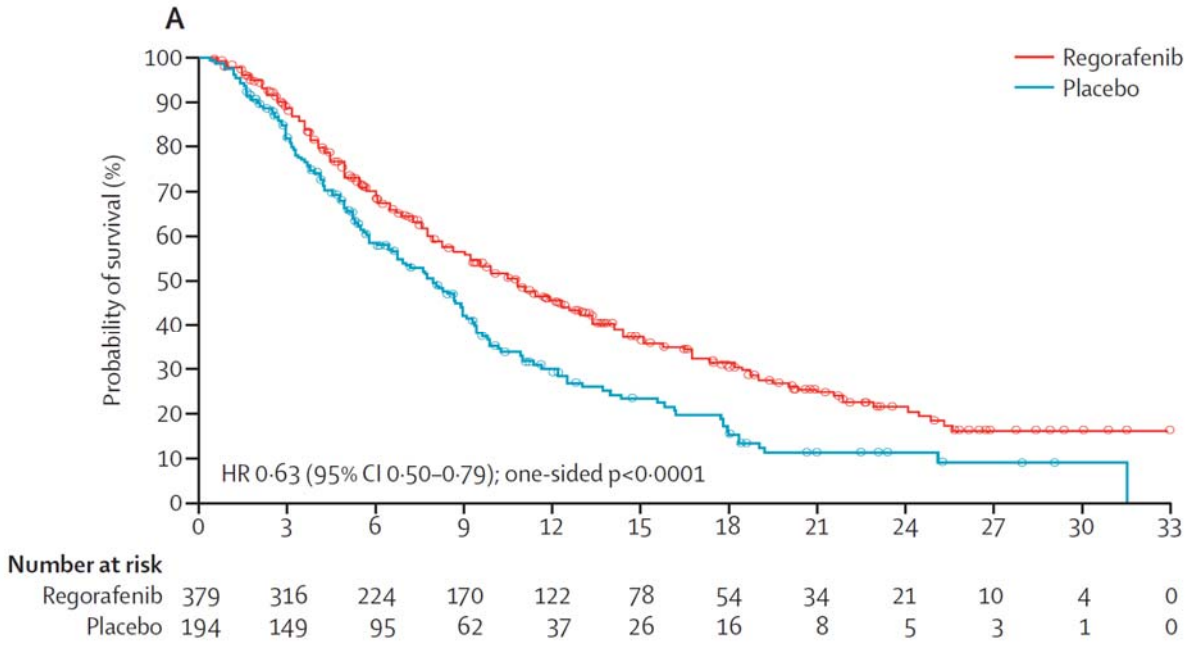
Patients' health-related quality-of-life and health utility values were measured with FACT-Hepatobiliary (FACT-Hep) and EQ-5D questionnaires, respectively. There was no clinically meaningful difference between regorafenib and placebo as measured by FACT-HEP total score, EQ-5D index score and EQ-5D VAS, which indicates that patients were able to tolerate treatment.

Primary endpoint (21, 22)

Overall Survival (OS)

Median overall survival was 10.6 months [95%CI 9.1, 12.1] in patients randomised to regorafenib compared with 7.8 months [95% CI 6.3, 8.8] in patients randomised to placebo. The one-sided p-value from the log rank test stratified using IVRS-entered data was statistically significant (p=0.000020) and the estimated hazard ratio for survival (regorafenib over placebo) was 0.63 (95% CI 0.50, 0.79), representing a 37% reduced risk of death in the regorafenib group compared with the placebo group.

Figure 4. Kaplan-Meier Curve for OS (FAS; mRECIST) (21)



See Appendix E for subgroup analysis of OS.

Sensitivity analyses of primary endpoint (OS) (22, 23)

As a sensitivity analyses, OS was analysed using a stratified one-sided log rank test stratified by the stratification data from RAVE (a validated electronic data entry system), and also using unstratified data (see text box below). Sensitivity analyses confirmed the robustness of the primary analysis of overall survival (Table 19).

Summary of analyses

Primary analysis - Performed according to treatment groups as randomised, with stratification as recorded in the IVRS data.

Sensitivity analyses

RAVE: Since differences may occur between the values of stratification variables entered by the investigator at the time of randomisation (via IVRS) and those collected on the case report form (CRF), the RAVE analysis uses the stratified data entered into the CRF as a sensitivity analysis.

Unstratified: Uses a one-sided log rank test without including stratification factors.

Table 19. Analyses of Overall survival in the RESORCE study (FAS; mRECIST)

	Regorafenib (N=379)	**Placebo (N=194)**
Number of patients (%) with event	233 (61.5%)	140 (72.2%)
Number of patients (%) censored	146 (38.5%)	54 (27.8%)
Median overall survival days (95% CI), Range (without censored values)	323 (276, 369) (9-767)	237 (192, 269) (12-946)
Median overall survival months (95% CI), Range (without censored values)	10.6 (9.1, 12.1) (0.3-25.2)	7.8 (6.3, 8.8) (0.4-31.1)
Primary analysis		
Hazard ratio [a]: Stratified IVRS	0.627	
95% CI for hazard ratio:	(0.500, 0.785)	
p-value (one-sided) from log rank test):	0.000020	
Sensitivity analyses		
Hazard ratio [a]: Stratified RAVE	[redacted]	
95% CI for hazard ratio:	[redacted]	
p-value (one-sided) from log rank test):	[redacted]	
Hazard ratio [a]: Unstratified	[redacted]	
95% CI for hazard ratio:	[redacted]	
p-value (one-sided) from log rank test):	[redacted]	

CI=confidence interval; FAS=full analysis set; IVRS=interactive voice response system; RAVE=validated electronic system for data collection.
[a] A hazard ratio <1 indicates superiority of regorafenib 160mg over placebo.
Median, percentile and other 95% CIs computed using Kaplan-Meier estimates. Hazard ratio and its 95% CI was based on either a stratified (IVRS), stratified (RAVE), or non-stratified Cox Regression Model.
Durations manually converted from days to months (1 month=30.44 days)

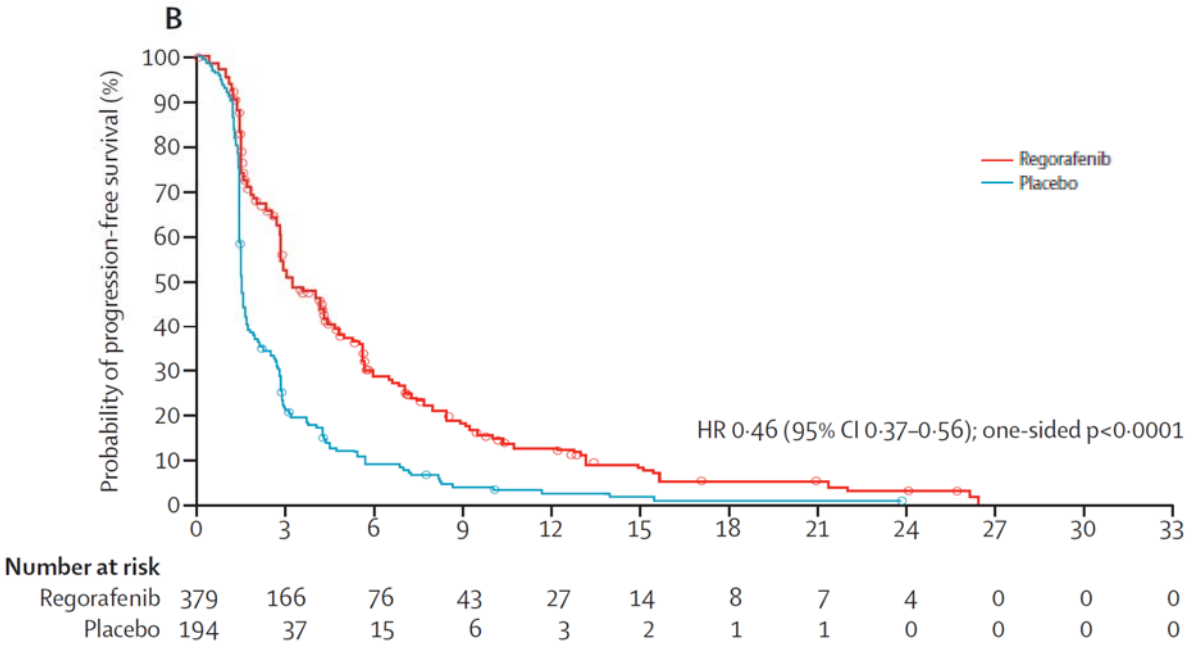
Secondary endpoints

Progression-free survival (PFS) (21, 22)

A clinically relevant treatment effect in favour of regorafenib with respect to PFS was demonstrated. Median PFS for regorafenib patients was 3.1 months (95% CI 2.8, 4.2) and for placebo patients was 1.5 months (95% CI 1.4, 1.6) (Hazard ratio [HR] 0.46, 95% CI 0.37, 0.56; p<0.0001) (Table 20).

See Appendix E for subgroup analysis of PFS.

Figure 5. KM estimates of the PFS rate during RESORCE (FAS; mRECIST) (21)



Sensitivity analyses of PFS

The results of the sensitivity analyses were supportive of and consistent with the primary analysis of PFS, showing statistically significant improvement in the regorafenib group compared with the placebo group (HR = [redacted]) Table 20.

Table 20. Analyses of Progression-free survival in the RESORCE study (FAS; mRECIST)

	Regorafenib (N=379)	**Placebo (N=194)**
Number of patients (%) with event	293 (77.3%)	181 (93.3%)
Number of patients (%) censored	86 (22.7%)	13 (6.7%)
Median PFS, days (95% CI), Range (without censored values)	95 (86 – 127) (9-792)	45 (44, 49) (5-464)
Median PFS, months (95% CI), Range (without censored values)	3.1 (2.8, 4.2) (0.3-26.0)	1.5 (1.4, 1.6) (0.2-15.2)
Primary analysis		
Hazard ratio [a]: Stratified IVRS	0.46	
95% CI for hazard ratio:	(0.37, 0.56)	
p-value (one-sided) from log rank test) [b]:	<0.0001	
Sensitivity analyses		
Hazard ratio [a]: Stratified RAVE	[redacted]	
95% CI for hazard ratio:	[redacted]	
p-value (one-sided) from log rank test)[b]:	[redacted]	
Hazard ratio [a]: Unstratified	[redacted]	
95% CI for hazard ratio:	[redacted]	
p-value (one-sided) from log rank test) [b]:	[redacted]	

CI = confidence interval; FAS = full analysis set; IVRS = interactive voice response system; mRECIST=modified RECIST; RECIST = Response Evaluation Criteria in Solid Tumours; Reg = regorafenib (160 mg).
[a] A Hazard ratio <1 indicates superiority of Regorafenib 160 mg (experimental) over Placebo (control).
[b] One-sided p-value from log rank test.
Median, percentile and other 95% CIs computed using Kaplan-Meier estimates. Hazard ratio and its 95% CI was based on either stratified (IVRS) or non-stratified Cox Regression Model. Durations manually converted from days to months (1 month = 30.44 days)

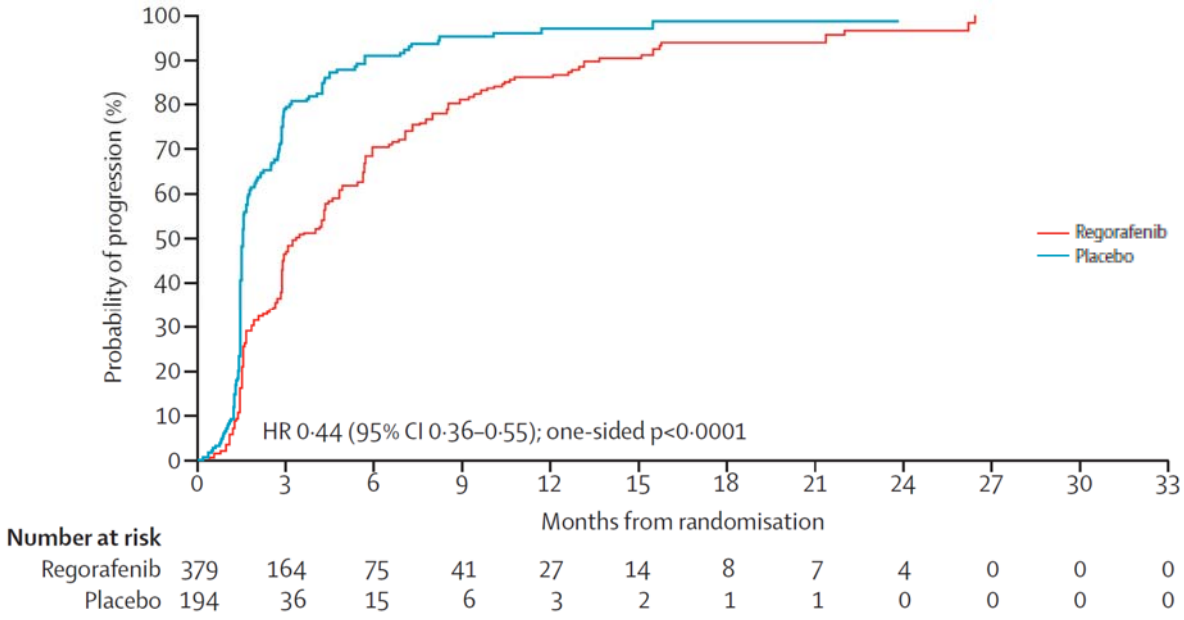
Time to Progression (TTP) (21, 22)

At the cut-off date for the final analysis (29th February 2016), by which time there had been 447 events, the percentage of patients with disease progression was 89.2% (n=173) in the placebo group and 72.3% (n=274) in the regorafenib group. Median TTP was 3.2 months (95% CI 2.9, 4.2) in the regorafenib group and 1.5 months (95% CI 1.4, 1.6) in the placebo group (HR 0.44, [95% CI: 0.36-0.55, p<0.0001]), equivalent to a 56% reduced risk in time to progression in the regorafenib group compared with the placebo group.

Figure 6 displays the KM estimates by treatment group for TTP. The estimated KM demonstrates a consistently longer TTP in the regorafenib group compared to the placebo group.

See Appendix E for subgroup analysis of TTP.

Figure 6. KM estimates of TTP during RESORCE (FAS; mRECIST) (21)



Sensitivity analyses of TTP

The results of the sensitivity analysis of TTP were supportive of and consistent with the primary analysis of TTP, showing statistically significant improvement in the regorafenib group compared with the placebo group (Table 21).

Table 21. Analyses of Time to progression (TTP) in the RESORCE study (FAS; mRECIST)

	Regorafenib (N=379)	Placebo (N=194)
Number of patients (%) with event	274 (72.3%)	173 (89.2%)
Number of patients (%) censored	105 (27.7%)	21 (10.8%)
Median TTP, days (95% CI), Range (without censored values)	97 (87 – 128) (11-792)	45 (44, 49) (5-464)
Median TTP, months (95% CI), Range (without censored values)	3.2 (2.9, 4.2) (0.4-26.0)	1.5 (1.4, 1.6) (0.2-15.2)
Primary analysis		
Hazard ratio [a]: Stratified IVRS	0.44	
95% CI for hazard ratio:	(0.36, 0.55)	
p-value (one-sided) from log rank test) [b]:	<0.0001	
Sensitivity analysis		
Hazard ratio [a]: Unstratified	[redacted]	
95% CI for hazard ratio:	[redacted]	
p-value (one-sided) from log rank test) [b]:	[redacted]	

CI = confidence interval; FAS = full analysis set; IVRS = interactive voice response system; mRECIST=modified RECIST; RECIST = Response Evaluation Criteria in Solid Tumours; Reg = regorafenib (160 mg).
[a] A Hazard ratio <1 indicates superiority of Regorafenib 160 mg (experimental) over Placebo (control).
[b] One-sided p-value from log rank test.
Median, percentile and other 95% CIs computed using Kaplan-Meier estimates. Hazard ratio and its 95% CI was based on either stratified (IVRS) or non-stratified Cox Regression Model. Durations manually converted from days to months (1 month = 30.44 days)

Objective tumour response rate (ORR) and disease control rate (DCR) (22, 23)

Response evaluation criteria in solid tumors (RECIST) is a well-established means of assessing tumour response, however, it was designed for assessing responses to cytotoxic agents and does not address measures of antitumour activity other than tumor shrinkage. Instead, when evaluating agents that reduce tumour vascularity and cell proliferation, resulting in stabilisation of tumour size despite central necrosis, it is considered more accurate to measure the extent of tumour necrosis and reduction in volume of viable tumour using contrast-enhanced radiological imaging (in the arterial phase of dynamic studies) (31). Due to HCC being a highly vascularised tumour, modified RECIST (mRECIST) offers clearly defined criteria for the assessment of this vascularisation and subsequent response to treatment with TKIs, such as regorafenib.

Briefly, for evaluation according to RECIST, complete response (CR) is defined as the absence of all target lesions; partial response (PR) and progressive disease (PD) as a greater than 30 % decrease and a greater than 20 % increase, respectively, in the sum of the longest diameters of the target lesions; and stable disease (SD) as neither PR nor PD. However, for evaluation according to mRECIST, CR is defined as the absence of arterially enhanced areas in all target lesions; PR and PD as the same degree of decrease and increase as in the RECIST criteria, these sums being those of the diameters of arterial enhanced areas in all target lesions rather than the sums of the diameters of the whole target lesions size; and SD as neither PR nor PD. When evaluating according to mRECIST, patients with no enhanced lesions were classified as non-measurable. The greatest variation (maximum reduction) in the sum of the greatest lesion dimensions for each patient are also recorded. For more details of RECIST 1.1 and mRECIST criteria see Appendix L.

The regorafenib group had a significantly higher objective response rate (ORR; CR+PR) (11% vs. 4%; p=0.0047) and disease control rate (DCR; CR+PR+SD) (65% vs. 36%; p<0.0001) than placebo based on mRECIST. Two reports of complete response (CR) (0.5%) were observed in the regorafenib arm (vs. 0 in the placebo arm) (Table 22).

Table 22. Response to therapy in the RESORCE study (FAS; mRECIST)

Best overall response	Regorafenib N=379 (100%) [95% CI]	Placebo N=194 (100%) [95% CI]
Complete response (CR)	2 (1%) [<1%; 2%]	0
Partial response (PR)	38 (10.0%) [7%; 14%]	8 (4%) [2%; 8%]
Stable disease (SD)	206 (54%) [49%; 59%]	62 (32%) [26%; 39%]
Non-CR / Non-PD	1 (0.3%) [0.0%; 1.5%]	0
Progressive disease (PD)	86 (23%) [19%; 27%]	108 (56%) [48%; 63%]
Not evaluable (NE)	19 (5%) [3%; 8%]	8 (4%) [2%; 8%]
Not assessed (NA)	27 (7%) [5%; 10%]	8 (4%) [2%; 8%]
Clinical progression	86 (23%) [19%; 27%]	40 (21%) [15%; 27%]
Response Rate	**40 (11%)**	**8 (4%)**
Disease Control Rate	**247 (65%)**	**70 (36%)**
Comparison of treatments – Inferential Statistics		

Regorafenib versus Placebo	Difference	[95% CI]	p-value
Response rate	-6.61	[-10.84, -2.39]	0.0047
Disease control rate	-29.31	[-37.52, -21.11]	<0.0001

CI=confidence interval; CR=complete response; FAS=full analysis set; HCC=hepatocellular carcinoma; mRECIST=modified RECIST for HCC; N=number of patients; NA=not assessed; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST= Response Evaluation Criteria in Solid Tumours; SD=stable disease

Maximum percent reduction in the size of target lesions (21, 22)

Patients in both treatment groups (per mRECIST or RECIST 1.1 criteria) demonstrated tumour shrinkage (any decrease in the sum of diameters of target lesions): mRECIST 23% (44/194) in the placebo group and 49% (184/379) in the regorafenib group; RECIST 1.1 criteria 14.4% (28/194) in the placebo group and 43.7% (166/379) in the regorafenib group.

Despite a relatively low ORR, it is clear that regorafenib has a therapeutic effect on HCC tumours by the numbers of patients experiencing tumour shrinkage or stable disease. Tumour shrinkage or disease stabilisation, is likely to translate into clinical benefit, which was confirmed by the results for median overall survival (10.6 months vs. 7.8 months), median PFS (3.1 months vs. 1.5 months) and TTP (3.1 months vs. 1.5 months) in comparison with placebo treatment.

Table 23. Maximum percent change in the size of target lesions (FAS)

Maximum percent change in target sum of longest diameter	Regorafenib (N=379)	Placebo (N=194)
mRECIST n	[redacted]	[redacted]
Reduction >30%	[redacted]	[redacted]
Reduction ≥20% but <30%	[redacted]	[redacted]
Reduction ≥10% but <20%	[redacted]	[redacted]
Reduction ≥0% but <10%	[redacted]	[redacted]
Growth ≥0%	141 (37%)	128 (66%)
Not Assessed	54 (14%)	22 (11%)

FAS = full analysis set; mRECIST = modified Response Evaluation Criteria in Solid Tumours; N = number of patients.

This information is graphically displayed in the waterfall plot in

Figure 7, showing more patients in the regorafenib group experiencing tumour shrinkage (as indicated by the vertical bars below the x-axis).

Figure 7. Maximum percent change from baseline in the size of target lesions by patient (mRECIST) (FAS)

Tertiary endpoints

Duration of response (DOR) (for PRs and CRs) (21, 22)

Duration of response was comparable between the regorafenib group and the placebo group.

Table 24. Duration of response (FAS; mRECIST)

	Regorafenib (N=40)	Placebo (N=8)
Number of patients (%) with event	30 (75.0%)	5 (62.5%)
Number of patients (%) censored	10 (25.0%)	3 (37.5%)
Median [95% CI], months	3.5 (1.9-4.5)	2.7 (1.9, NE)

CI = confidence interval; FAS = full analysis set; mRECIST = modified RECIST for HCC; N = number of patients; NE = Value cannot be estimated due to censored data; mRECIST = modified Response Evaluation Criteria in Solid Tumors.
Median, percentile and other 95% CIs computed using Kaplan-Meier estimates.

Duration of stable disease

Stable disease is measured from randomisation until the criteria for progression are met. The disease is considered to be in a 'steady state' where neither sufficient shrinkage to qualify for a response has occurred nor sufficient increase of tumour to qualify for progressive disease has occurred. There is also no unequivocal progression of existing non-target lesions and no appearance of new lesions.

Duration of stable disease was considerably longer in the regorafenib group than in the placebo group.

Table 25. Duration of stable disease (FAS; mRECIST)

	Regorafenib (N=206)	Placebo (N=62)
Number of patients (%) with event	151 (73.3%)	56 (90.3%)
Number of patients (%) censored	55 (26.7%)	6 (9.7%)
Median [95% CI] months,	5.5 (4.3 – 5.6)	3.1 (2.8, 4.2)

CI = confidence interval; FAS = full analysis set; mRECIST = modified RECIST for HCC; N = number of patients; RECIST = Response Evaluation Criteria in Solid Tumors.
Median, percentile and other 95% CIs computed using Kaplan-Meier estimates.

Figure 8. Kaplan-Meier curves of Duration of stable disease (mRECIST; FAS) (22)

Exploratory analysis - Overall survival measured from the start of prior sorafenib therapy

This OS analyses started from the beginning of prior sorafenib treatment and demonstrated that the sequence of sorafenib followed by regorafenib improves the median OS significantly from [redacted] months (95% CI: [redacted]) to [redacted] months (95% CI: [redacted]) versus placebo (difference = [redacted] months) – see Table 26. These results suggest that the sequential use of two multikinase inhibitors with partly overlapping target profiles provides a survival benefit in HCC.

Table 26. Overall survival from start of prior sorafenib treatment

		Regorafenib (N=379)	Placebo (N=194)
Time (days) from start of sorafenib to progression while on sorafenib	n N missing median (95% CI) (range)	[redacted]	[redacted]
Time (days) from start of sorafenib to progression on study medication	n N missing median (95% CI) (range)	[redacted]	[redacted]
Time (days) from start of sorafenib to death	n N missing median (95% CI) (range)	[redacted]	[redacted]

Health related Quality of Life and utility values (21-23)

During treatment, more than 80% of regorafenib and placebo patients completed questionnaires. Of these, approximately 90% in either treatment group were valid for analyses. No clinically meaningful differences were noted between the regorafenib and placebo groups in HRQoL. The EQ-5D Index, EQ-5D VAS and FACT-G scores were similar in the two treatment groups indicating patients could tolerate treatment. Although the LSM time-adjusted AUC analysis of FACT-Hep total and trial outcome index favoured placebo ($P<0.001$), the statistically significant differences were not clinically meaningful because they did not exceed minimally important thresholds for the differences as established in the literature (change of 8-9 points and 7-8 points, respectively) (32, 33).

Table 27. Summary of patient-reported outcomes; LSM time-adjusted AUC (FAS) (21)

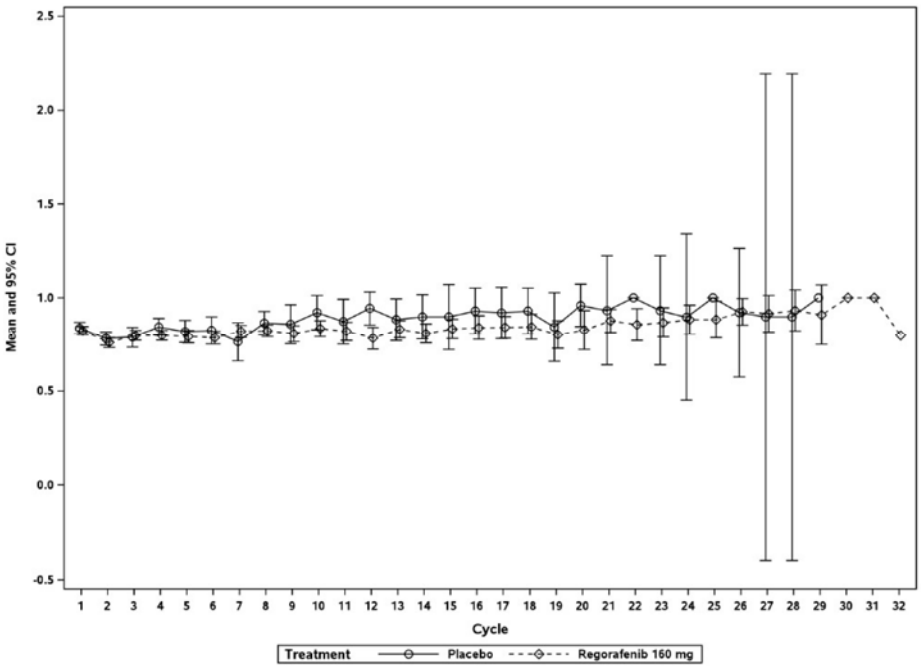
Least squares Mean (LSM) time-adjusted AUC [95% CI]	Regorafenib	Placebo	Difference	P-value	MID
EQ-5D index	0.76 (0.75, 0.78)	0.77 (0.75, 0.79)	-0.01 (-0.03, 0.02)	0.4695	0.1
EQ-5D VAS	71.68 (70.46, 72.90)	73.45 (71.84, 75.06)	-1.77 (-3.58, 0.04)	0.0558	10
FACT-G	75.14 (74.12, 76.16)	76.55 (75.20, 77.90)	-1.41 (-2.93, 0.11)	0.0698	6-7
FACT-Hep total	129.31 (127.84, 130.79)	133.17 (131.21, 135.12)	-3.85 (-6.06, -1.65)	0.0006	8-9
Trial outcome index	91.47 (90.30, 92.64)	95.52 (93.98, 97.07)	-4.05 (-5.79, -2.31)	<0.0001	7-8

AUC=area under curve; FACT=Functional Assessment of Cancer Therapy; FACT-G=FACT-General; FACT-Hep=FACT-hepatobiliary; LSM=Least squares mean; MID=minimally important difference; VAS=visual analogue scale;

EQ-5D

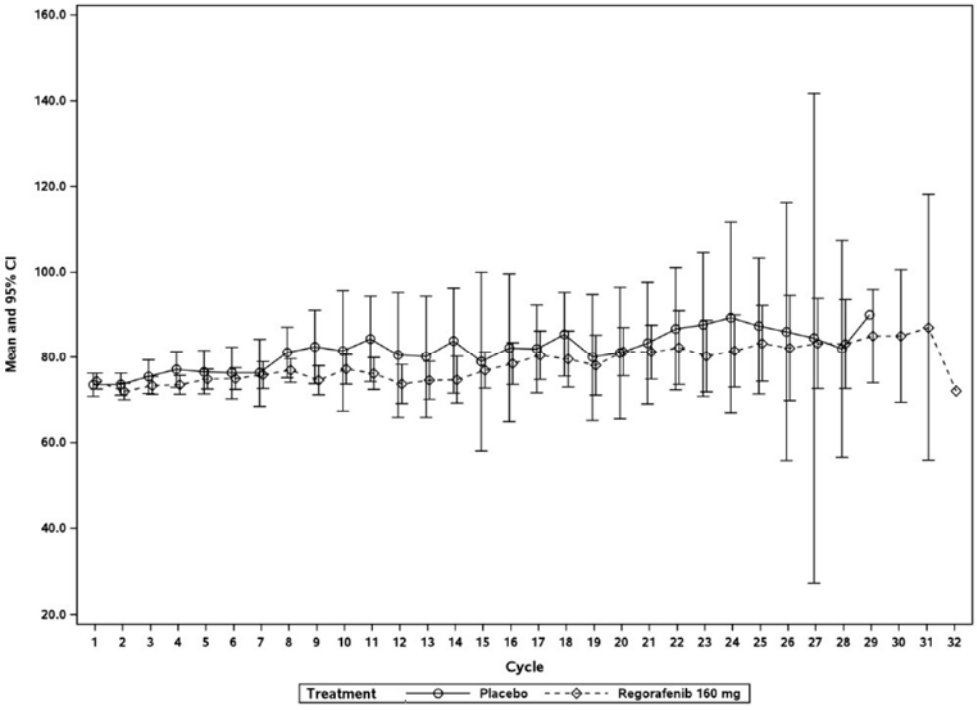
There were no clinically meaningful differences between the treatment groups. For the EQ-5D, higher scores represent better health status. [A change of at least 0.10 to 0.12 points on the EQ-5D index is considered to be a minimally important difference (MID). A change of at least 7 points on the VAS is considered as a MID.]

Figure 9. EQ-5D – means with 95% CI: EQ-5D index score (FAS)



CI=confidence interval; EQ-5D = EuroQol-5-Dimensional questionnaire

Figure 10. EQ-5D - means with 95% CI: EQ-5D VAS (FAS)

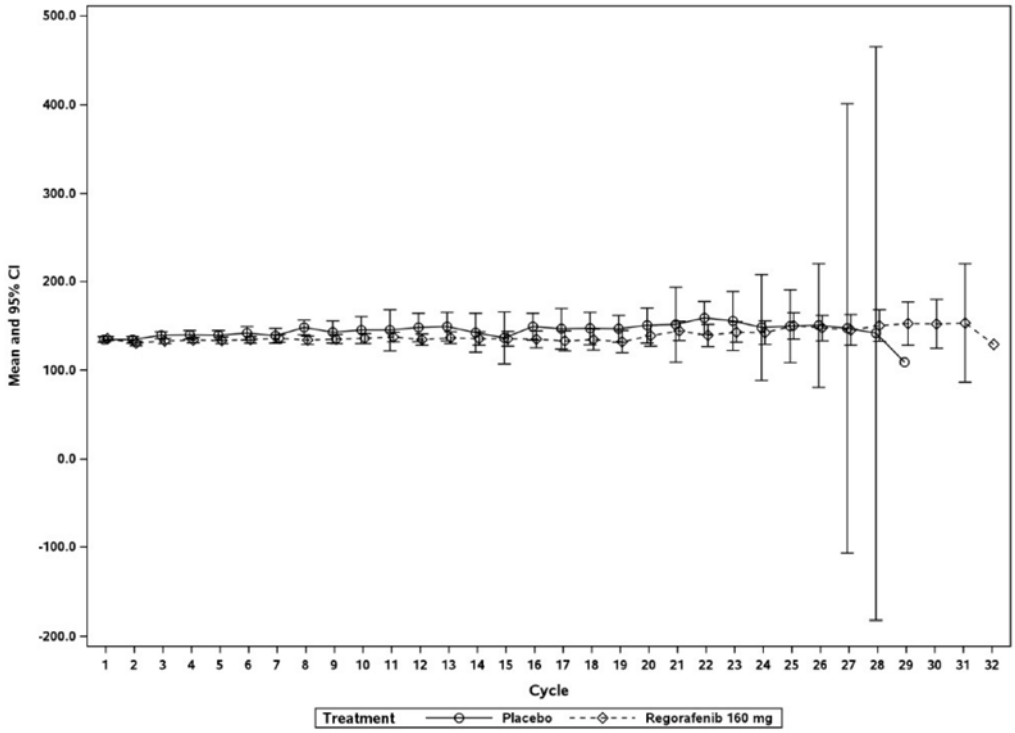


CI=confidence interval; EQ-5D = EuroQol-5-Dimensional questionnaire

Fact-Hep

There were no statistically significant and clinically meaningful differences between the treatment groups. Higher scores on all scales of the FACT-Hep questionnaire reflect better quality of life or fewer symptoms. The minimally important difference (MID) for the FACT-G subscales is 2–3 and for FACT-G total score is 6–7. The MID for HCS is 5–6 and the FACT-Hep total score is 8–9 (Trial Outcome Index [TOI] = 7–8).

Figure 11. FACT-Hep - means with 95% CI: FACT-Hep Total (FAS)

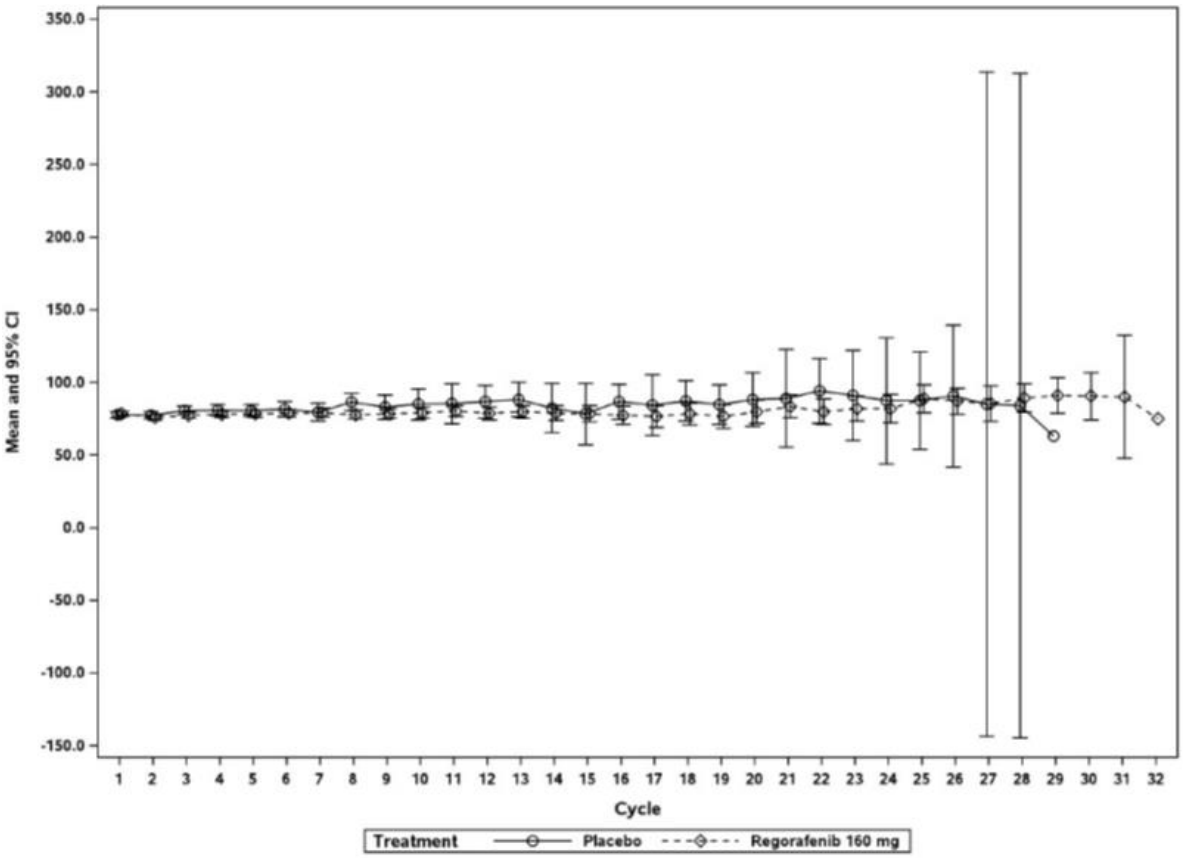


CI-Confidence interval; FACT-Hep = Functional Assessment of Cancer Therapy -Hepatobiliary.

FACT-G

Overall, mean FACT-G scores were higher in the placebo group, but these differences were not statistically significant.

Figure 12. FACT-G Total - means with 95% CI (FAS)



CI = Confidence interval; FACT-Hep = Functional Assessment of Cancer Therapy-Hepatobiliary.

Safety

Safety data are reported in Section B.2.10 – Adverse reactions.

B.2.7 Subgroup analysis

Pre-planned analyses of the primary and secondary efficacy variables (OS, PFS, TTP) for each treatment group were performed for the stratification variables:

- geographical region: Asia vs. rest of world (non-Asia)
- baseline ECOG performance status: 0, 1
- Baseline macrovascular invasion (presence, absence)

- Baseline extrahepatic disease (presence, absence),
- Baseline AFP (<400 ng/mL, ≥400 ng/mL),

And other pre-specified subgroups:

- Age: < 65 years, ≥ 65 years
- Sex: male, female
- Baseline Child-Pugh status (A5, A6),
- Aetiology (Hepatitis B, Hepatitis C, alcohol use)

As described in section B.2.4 Statistical analyses, sample size and study power was based around the primary efficacy endpoint (overall survival). The RESORCE study was therefore not powered to assess differential patient response to treatment in subgroups. In addition, the numbers of patients in some subgroups was small, with low event counts, meaning results of subgroup analyses should be interpreted with caution.

Descriptive statistics and hazard ratio estimates with 95% CI were provided at least within each subgroup category, provided there was a sufficient number of events in total within the subgroup across the treatment arms. If important effects were found in the subgroups, interaction analyses between the treatment and the subgroups were performed (24).

See Appendix E for results of subgroup analyses.

B.2.8 Meta-analysis

Not applicable. Evidence from only one RCT was available for analysis and relevant to the decision problem (RESORCE (21))

B.2.9 Indirect and mixed treatment comparisons

Evidence on the clinical benefits and adverse effects of regorafenib in patients with HCC who have progressed after sorafenib treatment is provided by the placebo-controlled study, RESORCE. Patients in both treatment groups in the RESORCE study were also able to receive Best Supportive Care (BSC), which would be the case in clinical practice,

to manage symptoms and any patient discomfort at this advanced stage of HCC. Hence, the RESORCE study comparator of placebo/BSC is the most relevant comparison and any indirect comparison unnecessary.

B.2.10 Adverse reactions

Summary

Results of the safety analyses of the RESORCE study suggest that regorafenib has a manageable toxicity profile in hepatocellular carcinoma patients who have progressed on prior sorafenib therapy. Adverse events were consistent with the safety profile already observed in previous clinical studies of regorafenib in metastatic colorectal cancer (mCRC) (34) and unresectable or metastatic gastrointestinal stromal tumours (GIST) (35). Across all indications, the most commonly reported adverse events with regorafenib are hand-foot skin reaction, asthenia / fatigue, diarrhoea, decreased appetite, and infection.

Introduction to adverse event data

Data on the safety of regorafenib in advanced HCC which has progressed after sorafenib is drawn from the RESORCE study, an international multicentre phase III double-blind, placebo-controlled RCT (21-23). In RESORCE, the population for safety analysis comprised all patients who received at least one dose of study medication (n=567; placebo n=193 and regorafenib 160mg o.d. n=374).

Of the patients valid for safety analysis in RESORCE, patients in the placebo group received an average (± standard deviation [S.D.]) daily dose of 157.4 (±10.3) mg study medication and those randomised to regorafenib received 144.1 (±21.3) mg. The overall median duration of treatment for patients in the regorafenib group, including time interrupted, was considerably longer than for patients in the placebo group (3.6 months [range=0.3-29.4] versus 1.9 months [range=0.2-27.4]) (21).

Summary of adverse events

Adverse events were classified using the National Cancer Institute (NCI) Common Terminology Criteria Adverse Event (CTCAE), version 4.03, and MedDRA (Medical Dictionary for Regulatory Activities) Version 19.0.

All patients in the regorafenib treatment group experienced at least one treatment-emergent adverse event (TEAE), compared with 93% of patients in the placebo group. Rates of grade ≥3 TEAEs were 79.7% with regorafenib and 58.5% with placebo. Most TEAEs were CTCAE Grade 3 with 56% of events in the regorafenib group and 32% in the placebo group.

HFSR was the most common TEAE (regorafenib = 51.3%; placebo = 6.7%) and drug-related TEAE (regorafenib = 50.8%; placebo = 5.7%) . Although frequent, hand-foot skin reaction was not reported as a serious adverse event in any patient; and was the reason for permanent discontinuation of study drug in only 7 (2%) patients treated with regorafenib (vs. 0 placebo patients). Drug-related hand-foot skin reaction is also commonly associated with other multi targeted kinase inhibitors and is generally manageable with dose modifications and proper care of the affected skin area. HFSR resulted in dose reductions in 20.1% patients treated with regorafenib. The SmPC lists dermatological toxicities (HFSR), in the “Special warnings and Precautions for use” section, with recommended dose modifications and measures provided in ‘Posology adjustments’, section 4.2.

Other common TEAEs (those events occurring in ≥ 10% of patients) included HFSR (regorafenib 51.3% vs. placebo 6.7%), Diarrhoea (41.2% vs. 15.0%), Hypertension (30.7% vs. 6.2%), Decreased appetite (30.7% vs. 14.0%) Fatigue (28.6% vs. 24.4%), AST increased (24.6% vs. 19.7%), Blood bilirubin increased (24.3% vs. 16.1%), Abdominal pain (21.1% vs. 15.5%), Pyrexia (19.8% vs. 6.7%), Dysphonia (17.9% vs. 1.6%), Constipation (17.4% vs. 10.9%), Nausea (17.1% vs. 13.5%), Ascites (15.5% vs. 16.1%), Asthenia (15.0% vs. 9.3%), Edema peripheral (15.0% vs. 13.5%), ALT increased (14.4% vs. 10.9%), Hypoalbuminaemia (13.9% vs. 7.3%), Anaemia (13.6% vs. 10.9%), Weight decreased (13.4% vs. 4.1%), Vomiting (12.6% vs. 6.7%), Abdominal pain upper (12.6% vs. 8.8%), Back pain (12.0% vs 8.8%), General physical health deterioration (11.8% vs. 14.0%), Cough (11.0% vs. 6.7%), and Muscle spasms (10.2% vs. 2.1%).

Table 28 summarises the incidence of CTCAE grade 3 and 4 TEAEs occurring in at least 1% of patients in either treatment group.

Table 28. CTCAE Grade 3 and 4 TEAEs with incidence rates of at least 1% in either treatment arm (SAF)

System Organ Class (SOC) Preferred Term	Regorafenib N=374 (100%)			Placebo N=193 (100%)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any Event	**374 (100%)**	**208 (55.6%)**	**40 (10.7%)**	**179 (92.7%)**	**61 (31.6%)**	**14 (7.3%)**
Blood & Lymphatic system disorders						
Anaemia	51 (13.6%)	14 (3.7%)	1 (0.3%)	21 (10.9%)	11 (5.7%)	0
Thrombocytopenia	8 (2.1%)	4 (1.1%)	1 (0.3%)	4 (2.1%)	0	0
Cardiac disorders	27 (7.2%)	5 (1.3%)	1 (0.3%)	9 (4.7%)	0	0
Gastrointestinal disorders						
Abdominal pain	79 (21.1%)	10 (2.7%)	0	30 (15.5%)	5 (2.6%)	0
Abdominal pain upper	47 (12.6%)	2 (0.5%)	0	17 (8.8%)	2 (1.0%)	0
Ascites	58 (15.5%)	16 (4.3%)	0	31 (16.1%)	11 (5.7%)	0
Diarrhoea	154	12 (3.2%)	0	29 (15.0%)	0	0
Gastrointestinal haemorrhage	(41.2%) 2 (0.5%)	1 (0.3%)	0	4 (2.1%)	2 (1.0%)	0
General disorders and administration site conditions						
Asthenia	56 (15.0%)	14 (3.7%)	0	18 (9.3%)	2 (1.0%)	0
Fatigue	107	22 (5.9%)	0	47 (24.4%)	7 (3.6%)	0
General physical health deterioration	(28.6%) 44 (11.8%)	13 (3.5%)	2 (0.5%)	27 (14.0%)	6 (3.1%)	3 (1.6%)
Hepatobiliary disorders						
Bile duct stenosis	0	0	0	4 (2.1%)	4 (2.1%)	0
Hepatic failure	9 (2.4%)	3 (0.8%)	3 (0.8%)	9 (4.7%)	2 (1.0%)	2 (1.0%)
Hepatic function abnormal	5 (1.3%)	2 (0.5%)	0	5 (2.6%)	4 (2.1%)	0
Hyperbilirubinaemia	14 (3.7%)	6 (1.6%)	1 (0.3%)	3 (1.6%)	2 (1.0%	1 (0.5%)
Jaundice	8 (2.1%)	2 (0.5%)	0	3 (1.6%)	3 (1.6%)	0
Infections and infestations						
Abdominal infection	3 (0.8%)	3 (0.8%)	0	2 (1.0%)	2 (1.0%)	0
Pneumonia	9 (2.4%)	5 (1.3%)	0	2 (1.0%)	1 (0.5%)	0
Injury, poisoning and procedural complications	24 (6.4%)	3 (0.8%)	0	14 (7.3%)	3 (1.6%)	0
Investigations						
Alanine aminotransferase increased	54 (14.4%)	9 (2.4%)	2 (0.5%)	21 (10.9%)	5 (2.6%)	0
Amylase increased	11 (2.9%)	6 (1.6%)	0	0	0	0
Aspartate aminotransferase increased	92 (24.6%)	37 (9.9%)	4 (1.1%)	38 (19.7%)	19 (9.8%)	3 (1.6%)
Bilirubin conjugate increased	7 (1.9%)	5 (1.3%)	0	1 (0.5%)	1 (0.5%)	0
Blood alkaline phosphate increased	22 (5.9%)	7 (1.9%)	0	8 (4.1%)	4 (2.1%)	0
Blood bilirubin increased	91 (24.3%)	28 (7.5%)	0	31 (16.1%)	13 (6.7%)	5 (2.6%)
GGT increased	22 (5.9%)	12 (3.2%)	0	12 (6.2%)	4 (2.1%)	1 (0.5%)
Lipase increased	27 (7.2%)	18 (4.8%)	7 (1.9%)	6 (3.1%)	3 (1.6%)	0
Neutrophil count decreased	11 (2.9%)	4 (1.1%)	0	2 (1.0%)	1 (0.5%)	0
Platelet count decreased	34 (9.1%)	10 (2.7%)	0	2 (1.0%)	0	0
Weight decreased	50 (13.4%)	7 (1.9%)	0	8 (4.1%)	0	0
White blood cell decreased	17 (4.5%)	4 (1.1%)	0	2 (1.0%)	0	0
Metabolism and nutrition disorders						
Decreased appetite	115	10 (2.7%)	0	27 (14.0%)	3 (1.6%)	0
Dehydration	(30.7%)	5 (1.3%)	0	0	0	0

System Organ Class (SOC) Preferred Term	Regorafenib N=374 (100%)			Placebo N=193 (100%)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Diabetes mellitus	7 (1.9%)	0	0	2 (1.0%)	2 (1.0%)	0
Hyperglycaemia	2 (0.5%)	4 (1.1%)	1 (0.3%)	5 (2.6%)	3 (1.6%)	1 (0.5%)
Hyperkalaemia	8 (2.1%)	4 (1.1%)	0	7 (3.6%)	1 (0.5%)	1 (0.5%)
Hypoalbuminaemia	12 (3.2%)	6 (1.6%)	0	14 (7.3%)	1 (0.5%)	0
Hypokalaemia	52 (13.9%)	9 (2.4%)	0	5 (2.6%)	2 (1.0%)	0
Hyponatraemia	26 (7.0%)	12 (3.2%)	3 (0.8%)	6 (3.1%)	4 (2.1%)	2 (1.0%)
Hypophosphataemia	21 (5.6%)	29 (7.8%)	2 (0.5%)	4 (2.1%)	3 (1.6%)	0
	36 (9.6%)					
Musculoskeletal and connective tissue disorders						
Back pain	45 (12.0%)	7 (1.9%)	1 (0.3%)	17 (8.8%)	2 (1.0%)	0
Musculoskeletal pain	17 (4.5%)	1 (0.3%)	0	11 (5.7%)	2 (1.0%)	0
Neoplasms benign, malignant, and unspecified incl. cysts and polyps						
Tumour pain	7 (1.9%)	5 (1.3%)	0	3 (1.6%)	1 (0.5%)	0
Nervous system disorders						
Hepatic encephalopathy	12 (3.2%)	4 (1.1%)	2 (0.5%)	7 (3.6%)	1 (0.5%)	0
Psychiatric disorders	45 (12.0%)	3 (0.8%)	1 (0.3%)	17 (8.8%)	2 (1.0%	0
Renal and urinary disorders						
Acute kidney injury	3 (0.8%)	1 (0.3%)	0	3 (1.6%)	2 (1.0%)	0
Proteinuria	32 (8.6%)	7 (1.9%)	0	2 (1.0%)	1 (0.5%)	0
Reproductive system & breast disorders	18 (4.8%)	0	0	10 (5.2%)	2 (1.0%)	0
Respiratory, thoracic and mediastinal disorders						
Haemoptysis	7 (1.9%)	1 (0.3%)	1 (0.3%)	3 (1.6%)	2 (1.0%)	0
Pleural effusion	15 (4.0%)	3 (0.8%)	0	11 (5.7%)	2 (1.0%)	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysaesthesia system[a]	192 (51.3%)	46 (12.3%)	0	13 (6.7%)	1 (0.5%)	0
Vascular disorders						
Hypertension	115 (30.7%)	55 (14.7%)	0	12 (6.2%)	9 (4.7%)	0

GGT=gamma-glutamyl transferase; N=number of patients; SAF=safety analysis set;
[a] Hand foot skin reaction (HFSR) per CTCAE v3.0 terminology

Drug-related TEAEs

A summary of treatment-related AEs can be found in Appendix F (Table 71). The most common drug-related TEAEs (>20% patients), also occurring at a higher frequency in the regorafenib group than in the placebo group include (hand-foot skin reaction, diarrhoea (33% vs. 9%), decreased appetite (24% vs. 6%), hypertension (23% vs. 5%) and fatigue (21.1% vs. 13.5%). These events were not unexpected based on the current knowledge of the safety profile of regorafenib. Hypertension is a known class effect for therapies targeting the VEGF/VEGFR pathway, probably related to its antiangiogenic effects (36, 37), and can be managed with dose modification and appropriate anti-hypertensive intervention.

Grade 3 drug-related adverse events included hypertension (13% in the regorafenib group vs. 3% in the placebo group), HFSR (13% vs. 1%), blood bilirubin increased (5.0% vs. 1.0%), AST increased (4.5% vs. 5%) and hypophosphataemia (4% vs. 1%). Drug-related Grade 4 TEAEs occurred in two patients in the placebo group (AST increased; renal failure) and very infrequently in the regorafenib group (4% [n=14]); the most common being AST increased (regorafenib group 1% [n=3] vs placebo group 1% [n=1]), ALT increased and hypophosphataemia (2 cases of each in the regorafenib group (1%).

AEs of special interest

Hepatobiliary and haemorrhage events are of special relevance in HCC as they are frequent complications of the underlying disease. Analysis of hepatobiliary and bleeding events in RESORCE ('Hepatic failure', drug-related Treatment-emergent serious adverse events [TESAEs] 'hepatobiliary disorders' Grade 4 and 5 and 'Bleeding/haemorrhage TEAEs Grade ≥3'; see Table 14 for definition of SAE), showed that treatment with regorafenib did not result in a significantly increased risk for the occurrence of such events.

Hepatic failure events (≥ Grade 3) were more frequently reported in the placebo group (4.7%; n=9) compared with the regorafenib group (2.4%; n=9). 'Hepatic failure' events included five deaths in the placebo group (2.6%), two of which were considered drug-related, and three deaths in patients receiving regorafenib (0.8%), not considered drug-related.

'Hepatobiliary disorders' (drug-related Grade 4 or 5 SAEs): A grade 4 event in the regorafenib group and two Grade 5 events ('hepatic failure) in the placebo group were considered study drug-related.

Grade 1 and grade 2 events of hyperbilirubinaemia, and increases in transaminases, however, are commonly reported TEAEs with regorafenib (see SmPC, Appendix C) and the recommendations are to perform liver function tests (ALT, AST and bilirubin) before initiation of treatment with regorafenib and monitor closely (at least every two weeks) during the first 2 months of treatment (thereafter, at least monthly / as clinically indicated).

'Bleeding/haemorrhage TEAEs Grade ≥3': The overall incidence of haemorrhage events of ≥ Grade 3 was higher in the placebo group (8%) compared with the regorafenib group (6%), although none of the events in the placebo group were considered as drug-related by the treating physician, whereas 6 'haemorrhage' events (1.6%) in regorafenib-treated patients were considered drug-related.

Table 29. Incidence of haemorrhage (≥ Grade 3) TEAEs (SAF)

System Organ Class (SOC) Preferred Term	Regorafenib N=374 (100%)			Placebo N=193 (100%)		
	≥ grade 3	Grade 3	Grade 4	≥ grade 3	Grade 3	Grade 4
Haemorrhages any	21 (6%)	11 (2.9%)	6 (1.6%)	15 (8%)	5 (2.6%)	3 (1.6%)
Haemorrhages drug-related	6 (1.6%)	3 (0.8%)	1 (0.3%)	0	0	0

SAF=safety analysis set

The regorafenib SmPC (see Appendix C) states that in clinical trials regorafenib was associated with an increased incidence of haemorrhagic events - mostly mild to moderate; however, some were fatal. Under 'Warnings & Precautions for use' it is recommended that blood counts and coagulation parameters be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding. In the event of severe bleeding necessitating urgent medical intervention, permanent discontinuation of regorafenib should be considered.

Serious adverse events (SAE)

A SAE is defined as any untoward medical occurrence that, at any dose results in death; is life-threatening (i.e. patient at risk of death at time of event); requires inpatient hospitalisation (unplanned, not associated with an AE, and >12 hours) or prolongation of existing hospitalisation; results in persistent or significant disability / incapacity; is a congenital anomaly / birth defect; or is another medically important serious event as judged by the investigator because it may jeopardise the patient or require intervention to prevent another serious condition.

Treatment-emergent SAEs were reported for a similar proportion of patients in each treatment group (Regorafenib = 44% [n=166]; Placebo = 47% [n=90]). These results were confounded by the fact that patients who were hospitalised within 30 days after their last dose of study medication intake due to progression of HCC were required to be included as treatment-emergent SAEs. The most common TESAEs (>2%) were general physical health deterioration (regorafenib = 10.4% patients vs. placebo 12.4%), ascites (regorafenib = 2.4%; placebo 3.1%) and hepatic failure (regorafenib = 2.4% vs. placebo 4.7%). Drug-related TESAEs were relatively low in both groups, but higher in regorafenib-treated patients compared with those receiving placebo (10% [n=39] vs. 3% [n=5]).

Laboratory parameters

In the RESORCE study, hypophosphataemia, as a laboratory abnormality (grade 3 or 4), was reported in 33.9% regorafenib-treated patients (n=125) compared with 6.9% (n=13) placebo patients. Hypophosphataemia was reported as the cause of dose interruption in 4 patients (1.1%) taking regorafenib. It did not result in dose reductions or permanent discontinuations of study drug. Other common grade 3 or grade 4 laboratory abnormalities occurring at a higher frequency in the regorafenib group (vs. placebo) included proteinuria (16.7% vs. 3.2%), decreased lymphocyte count (17.4% vs. 11.7%), and increased lipase (15.2% vs. 8.7%).

Adverse events leading to withdrawal

The rate of discontinuation of the study drug due to adverse events (25% [93/374] in the regorafenib group versus 19% [37/193] in the placebo group) indicates that most TEAEs

could be managed by dose modification and did not result in a permanent discontinuation of study drug. The most frequent adverse events leading to discontinuation of regorafenib treatment were general physical health deterioration (3.7% vs. placebo 2.1%), increased AST (2% [8/374] vs. 2% [3/193), increased blood bilirubin (2.1% vs. 3.6%) and HFSR (2% [7/374] vs. 0).

Dose reductions due to adverse events occurred in 47.9% of the patients in the regorafenib group and 7.8% of the placebo group. These included HFSR (20.1% vs. 0.5%), diarrhoea (4.3% vs. 0), fatigue (3.7% vs. 0) and increased blood bilirubin (3.5% vs. 0). The most common reason for discontinuing placebo was increased AST (2.1% vs. regorafenib: 2.7%).

Deaths

There were 50 deaths (13%) in the regorafenib group and 38 deaths (20%) in the placebo group. Deaths assessed as related to study drug were reported in 7 (2%) regorafenib patients and 2 (1.0%) placebo patients. The 7 deaths considered related to regorafenib were recorded as (1 of each case): duodenal perforation, meningorrhagia, haemorrhagic shock, hepatic encephalopathy, myocardial infarction and one event of which the primary cause of death was adverse event associated with clinical disease progression, for which the treating physician assessed the event as related to study medication.

Supporting data

No supportive studies were considered regarding the safety profile of regorafenib in HCC which has progressed after prior sorafenib. The overall safety profile seen in the RESORCE study was consistent with the known safety profile of regorafenib in other indications (GIST, mCRC) with overall no unexpected safety findings (see section 4.8 of SmPC, Appendix C).

Overview of the safety of the technology in relation to the decision problem

Regorafenib has been licensed and marketed since 2012 (US) / 2013 (Europe).

Adverse reactions in RESORCE study were in line with the expected profile in a population of patients with HCC who have progressed after prior sorafenib. In

RESORCE, most patients experienced at least one TEAE during the double-blind period of the study (regorafenib, n=374 [100%]; placebo, n= 179 [92.7%]). A high rate of TEAEs in both groups is expected for this pre-treated HCC patient population.

AEs were also consistent with the known safety profile of regorafenib observed in metastatic colorectal cancer (mCRC) (34) and unresectable or metastatic gastrointestinal stromal tumours (GIST) (35).

Overall, treatment with regorafenib was not associated with any clinical meaningful difference in patient reported quality of life compared to placebo. The most common AEs experienced with regorafenib in RESORCE (i.e. HFSR, diarrhoea, hypertension) are generally manageable with dose modifications and appropriate intervention (e.g. proper care of the affected skin, anti-hypertensives). The incidence of TEAEs leading to permanent treatment discontinuation (25% in the regorafenib group versus 19% in the placebo group) reflects this. Serious adverse events, reported in a similar proportion of patients in each treatment group (Regorafenib = 44%; Placebo = 47%), included 'general physical health deterioration' (regorafenib = 10.4% patients vs. placebo 12.4%), ascites (regorafenib = 2.4%; placebo 3.1%) and hepatic failure (regorafenib = 2.4% vs. placebo 4.7%). The most serious adverse drug reactions in patients receiving regorafenib are severe liver injury, haemorrhage, and gastrointestinal perforation and infection (see SmPC, Appendix C).

Subgroup analysis (geographic region, age, gender) was consistent with the results in the overall SAF population suggesting that regorafenib-treatment can be administered in a broad spectrum of patients.

It can be anticipated that regorafenib will have an acceptable, recognisable and manageable safety profile when used in England in the context of the decision problem.

B.2.11 Ongoing studies

No relevant ongoing studies are anticipated to provide additional evidence within the next 12 months. This has been confirmed by searching all records for 'regorafenib and liver cancer' on the www.clinicaltrials.gov website.

B.2.12 Innovation

With its multi-kinase, inhibitory profile, regorafenib offers an additional treatment option for individuals with unresectable HCC, for whom best supportive care is currently the only treatment option available following disease progression despite sorafenib therapy.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Principal findings from the clinical evidence: clinical benefits and harms

In this submission, regorafenib's effectiveness in patients with hepatocellular cancer (HCC) who have been previously treated with sorafenib is reviewed. Once they have progressed on sorafenib, this patient population has a poor prognosis and no other active treatment available to them. Patients at this difficult 'end' stage are typically managed with a best supportive care (BSC) approach, to relieve symptoms and aid comfort.

Clinical evidence to support the use of regorafenib in patients with hepatocellular cancer (HCC) who have been previously treated with sorafenib is provided by results from RESORCE, a prospective, phase 3, randomised, double-blind, placebo-controlled multicentre study. In this study, 573 patients with HCC, who have progressed on sorafenib, were randomised to regorafenib (plus BSC) or placebo (plus BSC). The primary endpoint of the study was overall survival (OS). Secondary endpoints included PFS, TTP, disease control rate (DCR) and tumour response (ORR). Analysis of results from RESORCE demonstrate regorafenib to be an effective treatment in extending survival and delaying further disease progression in this poor prognosis patient population.

RESORCE met its primary efficacy objective: Regorafenib treatment resulted in significantly longer OS as compared to placebo (HR= 0.63 [95% CI 0.50, 0.79], p<0.0001) (10.6 months vs. 7.8 months).

Analyses of secondary efficacy variables in RESORCE further substantiated primary efficacy results in demonstrating the efficacy of regorafenib over placebo. PFS was significantly longer in patients receiving regorafenib than placebo (HR= 0.46 [95% CI 0.37, 0.56], p<0.0001) (median PFS 3.1 months vs. 1.5 months). Median time to progression (TTP) was also significantly longer in the regorafenib arm than in the placebo arm (3.2 months versus 1.5 months, HR 0.44, 95% CI 0.36–0·55; p<0·0001). The treatment effect of regorafenib was robust - consistent across all pre-specified subgroups analysed (i.e. age, gender, geographical region, baseline ECOG Performance Status, AFP, Child-Pugh status (A5 vs. A6), presence or absence of macrovascular invasion or extrahepatic spread, as well as in patients with aetiologies of hepatitis B or C virus (HBV; HCV) infection or alcohol use) and by the various sensitivity analyses performed, supporting a broad applicability of regorafenib in HCC patients.

A higher objective response rate (CR+PR) was also observed in the regorafenib group (11% vs. 4%; p=0.0047) and the disease control rate (DCR) (CR + PR + SD [SD maintained for 6 weeks]) was significantly higher in the regorafenib group (65%) vs. the placebo group (36%) (p<0.0001). Given that late stage HCC is a difficult cancer to treat, with very few treatments having any beneficial impact on the disease and patient survival, a higher response rate - including 2 reports of complete responses - plus a doubling of the disease control rate is a significant therapeutic achievement. In approximately half (49%; 184/379) of patients receiving regorafenib, there was evidence of tumour shrinkage (vs. 23%; 44/194 placebo patients). Tumour shrinkage and / or disease stabilisation, is likely to translate into clinical benefit, which was confirmed by the results for median overall survival (10.6 months vs. 7.8 months), median PFS (3.1 months vs. 1.5 months) and TTP (3.1 months vs. 1.5 months) in comparison with placebo treatment.

The beneficial clinical profile of regorafenib was accompanied by a manageable safety profile, with adverse events in RESORCE consistent with the safety profile already observed in previous clinical studies of regorafenib in metastatic colorectal cancer (mCRC) (34) and unresectable or metastatic gastrointestinal stromal tumours (GIST) (35).

Overall, treatment with regorafenib was not associated with any clinical meaningful difference in patient reported quality of life compared to placebo. Common adverse events

included hand-foot skin reaction (HFSR), diarrhoea, and hypertension - generally manageable by dose modification / appropriate treatment without the need to discontinue treatment. The incidence of TEAEs leading to permanent treatment discontinuation (25% [93/374] in the regorafenib group versus 19% [37/193] in the placebo group) reflects this. The most serious adverse drug reactions in patients receiving regorafenib are severe liver injury, haemorrhage, and gastrointestinal perforation and infection (see SmPC, Appendix C). Subgroup analysis (geographic region, age, gender) was consistent with the results in the overall SAF population supporting the findings of the efficacy subgroup analyses that regorafenib-treatment can be administered in a broad spectrum of patients.

A key issue for clinicians involved in treating HCC, which has progressed with sorafenib treatment, is the poor prognosis for patients at this stage of disease and the lack of effective treatment options. Regorafenib provides the clinical benefits of extending survival, delaying disease progression, tumour shrinkage and disease stabilisation in this difficult to treat patient population. Efficacy and safety results from RESORCE establish a favourable risk/benefit profile for regorafenib in HCC patients who progressed on prior sorafenib treatment.

Strengths and limitations of the clinical evidence base

A key strength to the clinical evidence base is that the significant results for survival and response, in patients treated with regorafenib, signify there is now an effective treatment option available to HCC patients who have progressed on sorafenib.

The evidence base is derived from a well-designed trial i.e. large (relative to this patient population), prospective, randomised, double-blind, placebo-controlled, multicentre, and adequately powered. A further strength is the selection of overall survival as the primary endpoint. Overall survival is an important outcome for HCC patients and is also the most easily defined and least subject to investigator bias. Other efficacy endpoints related to disease progression and tumour response i.e. TTP, PFS, DCR, ORR, are also standard parameters for documenting response of solid tumours (38). In addition, the efficacy and safety of regorafenib was corroborated by subgroup and sensitivity analyses, indicating the robustness of the results and its applicability to a broad spectrum of patients, as would be seen in clinical practice.

Recognised limitations to RESORCE include:

- In line with standard clinical trial design, only patients with Child-Pugh status A and ECOG performance status of 0 or 1 were included in the study. Patients with Child-Pugh A liver function were included to avoid the potential confounding effect of impaired liver function on survival.
- The study was restricted to patients who could tolerate sorafenib (for a definition of tolerability see.Table 6). The efficacy in patients unable to tolerate sorafenib is not known.

Relevance of the evidence base to the decision problem and the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in routine clinical practice

The decision problem addressed in the submission is the clinical and cost effectiveness of regorafenib within its licensed indication for previously treated unresectable hepatocellular carcinoma.

Relevance to the population in the decision problem

The population included within the RESORCE study is generally reflective of the population defined within the decision problem and likely within clinical practice in England.

According to the anticipated licence, regorafenib will be used in patients who have progressed following treatment with sorafenib. An audit of sorafenib-treated patients conducted by King et al (2017) (39) provides the baseline characteristics of patients started on sorafenib in the UK during the period 2007 – 2013. Sorafenib-treated patients were identified via the Cancer Drugs Fund and local databases. Data were collected retrospectively from medical records according to a standard case report form. Data were obtained for 448 sorafenib-treated patients from 15 hospitals.

The patient characteristics from the audit provide the closest indication of the characteristics of patients who could be eligible for treatment with regorafenib. Table 30 shows the characteristics of patients in RESORCE compared to the audit by King et al.

Table 30. Baseline characteristics of patients receiving Sorafenib versus those of patients enrolled in the RESORCE study

	Regorafenib (RESORCE) N=379 (%)	**Observational (King et al) N=448 (%)**
Age (yr) (mean ± S.D.)	61.8 ±12.4	NR
Median age (range)	64 (54-71)	68
< 65 years	199 (52.5)	NR
≥ 65 years	180 (47.5)	NR
Sex – no. (%)		
Male	333 (87.9)	325 (72.5%)
Female	46 (12.1)	66 (14.7%)
Not reported		57 (12.7%)
Race		
White	138 (36.4)	NR
Black	6 (1.6)	NR
Asian	156 (41.2)	NR
White / Black	2 (0.5)	NR
Not reported	77 (20.3)	NR
Region – no. (%)		
Asia	143 (37.7)	Not applicable
Rest of World	236 (62.3)	Not applicable
Cause of disease (Aetiology)* – no. (%)		
Hepatitis C	78 (20.6)	70 (15.6%)
Alcohol use	90 (23.8)	110 (24.6%)
Hepatitis B	143 (37.7)	55 (12.3%)
Genetic / metabolic	16 (4.2)	NR
Non-Alcoholic steatohepatitis	25 (6.6)	NR
Unknown	66 (17.4)	NR
Other	12 (3.2)	NR
ECOG performance status – no. (%)		
0	247 (65)	117 (26.1%)
1	132 (35)	218 (48.7%)
2	0 (0)	94 (21.0%)
3	0 (0)	6 (1.3%)
No data	0 (0)	13 (2.9%)
BCLC stage - no. (%)		
A (early)	1 (0.3)	3 (0.7%)
B (intermediate)	53 (14.0)	104 (23.2%)

C (advanced)	325 (85.8)	322 (71.9%)
No data	0 (0)	19 (4.2%)
Macroscopic vascular invasion – no. (%)		
Yes	110 (29.0)	91 (20.3%)**
No	269 (71.0)	161 (35.9%)**
No data		196 (43.8%)
Extrahepatic disease – no. (%)		
Yes	265 (69.9)	172 (38.4%)
No	114 (30.1)	269 (60.0%)
No data	0(0)	7 (1.6%)
Macroscopic vascular invasion and/or extrahepatic disease – no. (%)	304 (80)	NR
Child-Pugh class – no (%)		
A	373 (98.4)	343 (76.6%)
B†	5 (1.3)	72 (16.1%)
C	0(0)	2 (0.4%)
No data	0(0)	31 (6.9%)
Child-Pugh score – no (%)		
5	244 (64.4)	NR
6	129 (34.0)	NR
7†	5 (1.3)	NR
8	0	NR
Alpha-fetoprotein(AFP) (ng/ml)		NR
Mean (± S.D.)	13507.9 (±49056.8)	NR
median (range)	183.2 (1.0-477591.0)	NR
<400 ng/mL	217 (57.3)	227 (50.7%)
≥400 ng/mL	162 (42.7)	141 (31.5%)

Previous therapy – no. (%)		
Local anti-cancer therapy	256 (67.9)	Yes - 190 (42.4%)
Including use of drug given locally	224 (59.1)	
Radiotherapy	48 (12.7)	
Systemic anticancer therapy	379 (100)	

S.D.=standard deviation
* Patients may have had more than one aetiology of HCC
** reports vascular invasion
† The information in this table is based on the last observations on or before the first study drug intake. Changes may have occurred between the screening of patients and their first day of study drug intake. During the study, it was found that 3 patients were on anticoagulant medication which, per the study protocol, led to Child-Pugh classification of B.

The RESORCE study population is generally comparable to the typical population of patients with advanced HCC for most aspects: there is a majority of males, similar proportions of patients with hepatitis C, similar alcohol consumption, and broadly

comparable BCLC staging. Patients in clinical practice also predominantly have ECOG status 0-1 and are mostly of Child-Pugh A class.

However, there are some differences:

- a minority of patients in the clinical setting had ECOG PS >=2. This patient group was not represented in the RESORCE study. In addition the RESORCE study did not include Child-Pugh B patients.
- there were more patients in RESORCE with hepatitis B.
- Although not reported in the King et al study, the proportion of Asians is unlikely to be as high as 40% as it was in RESORCE

Whether the above differences affect the applicability of the RESORCE study results to England is dependent on whether these differences are predictive of outcomes and the likelihood of use in these patient groups.

ECOG status and Child-Pugh Class

Correlation with survival benefit
The study by King et al showed an impact of ECOG performance status and higher Child-Pugh Class on overall survival i.e. those with poorer PS or poorer liver function having a lower overall survival.

Extent of use in clinical practice
Regorafenib's expected licence is for use following sorafenib. Patients are eligible for sorafenib under the CDF if they have Child Pugh A or Child Pugh B (with low disease burden) status. At this advanced stage of the disease the use of further chemotherapy following sorafenib is anticipated to be reserved for 'fitter' patients. We anticipate that the use of regorafenib in patients with a poor capacity to benefit would be low.

Hepatitis B

Correlation with survival benefit
The Kings analysis indicates that the presence/absence of hepatitis B is not a predictor of outcome. This is supported by the results of the RESORCE study which did not show a significant difference in efficacy for those with/without hepatitis B.

Asian

Correlation with survival benefit

In the RESORCE study there was no significant difference in the hazard ratios for OS between Asians and the rest of the world - with both populations benefitting to a similar extent from treatment - see Table 31.

Table 31. Summary subgroup analyses of overall survival in the RESORCE study - inferential statistics (FAS) (21, 22)

		Hazard ratio	
Variable	**Subgroup**	**Estimate**	**95% CI**
Geographical Region	**Asia**	0.651	(0.46, 0.92)
	ROW	0.684	(0.52, 0.90)

A hazard ratio <1 indicates superiority of regorafenib 160 mg over placebo. Hazard ratio and CIs are based on an unstratified Cox Regression Model.

Conclusion

Patients with advanced HCC in England show comparable characteristics to those enrolled in the RESORCE study. There were some differences in the proportions of Asians, patients with poorer ECOG PS, patients with Hepatitis B and Child-Pugh B class. In respect of a higher proportion of Asians in the RESORCE study this is not expected to affect generalisability as both populations benefit to a similar extent. Hepatitis B has not been found to be significantly correlated with survival and therefore this difference between RESORCE and English patients is expected to have no impact on generalisability. In terms of ECOG PS and Child-Pugh B class, there is evidence of the reduced benefit of TKI inhibitors in these patients groups. However, we anticipate that the use of regorafenib in these patients would be low. We believe that the results of the RESORCE study are generalisable to the clinical setting in England.

The efficacy of regorafenib was consistent across all other pre-specified subgroups analysed (i.e. age, gender, baseline ECOG Performance Status, AFP, Child-Pugh status (A5 vs. A6), presence or absence of macrovascular invasion or extrahepatic spread, as well as in patients with aetiologies of hepatitis B or C virus (HBV; HCV) infection or alcohol use), supporting a broad applicability of regorafenib in HCC patients.

Relevance of the Comparator

Prior to the results from RESORCE, there were no recognised effective treatment options for HCC patients who have progressed on sorafenib. The main alternative treatment to regorafenib is best supportive (palliative) care (BSC) to help alleviate symptoms. Best supportive care covers a wide range of treatment options from pain relief to counselling and is intended to maximise quality of life without a specific antineoplastic regimen.

Placebo plus BSC was therefore selected as the medically appropriate control group (vs. regorafenib plus BSC) due to lack of other standard treatments.

Relevance of the Intervention

In RESORCE, regorafenib was administered at the same dosage as that recommended in the Summary of Product Characteristics, and followed in clinical practice. It is an oral agent, convenient to administer, with a simple dosing regimen (four 40mg tablets once daily for 3 weeks followed by one week off therapy). Oral therapy avoids patients having to attend hospital for intravenous chemotherapy. No dose adjustment is needed for age, sex, bodyweight, mild or moderate renal or hepatic impairment.

Management of suspected adverse drug reactions in clinical practice may require temporary interruption or dose reduction of regorafenib therapy. Such dose reduction recommendations applied during the RESORCE study. In addition, monitoring of liver function and blood pressure were features within RESORCE and are included in the SmPC.

Relevance of the Outcomes assessed in clinical trials to clinical benefits experienced by patients in routine clinical practice

Key impacts of advanced HCC which has progressed with sorafenib therapy, are reduced life expectancy, complications and symptoms due to tumour enlargement and metastatic spread, and as a consequence, a reduction in patient quality of life. Outcome measures in the RESORCE study therefore focused on measuring survival differences between regorafenib and placebo and treatment effects on delaying disease progression, amelioration of symptoms, and health-related quality of life, all of which are directly relevant to patients within clinical practice.

All efficacy and safety assessments in the RESORCE study were standard variables and methods for clinical studies in oncology. They are widely recognised as valid, reliable, accurate and relevant to clinical practice.

The primary endpoint in RESORCE was overall survival. It is often the gold standard endpoint in the evaluation of new therapies in many cancers and is the most important endpoint to patients and the most easily defined and least subject to investigator bias (40). A treatment that can increase survival vs. best supportive care alone would provide a benefit for patients and addresses an unmet need in this patient population. Regorafenib increased median OS as compared to placebo (HR= 0.627 [95% CI 0.500, 0.785], p=0.000020) (10.6 months vs. 7.8 months). The modelled mean survival benefit ranged from 3.92 to 6.85 months depending on the extrapolation distribution used (see Table 106).

RESORCE also assessed endpoints relating to disease progression and tumour response. TTP, PFS, DCR, ORR, are also standard indicators for the evaluation of anticancer agents (38). In RESORCE, tumour response evaluations were measured using both the more up to date mRECIST criteria, and also the RECIST criteria (v.1.1). The analyses of secondary efficacy variables in RESORCE study were consistent with the primary efficacy results in demonstrating the efficacy of regorafenib over placebo in the treatment of HCC.

It is important that new cancer treatments do not significantly impact patient quality of life and that the achieved benefits of treatment are not outweighed by risks and major deterioration of patient quality of life. Patients' health-related quality-of-life and health utility values were measured with FACT-Hepatobiliary (FACT-Hep) and EQ-5D questionnaires, respectively. These are validated tools applicable for international clinical trial settings. FACT-Hep is disease-specific and EQ-5D used in a wide range of cancer patient populations, irrespective of specific diagnosis. There was no clinically meaningful difference between regorafenib and placebo as measured by FACT-HEP total score, EQ-5D index score and EQ-5D VAS.

Safety was an additional endpoint measured in the RESORCE study. This is patient-relevant and the results verify the general tolerability and acceptability of regorafenib in advanced unresectable HCC. The safety profile and patient tolerability of regorafenib was evaluated at every study visit throughout the RESORCE study. Safety analyses confirm that regorafenib has a manageable toxicity profile in hepatocellular carcinoma patients who have progressed on prior sorafenib therapy. Adverse events were consistent with the safety profile already observed in previous clinical studies of regorafenib in metastatic colorectal cancer (mCRC) (34) and unresectable or metastatic gastrointestinal stromal tumours (GIST) (35). Across all indications, the most commonly reported adverse events with regorafenib are hand-foot skin reaction, asthenia / fatigue, diarrhoea, decreased appetite, and infection.

In summary, the above review of the evidence base in relation to key factors of the decision problem e.g. population, outcomes, and important endpoints, demonstrates the relevance and applicability of the results of the RESORCE study to routine clinical practice in England.

End of life criteria

Regorafenib, in the indication proposed within this submission, is to be considered as a 'life extending treatment at the end of life'.

Life expectancy

It is intended that regorafenib, in the indication proposed within this submission, be considered as a 'life extending treatment at the end of life' on the basis that the addition of regorafenib to BSC resulted in a significantly better median OS as compared to placebo plus BSC (10.6 months vs. 7.8 months; hazard ratio [HR] = 0.627 [95% CI 0.500, 0.785], p=0.000020). As such, regorafenib fulfils the following amended criteria set out by NICE in the '*Guide to the methods of technology appraisal (PMG19 Addendum A - Final amendments to the NICE technology appraisal processes and methods guides to support the proposed new Cancer Drugs Fund (CDF) arrangements) '*

Life expectancy: 'the treatment is indicated for patients with a short life expectancy, normally less than 24 months'

Life expectancy of patients with advanced HCC (BCLC Stage C). The European Clinical Practice Guidelines for HCC (European Society for Medical Oncology [ESMO]-European Society for Digestive Oncology [ESDO] guidelines (18)) document that without treatment, the median survival for stage C HCC is between 4 and 8 months. With treatment, e.g. sorafenib, the median survival for stage C HCC is between 6 and 11 months.

In the RESORCE study, patients taking regorafenib had a median overall survival of 10.6 months vs 7.8 months for placebo (hazard ratio [HR], 0.62; 95% confidence interval[CI], 0.50–0.78; P <0.001)(21).

Life extension: 'there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.'

As mentioned above, the RESORCE study, in which regorafenib is compared with placebo plus best supportive care, demonstrates increased median overall survival time of 2.8 months in patients treated with regorafenib (21). The average survival benefit is not

available from the RESORCE study but has been modelled - see Cost-effectiveness section. The modelled mean survival benefit ranged from 3.93 to 6.85 months depending on the method of extrapolation used (see Table 106).

Patients with HCC in England

The expected licence for regorafenib is for patients who have been previously treated with sorafenib. Therefore, estimating the number of patients on sorafenib is the best base from which to estimate the use of regorafenib.

As sorafenib has been available since 2008, and on the CDF for several years, the actual numbers of patients receiving this treatment are known and do not need to be estimated.

According to CDF figures there were 538 notifications for sorafenib in HCC in 2015 (http://webarchive.nationalarchives.gov.uk/20151223153822/https://www.england.nhs.uk/ourwork/pe/cdf/). This constitutes the potential eligible population for regorafenib. Bayer estimates that a maximum of [redacted]% ([redacted]) of these patients will receive regorafenib.

Table 32. End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Patients in the RESORCE study in the placebo arm had a median survival of 7.8 months	Section B.2.6 Page 56
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	The median survival benefit observed in RESORCE study was 2.8 months. The modelled average survival benefit ranges from 3.92 to 6.85 months depending on the extrapolation curve used (see Table 106).	Section B.2.6 Page 56 & Table 106 (Appendix J)

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

Details of the cost-effectiveness systematic literature review are available in Appendix G. No cost-effectiveness studies were identified relating to the use of regorafenib in patients with advanced HCC. Cost-effectiveness studies were located involving the use of Best Supportive/Palliative care. As BSC is a non-active treatment these evaluations typically were in comparison to sorafenib. Although it is not a comparator treatment, sorafenib was included in the search terms and considered of value as it is the only other systemic treatment licensed in patients with advanced HCC. Sorafenib has been compared against a range of comparators.

Twenty-three publications were identified. The study by Hubert et al (2016) concerned budget impact alone (41) and three abstracts were also presented as full-text papers (Chan and Leung 2016, Leung et al 2016, Parikh et al 2016) (42-46) (47) meaning 19 distinct economic evaluations were identified.

Of the 19 economic evaluations, 15 used a Markov model as modelling approach analysis (43, 47-60) and one publication did not provide information about the analysis approach (61).

Thirteen of these models were comprised of 3 health states i.e. preprogression/stable disease; progression; death. Two Markov models had different health states being based on BCLC disease staging (61) or including a post-transplantation health state (59). In the 11 studies involving BSC/palliative care, all were compared against sorafenib – in these studies BSC/palliative care was always found to be less effective and less costly in comparison to active treatment. The evidence base for the located studies was primarily based on phase III trial data for sorafenib. All models extrapolated the treatment effect beyond the duration of the trial.

The economic evaluations identified in the literature search are outline in Table 33.

Table 33. Summary of published cost-effectiveness studies

	Study	Year	Summary of model/analysis	Patient population	QALYS (intervention, comparator)	Cost (currency) (intervention, comparator)	Base case results (ICER or cost benefit)
1	**Chaplin et al 2015 (50)**	2015	A Markov model to evaluate the cost effectiveness of Y-90 versus sorafenib. The model consists of three health states (stable disease, progression & death) and has a time horizon of 10 years. Resource use. Costs and effectiveness data were taken from the literature	Advanced HCC patients	Y-90: 1.12 Sorafenib: 0.85	Y-90: £21,441 Sorafenib: £34,050	No ICER reported, Y-90 dominated
2	**Connock et al 2010 (61)**	2010	Model design not reported but information about inputs is provided. Costs and resource use data was based on expert opinion, which was collected by a survey. Effectiveness data was collected from the SHARP study, one Asia-Pacific RCT study and one open label uncontrolled study.	Advanced HCC patients	Sorafenib: NR Placebo: NR	Sorafenib: NR Placebo: NR	£ 64,754 per QALY gained

3	**NICE 2010 (***TA189)* **(54)**	2010	A Markov model to evaluate the cost-effectiveness of Sorafenib +BSC vs placebo(PBO)+BSC from a NHS perspective. The model consists of four distinct health states (first line treatment- non progressive advanced disease, first line treatment – progressive disease, BSC-progressive disease, Death). The model takes into account a cycle length of 1 month over a life time horizon. Cost and resource use parameters in the model were estimated from primary (SHARP trial) and secondary sources. The estimates of costs of adverse events and resource use were based on a survey of UK clinicians. Effectiveness data was obtained from SHARP study, one Asia-Pacific RCT study and one open label uncontrolled study	Advanced HCC patients	Sorafenib: NR Placebo: NR	Sorafenib: NR Placebo: NR	£64,754 per QALY gained

4	**SMC 2015***(SMC.No. 482/08)* **(56)**	2015	A Markov model was used to evaluate the cost-effectiveness of Sorafenib vs placebo from a NHS perspective. Three health states were defined. Patients started in the PFS health state where they received treatment with either sorafenib or BSC and then remained on treatment until disease progression or a treatment-limiting adverse event occurred. On moving to the progressed disease health state, patients could continue on sorafenib (reflecting 7.7% of patients who continued on treatment beyond progression in the pivotal study) or switch to BSC. For this Markov model a time horizon of 15 years was used. Drug acquisition cost of sorafenib was based on the mean dose per day and mean treatment duration used in the study. Other health state costs and resource use were based on expert opinion. Effectiveness data was collected from the SHARP study, one Asia-Pacific RCT study and one open label uncontrolled study	Patients with advanced HCC not eligible for, or progressed after, surgical or loco-regional treatments. Patients were required to have at least one lesion that was measurable according to Response Evaluation Criteria in Solid Tumours (RECIST) and had not been previously treated with systemic therapy. In addition, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2, life expectancy of 12 weeks, adequate haematologic and renal function and Child-Pugh A liver function status.	Sorafenib vs PBO: Incremental QALY gain: 0.367	Sorafenib vs PBO: Incremental cost: £13,809	£37,670 per QALY gained (in combination with Patient Access Scheme)

5	**SMC 2011** *(SMC.No. 482/08)* **(55)**	2010	A Markov model was used to evaluate the cost-effectiveness of Sorafenib vs placebo from a NHS perspective. In the model three health states were included (progression free survival, progressive disease and death). For this model a time horizon of 14 years was applied. Cost and resource use data were based on expert opinion and effectiveness data was collected from a phase III placebo-controlled, double-blind study	Patients with advanced HCC not eligible for, or progressed after, surgical or loco-regional treatments. Patients were required to have at least one lesion that was measurable according to Response Evaluation Criteria in Solid Tumours (RECIST) and had not been previously treated with systemic therapy. In addition, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2, life expectancy of 12 weeks, adequate haematologic and renal function and Child-Pugh A liver function status.	Sorafenib vs PBO: Incremental QALY gain: 0.36	Sorafenib: NR PBO: NR	£ 67,012 per QALY

6	**SMC 2008** *(SMC.No. 482/08)* **(62)**	2008	A Cost-utility analysis was used to evaluate the cost-effectiveness of Sorafenib vs placebo from a NHS perspective. A time horizon of 14 years was used. Cost and resource use data was based on expert opinion and the effectiveness data was collected from one phase III placebo-controlled, double-blind trial	Patients with advanced HCC not eligible for, or progressed after, surgical or loco-regional treatments. Patients were required to have at least one lesion that was measurable according to Response Evaluation Criteria in Solid Tumours (RECIST) and had not been previously treated with systemic therapy. In addition, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2, life expectancy of 12 weeks, adequate haematologic and renal function and Child-Pugh A liver function status.	Sorafenib vs PBO: 0.52 years gain in life expectancy	Sorafenib: NR Placebo: NR	£45,596 per life year gained

7	Carr et al 2010 (49)	2010	A Markov model was used to evaluate the cost effectiveness of Sorafenib vs. BSC in advanced HCC from a US third-party-payer perspective. The model consisted of 4 health states:1st line no progression, 1st line continued post progression, BSC post progression and death. For this model a time horizon of 14 years, a cycle length of 1 month, and a discounting rate of 3% for both costs and effects, were used. The following model assumptions were taken into account • The HCC population and the efficacy data from the SHARP trial, were generalisable to the USA; • Resource use based on US expert opinion; • From the grade 3 or 4 AE occurring in at least 10% of the sorafenib patients,were assumed to have cost consequences and were included in the analysis; • AE rate constant over time • Patients continued on sorafenib treatment for 1 further month after progression.	In this model patients with advanced HCC were included. Criteria that applied to these patients were: • Life expectancy of at least 12 weeks • at least one tumour lesion that had not been previously treated with local therapy • an ECOG PS of 0,1 or 2	Sorafenib: 1.58 LY BSC: 1.02 LY	Sorafenib: $29,582 BSC: $0	$62,473 per LY gained

8	Camma et al 2013 (48)	2012	A Markov model was used to assess the cost effectiveness of sorafenib versus BSC. The model consisted of 3 health states: BCLC B HCC, BCLC C HCC and death. The health states were mutually exclusive, i.e., a patient could experience a single health state at any given time. For each transition, we obtained the time-dependent transition rates by assuming a Weibull distribution, parameters of which were estimated using available data. For this model a time horizon of 5 years and a discounting rate of 3% for both costs and effects were used. The analysis was conducted from an Italian third-party managed-care payer perspective. Cost and resource used were obtained from literature. Effectiveness data came from the SOFIA study and (NICE) technology appraisal guidance 178.	For this model a cohort of Caucasian male patients was assumed. The following inclusion criteria were used: • The patients were 67 years' old • Diagnosed with either BCLC C HCC (75%), or BCLC B HCC who failed locoregional therapies (25%) • had well-compensated cirrhosis, ECOG performance status of 0-1	• Full dose Sorafenib for BCLC B+C; LYG: 0.18 QALY:0.16 • Dose-adjusted Sorafenib for BCLC B+C: LYG:0.59 QALY:0.44 • Full dose Sorafenib for BCLC B: LYG:0.4 QALY 0.32 • Dose-adjusted Sorafenib for BCLC B: LYG: 0.5 QALY: 0.38 • Full dose Sorafenib for BCLC C: LYG:0.18 QALY:0.16 • Dose-adjusted Sorafenib for BCLC C: LYG:0.59 QALY 0.44 BSC: 0	• Full dose Sorafenib for BCLC B+C: €16,081 • Dose-adjusted Sorafenib for BCLC B+C: €19,994 • Full dose Sorafenib for BCLC B: €24,224 • Dose-adjusted Sorafenib for BCLC B: €26,914 • Full dose Sorafenib for BCLC C: €14,841 • Dose-adjusted Sorafenib for BCLC C: €16,665 • BSC: €4142	• Full dose for BCLC B+C; €63,197/LYG and €69,344/QALY • Dose-adjusted for BCLC B+C: €25,874/LYG and €34,534/QALY • Full dose for BCLC B: €44,794/LYG and €57,385/QALY • Dose-adjusted for BCLC B: €41,782/LYG and €54,881/QALY • Full dose for BCLC C: €59,922/LYG and €65,551/QALY • Dose-adjusted for BCLC C: €20,896/LYG and

9	Muszbek et al 2008 (53)	2008	A Markov model with 4 health states was used to assess the cost-effectiveness of sorafenib versus BSC from a Canadian Provincial Ministry of Health perspective. The four main health states included: First line treatment – no progression; First line treatment continued – post progression; BSC – post progression; Death. Patients received first-line treatment until documentation of disease progression or until a treatment-limiting adverse event (AE) occurred. At the point of progression, patients on sorafenib could either continue on first-line treatment with sorafenib or switch to BSC (palliative care). Patients on first line treatment with BSC continued on BSC post progression. For this model a time horizon of 14 years, a cycle length of 1 month, and a discounting rate of 5% for both costs and effects were used. Costs were obtained from several Canadian costing databases and resource use was obtained from expert opinion. Effectiveness data used came from the SHARP trial.	Patients included in the model were diagnosed with advanced HCC. Other inclusion criteria used were: • 18 years or older • At least life expectancy of 12 weeks • Unsuitable for surgical or loco-regional treatments. • At least one tumour lesion that had not been previously treated • ECOG PS 0,1 or 2	Sorafenib: 1.51 LY BSC: 1.02 LY	Sorafenib: CAN$47,272 BSC: CAN$10,309	CAN$75,759 per life year gained

10	Muszbec, Vioix et al 2010 (52)	2010	A Markov model was used to assess the cost effectiveness of sorafenib+ BSC versus BSC alone from a Brazilian private health care system perspective. For this model a lifetime horizon and discount rate of 5% for both costs and effects were used. Cost and resource use came from expert opinion and effectiveness data was obtained from the SHARP trial.	Advanced HCC	Incremental LYG: 0.49 LY	Sorafenib: US$58,977 BSC: $5,936	US$108,230 per life year gained
11	Muszbec, Munir et al 2010(51)	2010	A Markov model was used to assess the cost effectiveness of sorafenib+ BSC versus BSC alone from a Brazilian public health care system perspective. For this model a lifetime horizon and discount rate of 5% for both costs and effects were used. Cost and resource use came from expert opinion and effectiveness data was obtained from the SHARP trial.	Advanced HCC	Incremental LYG: 0.49 LY	Sorafenib: NR BSC: NR	US$77,923 per life year gained

12	Zhang, Yang et al 2015 (57)	2015	Decision analytic Markov model was used to assess the cost-effectiveness of sorafenib versus BSC from the Chinese payer perspective. The model consisted of three health states: Progression-free survival, progressive disease and death. For this model a cycle length of 1 month and discount rate of 3% for both costs and effects were used. A patient was considered to be in one of these three states at any given time. All patients began from the PFS state and evolved from one state to another on the basis of the transition probabilities as well as the transition direction. Transition probabilities of health states were estimated as follows: P (1 month) = 1 − (0.5)(1/median time to event); this equation was derived from the following equations: P= 1 − e −R and R= − ln[0.5]/(time to event/number of treatment cycles). Effectiveness data came from this publication for Sorafenib, from an Asia-pacific trial and (NICE) technology appraisal guidance 178.	Patients included in the model were diagnosed with advanced HCC. Other inclusion criteria included: • ECOG performance status: 0–2; • age at least 18 years; • Treatment with Sorafenib as a first-line treatment regimen from 2010 to 2013 until disease progression or intolerance of adverse events (AEs); • Child-Pugh class A or B • Adequate hematologic/clotting and renal function	Incremental QALY: 0.18 QALYs	Sorafenib: $19,495.05 BSC: $897.21:	$101,399.11 per QALY

13*	Chan et al 2016 & Leung et al 2016 (42) (43)*	2016	A Markov model was developed to assess the cost effectiveness of sorafenib versus Stereotactic body radiotherapy (SBRT) from a National Health Insurance Bureau perspective. The model consisted of three health states; stable disease, progressive disease and death. For this model a time horizon of 5 years, a cycle length of 1 month, and discount rate of 3% for costs and effects were used. The model did not include deaths from natural causes occurring in any health state. Death from cancer was assumed to happen after disease progression. Cost were obtained from a costing database and resource use was based on expert opinion. For effectiveness data the SHARP study and sequential phase I and II trials of SBRT were used	Advanced HCC	Sorafenib: 3.07 QALY SBRT: 2.81 QALY	Sorafenib: NT$ 21,66,079.7 SBRT: NT$ 1,197,039.2	NT$3,788,238 per QALY

14 †	Hubert et al 2016 (41)	2016	A budget impact analysis was conducted to determine the budget impact of transarterial radioemobilisation (TARE) with Yttrium-90 Glass microspheres versus transarterial chemoembolization (TACE) and sorafenib for hepatocellular carcinoma from a Canadian hospital perspective. Costs were obtained from a costing database and resource use was based on expert opinion	Patients with hepatocellular carcinoma (HCC) at intermediate (BCLC-B stage) or advanced (BCLC-C) stage.	NR	NR	For a Canadian hospital managing 200 HCC patients annually, reimbursing TARE incurred savings of approximately $37,000, $55,000 and $75,000 in years 1, 2 and 3. In year 3, it includes incremental costs of $207,000 for device acquisition, savings of $281,000 for administration and savings of $1,000 in AE management.

15	Rognoni et al 2017 (59)	2017	A Markov model evaluating the cost-effectiveness of transarterial radioembolisation (TARE) and sorafenib from an Italian healthcare perspective. The model incorporates five health states: stable disease, progression, death for disease, death for other causes and post-transplantation. The model has a cycle length of one month over a life time horizon.	Intermediate HCC patients Advanced HCC patients	TARE QALY's Intermediate stage: 1.178 Advanced stage: 0.639 Sorafenib QALY's Intermediate stage: 0.638 Advanced stage: 0.568 TARE LYG Intermediate stage: 2.531 Advanced stage: 1.445 Sorafenib LYG Intermediate stage: 1.575 Advanced stage: 1.306	TARE Intermediate stage: € 31.071 Advanced stage: € 21,961 Sorafenib Intermediate stage: € 29,289 Advanced stage: € 30,750	Intermediate stage: ICER: € 1.865 per LYG ICUR: € 3.302 per QALY Advanced stage: ICER: dominant CUR: dominant
16*	Parikh et al 2016 and Parikh et al 2017 (44) **(45)**	2017	A secondary analysis of SEER-Medicare data to evaluate survival benefit and cost-effectiveness of sorafenib from the Medicare perspective.	Advanced HCC patients enrolled in Medicare parts A & B.	Sorafenib Median survival: 0.41 Control group Median survival: 0.17	Sorafenib: $ 31.364 Control group: $ 10.950	$84.250 per LYG

17*	Zhang et al 2016, Zhang et al 2016 (46) (47)	2016	A Markov model to evaluate the cost-effectiveness of FOLFOX4 compared to sorafenib from the Chinese societal perspective. The clinical data for the model were obtained from the EACH trial and the ORIENTAL trial. The model incorporated three health states: progression free survival, progressive disease and death. A cycle length of 1 month over a time horizon of 10-years was taken into account.	Patients with advanced HCC with an average age of 49.53 years in the FOLFOX4 group and 51 years in the sorafenib group.	FOLFOX4: 0.3808 Sorafenib: 0.3935	FOLFOX4: $ 68.76.02 Sorafenib: $ 18.748	$934,801.57/ QALY
18	Zhang, Yang et al 2016 (60)	2016	A Markov model comprising three health states: progression free survival, progressive disease and death was created to assess the cost-effectiveness of antiviral therapy + sorafenib compared to sorafenib form the Chinese patient's perspective. The cycle length was 1 month over a life span time horizon. Efficacy data were derived from medical records.	Patients with confirmed advanced HCC (histologically or clinically confirmed); Eastern Cooperative Oncology Group (ECOG) performance status (PS): 0-2; Child-Pugh liver function class A/B; treatment with sorafenib as first-line regimen from 2010 to 2013; detectable hepatitis B surface antigen (HBsAg) positive; without co-infection with other viruses	Antiviral therapy + Sorafenib: 0.68 Sorafenib: 0.42	Antiviral therapy + sorafenib: $25.026,04 Sorafenib: $20.249,64	$18,370.77/ QALY

19	Qin et al 2016 (58)	2016	A Markov model was constructed to assess the cost-effectiveness of FOLFOX4 compared to sorafenib using a one-month cycle length over a life-time horizon. The analysis was conducted from the Chinese health care -and patient perspective. Overall- and progression-free survival rates and rates of adverse events (AE) were obtained from two randomized controlled studies of advanced HCC patients from Asia; EACH for FOLFOX4 and ORIENTAL for sorafenib.	Patients with advanced HCC	FOLFOX4: 0.42 Sorafenib: 0.38	FOLFOX4: ¥54,358 Sorafenib: ¥121,408	NR: based on own calculations (Δcosts/ΔQALYs), the ICER is: ¥-1.676.250 per QALY in favour of FOLFOX4
20	Lockart et al 2016 (63)	2016	Hospital records were reviewed to identify HCC-patients to explore time to initiation, treatment tolerability, dosing adjustments, duration of therapy and to estimate the cost per patient treated at a metropolitan tertiary hospital.	Patients who were treated with sorafenib and were treated at a metropolitan tertiary hospital	Not reported	Sorafenib (per patient): $29,873	Not reported

* - both publications refer to the same economic model, † – budget impact evaluation and not an economic model

B.3.2 Economic analysis

The results of the economic literature search show that the majority of models in this disease area have Markov designs and are structured around 3 health states i.e. 1) preprogression/stable 2) progressed disease, and 3) death. The models submitted to UK Health Technology Assessment bodies in advanced HCC have compared sorafenib against BSC and were prepared by Bayer. These were Markov models and in terms of model structure have been accepted. In keeping with the previous models in this disease area a *de novo* economic model has been built around three health states 1) Progression free 2) progression and 3) death. This 'standard' three-state Markov model is well-established in the oncology disease area and appropriate for the modelling of the cost-effectiveness of regorafenib against best supportive care.

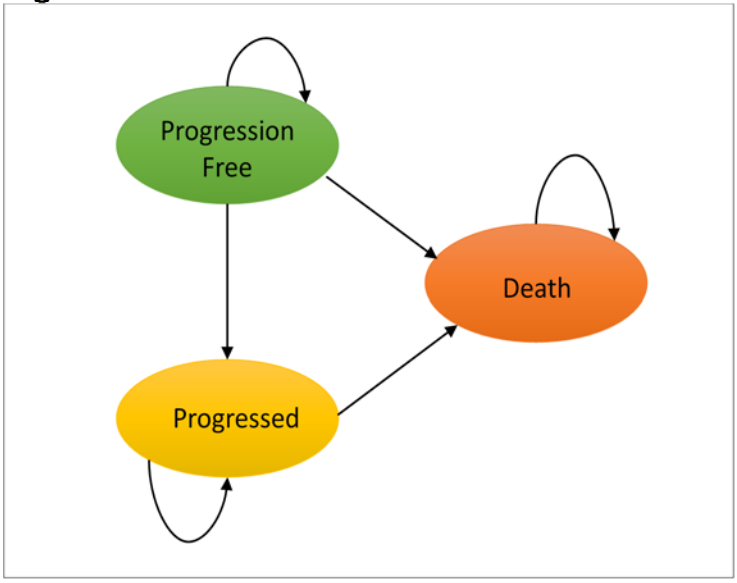
Patient population

Adult patients with advanced HCC who have been previously treated with sorafenib.

Model structure

A Markov model, presented in Figure 13, was developed in Microsoft Excel to compare treatment with regorafenib to BSC alone i.e. regorafenib (+ BSC) compared to placebo (+ BSC). Area under the curve survival analysis was used to estimate the proportion of patients in the three health states over time. This approach does not require explicit transition probabilities to be defined between health states. The partitioned survival model framework is a commonly used approach in advanced oncology indications and has been used in previous NICE submissions (54).

Figure 13. Model structure



All patients enter the model in the progression free (stable disease) health state and are at risk of disease progression or death. Patients receive second-line treatment (with regorafenib or BSC) until documented disease progression or until a treatment limiting adverse event occurs or death. In the RESORCE study some patients continued to receive treatment post-progression and this is factored into the model – see below:

- Progression free – within this health state it is assumed that the patient's disease is in a stable or responding state and not actively progressing. Progression was defined in the RESORCE trial according to the RECIST and mRECIST criteria (Table 14 and Appendix L). In this health state patient's quality of life is assumed to be higher than patients whose disease has progressed. Patients can experience adverse events in any cycle (according to the treatment received) and incur disutility associated with such events.

- Progressed disease – patients enter this health state if their disease progresses (according to modified RECIST criteria). In clinical practice patients would typically discontinue regorafenib at the time of progression and continue to receive BSC alone. However, in the RESORCE trial some patients continued to be treated once progressed and therefore in the model a

proportion of patients also continue to receive regorafenib for a short period of time (as per the RESORCE study)

- Death – this is an absorbing health state

Cycle length

The cycle length is 28 days which is in keeping with the dosing schedule for regorafenib i.e. one cycle is 3 weeks treatment followed by one week off treatment.

Half cycle correction is applied.

Time horizon

A lifetime horizon (15-years) is used in the base case. This duration is sufficient to capture the survival differences between regorafenib and BSC.

Table 34. Features of the economic analysis

	Previous appraisals	Current appraisal	
Factor	**Sorafenib CDF reappraisal [ID1012]**	**Chosen values**	**Justification**
Time horizon	14 years	Lifetime (15 years)	In this disease 15-years is effectively a lifetime time horizon which is appropriate in disease areas where differences in survival are expected.
Effect beyond the duration of the trial evidence	Overall survival extrapolated based on lognormal parametric curve	Overall survival extrapolated based on lognormal parametric curve	The lognormal provided the best fit statistically and was clinically plausible. Scenario analyses using other extrapolations are also presented
Source of utilities	The FACT-G patient reported outcome questionnaire was administered during the SHARP study. Based on the algorithm by Dobrez et al, four items from the FACT-G part of FACT-Hep (were selected and used to estimate utility scores based on correlation with Eastern Clinical Oncology Group performance status scores and TTO utilities Pre-progression utility: 0.689 Post-progression utility: 0.711 Adverse events disutility: -0.009	Based on EQ-5D data collected during the RESORCE study Pre-progression utility: 0.811 Post-progression utility: 0.763 Adverse events disutility: 0.014	Other than utility values from the SHARP study, no other published values were found for a population with advanced HCC according to progression status. The EQ-5D patient level data, collected during the RESORCE study, aligns with the NICE reference case and are the most appropriate values for use in this appraisal.

Source of costs	A physician survey was conducted to estimate resource use for patients on sorafenib	The resource units as submitted by Bayer for the CDF reappraisal of sorafenib are used with unit costs applied from 2015/16	Sorafenib has been available for use in advanced HCC since 2008 and consequently physicians are able to estimate resource use based on actual clinical experience. Conversely there is no experience in the clinical setting relating to the use of regorafenib in the same disease area. The resource units used for sorafenib are considered applicable for use for regorafenib as: • the burden of disease experienced by patients on sorafenib and regorafenib is comparable as shown by the near identical median survival of BSC patients in the SHARP (sorafenib) and RESORCE (regorafenib) studies i.e. 7.9 and 7.8 months, respectively • both sorafenib and regorafenib are from the same drug class • the use of the same resource estimates helps ensure consistency across appraisals

Intervention technology and comparators

The intervention considered is regorafenib 160mg (4 x 40mg tablets) administered daily for 3 weeks followed by the fourth week off treatment - as per the licenced dosing posology. This treatment schedule continues until progression, unacceptable toxicity or death. Some patients may continue treatment post-progression if the treating physician considered some benefit was being experienced by the patient. Post-progression treatment was allowed in the study, and is included in the economic model according to what was observed in the RESORCE study. Patients in the RESORCE study received dose reductions in the event of adverse events - see 'Dose modification'.

The comparator to regorafenib is BSC. Best supportive care includes any concomitant medications: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumour agents or antineoplastic chemo/hormonal, immunotherapy.

Treatment continuation rule

As stated above, in the base case analysis the post-progression treatment is implemented in the model as per the RESORCE study. It is expected that in clinical practice the extent of post-progression treatment would be less as many physicians wouldn't treat beyond progression. Scenario analyses are presented whereby the extent of post-progression treatment is limited.

B.3.3 Clinical parameters and variables

Clinical inputs

The efficacy and clinical data used in the cost-effectiveness model are based upon the RESORCE study. The inputs used in the cost-effectiveness analysis include:

1. progression free survival (PFS)
2. overall survival (OS)
3. discontinuation from treatment i.e. discontinuation rates are different in the progression free and progressed disease health states.
4. Dose modifications
5. Adverse events

The inputs were derived using patient-level data from RESORCE and are described in detail below.

Extrapolation of outcomes beyond the trial period

At the date of data lock (29 February 2016) 61.5% of patients in the regorafenib group and 72.2% of patients in the BSC group had died meaning that the overall survival data was not mature (see 'Primary Endpoint' – page 56). Consequently overall survival needed to be extrapolated in the economic model. Conversely, for PFS the Kaplan-Meier data show that both treatment arms reach zero within the period of the trial i.e. a probability of zero of not having progressed by 29 months for both treatment arms. The PFS data from RESORCE therefore represents the full pattern of progression and that the analysis would not benefit from curve-fitting.

Overall survival

For OS, standard parametric curve fitting was performed using patient-level data from RESORCE. A systematic approach was taken to determine how to model OS. Firstly, it was assessed whether the cox proportional hazards assumption was violated or not. Next, parametric fits (with the following distributions were fitted to the trial data to each arm, as recommended in the NICE DSU guidance:

- Exponential
- Weibull
- Gompertz
- Gamma
- Lognormal
- Loglogistic

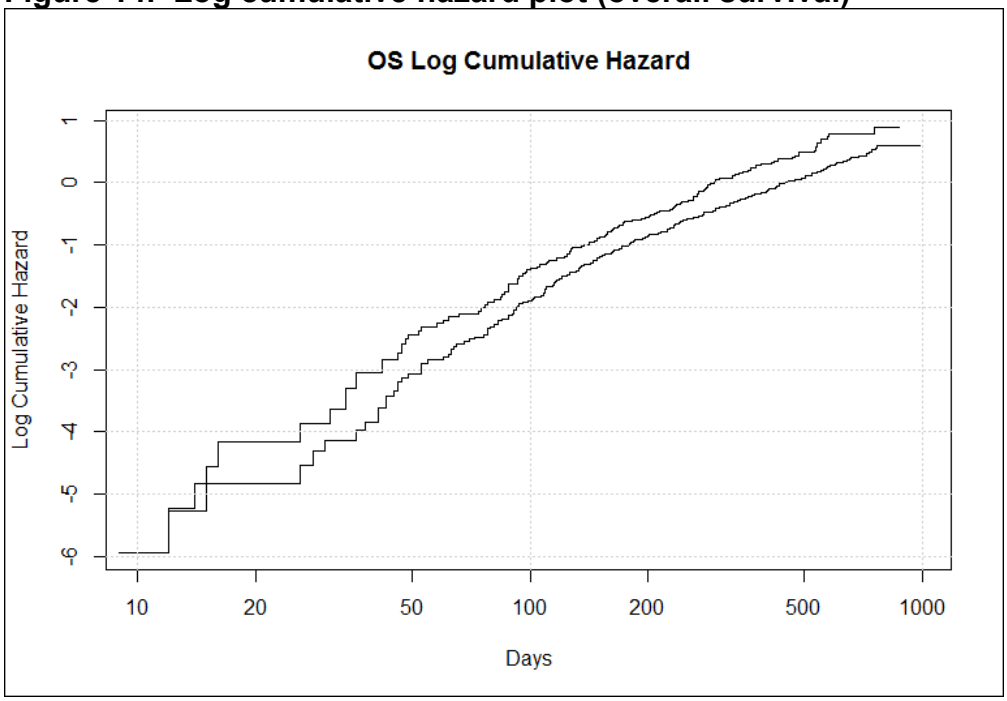
Fits were estimated either independently for each trial arm or dependently – fitting one model for both arms and estimating a treatment effect between the regorafenib and BSC arms – depending on whether the proportional hazards assumption could be deemed to hold.

The different parametric fits were examined for whether they fitted the data well 1) visually 2) statistically (using AIC and BIC criterion), and 3) and according to clinical plausibility.

Assessment of proportionality of hazards observed in RESORCE

The choice of parametric survival extrapolation model for OS was first informed by assessing whether the proportional hazards assumption holds in the trial data. Visual inspection of the log cumulative hazard plot was undertaken to determine whether the BSC and regorafenib arms of the trial have parallel log cumulative hazards over time. In Figure 14, the top curve represents the BSC trial data and the bottom regorafenib.

Figure 14. Log cumulative hazard plot (overall survival)



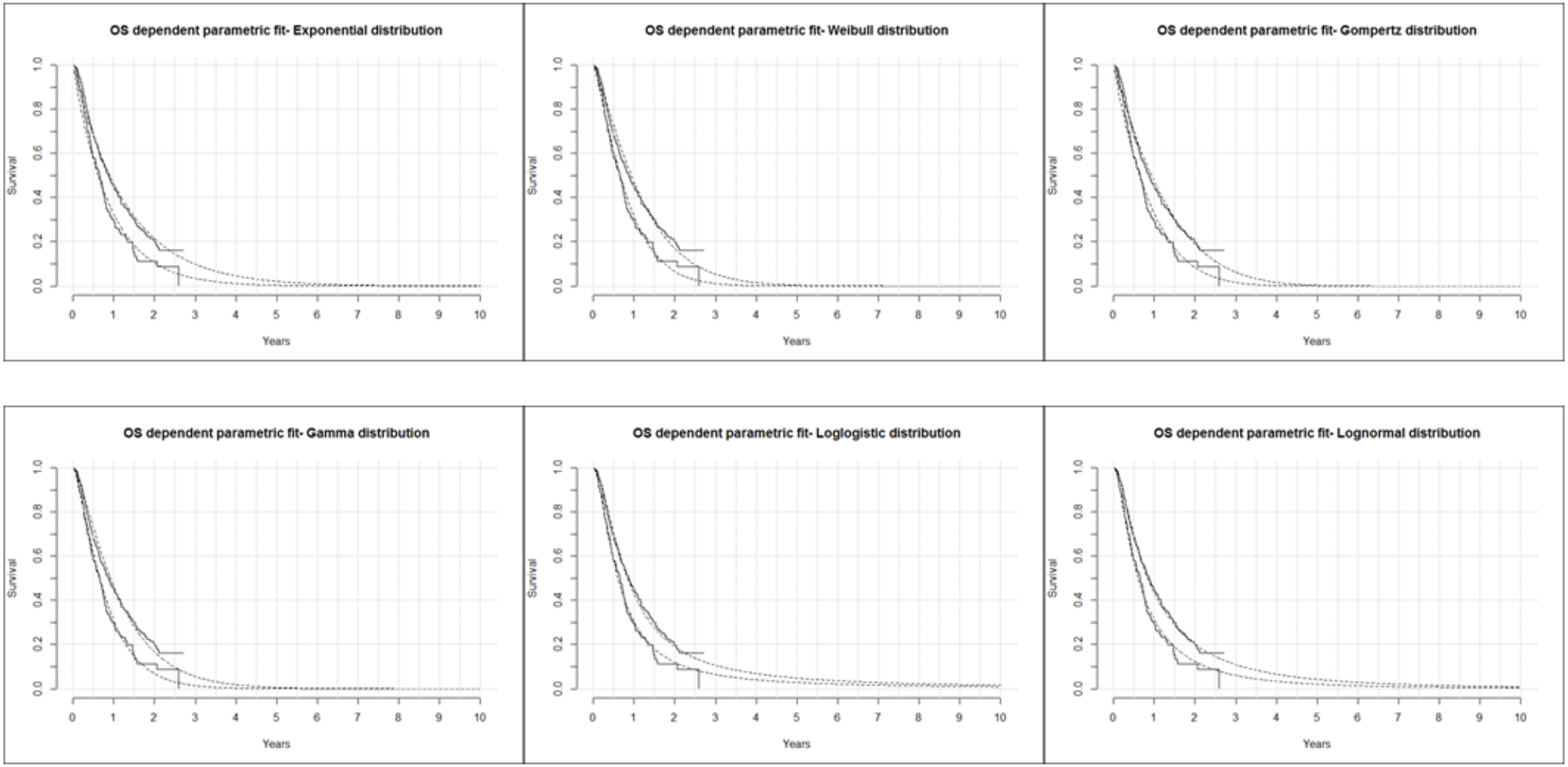
Top curve – BSC; bottom curve – regorafenib

Besides a crossing of the treatment arms around day 15, the BSC and regorafenib arms of the RESORCE trial appear parallel over time. A Grambsch and Therneau's correlation test between Schoenfeld residuals and the log of time resulted in a p-value of 0.331; this value is not statistically significant, so the proportional hazards assumption is not violated. Coupled with the largely parallel log cumulative hazard curves, this result suggests that the proportional hazards assumption is plausible, so survival was modelled using dependent survival curves.

Dependent survival models

For each of the six distributions, a single parametric curve was fitted to both the BSC and regorafenib arms in the RESORCE trial with an adjustment factor (a coefficient) for the treatment effect of regorafenib on the scale and shape of the curves. These curves are presented in Figure 15. Enlarged versions of these curves can be found in Appendix N.

Figure 15. Dependent parametric fits (overall survival)



The dotted curves are the fitted extrapolations, and the solid curves are the raw trial data. The upper curves represent the regorafenib arm, and the lower curves represent the BSC arm

Statistical Fit

Table 35 shows the estimated fit distributions arranged from the one with the lowest AIC and/or BIC to the highest AIC and/or BIC. The Lognormal and Loglogistic curves fit the data best based on these measures.

Table 35. AIC and BIC from lowest to highest – OS dependent distributions

Distribution	AIC	BIC
Lognormal	5197.513	5210.565
Loglogistic	5199.734	5212.787
Gamma	5211.014	5224.067
Weibull	5218.877	5231.929
Gompertz	5238.261	5251.314
Exponential	5239.994	5248.696

Visual fit

Visual inspection of the fitted OS extrapolations (Figure 15) suggests that all extrapolations fit the data relatively well. The Lognormal and Loglogistic curves have longer tails therefore predicting a greater chance of survival at the outer timepoints. While all other models estimate survival to be 0% after 5 years for the BSC arm, the loglogistic and lognormal extrapolations estimate that 3% and 2% of patients will be still be alive, respectively. The Weibull, Gompertz, and Gamma fit the data visually well, with an underestimation of survival in the regorafenib arm after about 2 years. Their tails eventually converge to zero by 5 years (the Gamma curve reaches zero very shortly after 5 years).

Clinical validity

Beyond the trial data there is no clinical evidence for regorafenib to support the selection of one curve over another. Table 36 shows the survival probabilities predicted by each curve alongside Kaplan-Meier (KM) data from the RESORCE trial. A pragmatic but systemic approach was taken with respect to determining which curve(s) were the most clinically plausible.

The predictions from each of the curves at the 35 cycle timepoint (the point at which the primary endpoint was reached and data lock performed) are compared to the Kaplan-Meier curve. Those with predicted survival that were furthest from the trial

results were considered clinically implausible and were removed. Beyond the trial data it was more difficult to establish a 'clear winner' for selection. The predictions of survival at different points in time are discussed to help inform clinical plausibility.

At the 35 cycles timepoint the Kaplan-Meier data shows 9% of patients alive in the BSC arm and 16% in the regorafenib arm. All the parametric curves underestimate the survival versus what was observed in the RESORCE study. The loglogistic and lognormal curves provided the closest match to the KM data for both the regorafenib and BSC arms. The Weibull, Gompertz and Gamma curves significantly underestimated the survival in both arms at the 35 cycle timepoint and can be considered clinically implausible on this basis. The exponential curve was a mixed case i.e. it provided as close a match to the trial data as the loglogistic and lognormal curves for the regorafenib arm, however it was further away from the BSC KM data at this timepoint.

At the 5-year timepoint there is no clinical data against which to compare the parametric curves. At this timepoint the exponential curve predicts no survival in the BSC arm and 2% in the regorafenib arm. In contrast both the loglogistic and lognormal arms predict a small chance of survival in the BSC arm with a slightly greater chance of survival in the regorafenib arm – the difference between the arms being consistent at 2% for each of the curves.

At the 10-year timepoint the exponential curves predicts no survival in either arm. The lognormal curve predicts no survival in the BSC arm and 1% survival in the regorafenib arm. The loglogistic curve is the only curve to predict survival, albeit small, in the BSC arm at this timepoint.

Assessment of clinical plausibility

Based on the above, 3 curves demonstrate clinical plausibility i.e. exponential, loglogistic and the lognormal. Based on the significant underestimation of BSC survival at the 35 cycle timepoint the exponential curve is considered the least plausible of the three. In some respect the lognormal might be considered to have marginally more plausibility than the loglogistic curve as it estimates no survival at the 10-year timepoint for BSC and a lower chance of survival compared to the

loglogistic curve. However, the differences are very small and both the lognormal and loglogistic curves could be considered clinically plausible.

Table 36. Overall survival probabilities

	Kaplan-Meier	Loglogistic	Weibull	Lognormal	Gompertz	Exponential	Gamma
Regorafenib							
2 years	0.21	0.19	0.17	0.20	0.19	0.21	0.17
35 cycles	0.16	0.13	0.08	0.13	0.09	0.13	0.08
5 years		0.05	0	0.04	0	0.02	0.01
10 years		0.02	0	0.01	0	0	0
BSC							
2 years	0.11	0.12	0.07	0.12	0.08	0.11	0.07
35 cycles	0.09	0.08	0.02	0.07	0.03	0.05	0.02
5 years		0.03	0	0.02	0	0	0
10 years		0.01	0	0	0	0	0
Difference: regorafenib minus BSC							
2 years	0.11	0.07	0.10	0.08	0.11	0.1	0.1
35 cycles	0.07	0.05	0.06	0.06	0.06	0.08	0.06
5 years		0.02	0	0.02	0	0.02	0.01
10 years		0.01	0	0.01	0	0	0

Summary

After consideration of the information above (statistical fit, visual fit and clinical plausibility) it is considered that the lognormal curve is the most appropriate choice for extrapolation beyond the trial to the data. The loglogistic curve also represents a plausible alternative.

Support for the use of the lognormal curve also comes from the NICE appraisals of sorafenib where the lognormal curve was also found to be the best fit. Being in a comparable population the best fitting curve for sorafenib also provides some support for the choice of curve for regorafenib.

Scenario analyses presenting cost-effectiveness using each of the parametric distributions is also presented in this submission (see Scenario analysis – page 160).

Adverse events

Treatment-emergent adverse events (TEAEs) in the model are limited to grade 3/4 events that occurred in ≥5% of patients in either the regorafenib or BSC arms of the

RESORCE trial. This is a standard approach to including TEAEs, as grade 3/4 events are likely to be both costlier and have a greater impact on patient's quality of life than grade 1/2 events. TEAEs included in the model are:

- Anaemia
- Ascites
- Aspartate aminotransferase increase
- Blood bilirubin increase
- Fatigue
- Hypertension
- Hypophosphatemia
- Palmar-plantar erythrodysaesthesia syndrome (Hand Foot Skin reaction – HFSR)

Analyses

The rate per cycle for TEAEs (using CTCAE definitions) was calculated using patient-level data. If an adverse event occurred in two subsequent cycles, the adverse event was registered in both cycles. Duplicates and additional recordings of the same TEAE within one cycle in the same subject were removed. If a patient experienced more than one TEAE – e.g. anaemia and hypertension – within one cycle, both were taken into account.

The proportions of the TEAEs per number of patients within a cycle are presented in Table 38. This enabled the overall average of the TEAEs to be calculated per treatment arm. These averages are given in the last row of Table 38. In this calculation every episode of TEAEs were taken into account and therefore captured multiple TEAEs in the same patient. For the patients on regorafenib, on average 5.55% TEAEs occurred in each cycle. This average proportion was calculated by adding all average proportions for each TEAE in the regorafenib group (i.e. 0.40+0.45+0.74+0.41+0.38+1.15+1.25+0.77=5.55). For the patients on BSC, this proportion was 5.06%. These two proportions were used to apply TEAE-associated costs and to apply adverse event disutility. The overall treatment-arm specific TEAE rates (Table 37) are applied each cycle to patients who are on treatment i.e.

- A per cycle rate of 5.55% is applied to regorafenib patients who are on treatment (pre and post-progression)

- A per cycle rate of 5.06% is applied to BSC patients who are on treatment (pre and post-progression)

Table 37. Rate (per cycle) of grade 3 or 4 TEAEs

	Rate per cycle
Regorafenib	5.55%
BSC	5.06%

Table 38. Proportions of TEAE in SAF population per cycle, stratified by treatment arm

Cycle	Anaemia		Ascites		Aspartate aminotransferase increase		Blood bilirubin increase		Fatigue		Hypertension		Hypophosphatemia		Palmar-plantar erythrodysaesthesia syndrome	
	REG	BSC	REG	BSC	REG	BSC	REG	BSC	REG	BSC	REG	BSC	REG	BSC	REG	BSC
1	0.27	0.54	0.27	0.54	6.01	3.80	3.55	1.09	2.19	1.09	9.29	2.72	3.01	1.09	7.10	0.54
2	0.91	1.17	0.30	4.09	1.82	4.68	2.73	2.34	1.21	1.17	6.06	1.17	2.73	0.00	2.42	0.58
3	0.39	1.04	1.95	1.04	0.78	5.21	1.17	2.08	0.00	0.00	2.73	1.04	1.56	1.04	1.95	0.00
4	1.38	1.52	0.92	0.00	1.84	4.55	0.00	4.55	1.38	0.00	2.30	0.00	2.76	0.00	1.38	0.00
5	1.10	4.00	0.00	0.00	1.66	4.00	1.10	0.00	2.21	0.00	1.10	0.00	1.66	0.00	1.66	0.00
6	0.65	0.00	1.95	3.03	1.95	3.03	1.30	3.03	1.30	0.00	0.65	0.00	1.30	0.00	0.65	0.00
7	1.60	0.00	0.00	3.70	1.60	3.70	0.80	3.70	0.00	0.00	0.00	0.00	1.60	0.00	0.80	0.00
8	0.91	5.26	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.26	0.00	5.26	0.91	0.00	2.73	0.00
9	0.00	7.14	0.00	0.00	0.00	0.00	1.08	0.00	1.08	0.00	3.23	0.00	0.00	0.00	1.08	0.00
10	0.00	0.00	1.19	0.00	1.19	0.00	0.00	0.00	0.00	0.00	1.19	0.00	0.00	0.00	0.00	0.00
11	3.90	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.30	0.00	0.00	0.00
12	0.00	0.00	0.00	11.11	1.54	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
13	0.00	11.11	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
14	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.13	0.00	0.00	0.00
15	0.00	0.00	0.00	16.67	0.00	0.00	0.00	0.00	0.00	0.00	4.35	0.00	0.00	0.00	0.00	0.00
16	0.00	0.00	2.63	0.00	0.00	0.00	0.00	0.00	2.63	0.00	0.00	0.00	0.00	0.00	0.00	0.00
17	0.00	0.00	0.00	0.00	3.23	0.00	0.00	0.00	0.00	0.00	6.45	0.00	0.00	0.00	0.00	0.00
18	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	3.57	0.00	0.00	0.00
19	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
20	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.55	0.00	0.00	0.00
21	0.00	0.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
22	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	5.56	0.00
23	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
24	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

25	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
26	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
27	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
28	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	14.29	0.00	0.00	0.00
29	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30	0.00	--	0.00	--	0.00	--	0.00	--	0.00	--	0.00	--	0.00	--	0.00	--
31	0.00	--	0.00	--	0.00	--	0.00	--	0.00	--	0.00	--	0.00	--	0.00	--
32	0.00	--	0.00	--	0.00	--	0.00	--	0.00	--	0.00	--	0.00	--	0.00	--
EOT	2.22	0.88	0.56	2.63	2.78	3.51	1.67	4.39	0.56	0.00	0.56	0.88	0.00	0.88	0.00	0.00
Average	0.40	1.09	0.45	1.43	0.74	1.08	0.41	0.71	0.38	0.25	1.15	0.37	1.25	0.10	0.77	0.04

EOT – end of treatment; REG -regorafenib; BSC – best supportive care

Discontinuation from treatment

The RESORCE trial included patients who received treatment after progression. In the trial, patients also discontinued at, and before progression. These groups were identified and stratified by treatment arm. The modelling of treatment discontinuation is described below.

Discontinuation of treatment for any reason is modelled throughout these three phases:

- Before disease progression
- At the point of progression (i.e. during the final treatment cycle before progressing)
- After the disease has progressed

Discontinuation before progression

[redacted] patients out of 293 ([redacted]%) treated with regorafenib discontinued treatment for an average of 13.71 days before moving to the progressed health state, i.e. less than a full 28-day cycle (see Table 39). For the purpose of the model, it is assumed that patients who progressed during their final treatment cycle incur the full cost of regorafenib for that cycle.

In the model, [redacted]% of patients (out of [redacted]) discontinued treatment for more than one cycle prior to disease progression. The median PFS in the model is 3.1 months, therefore it assumed that on average [redacted]% (using a rate to probability calculation of 1-EXP(ln(1-[redacted]3.1) of patients will discontinue treatment during each pre-progression cycle.

Discontinuation after progression

[redacted] of patients continued to receive regorafenib after disease progression (Table 39). Patients who continued to receive regorafenib after progression continued for an average duration of [redacted] days (approx. [redacted] treatment cycles, median: [redacted] days; range: 1-629 days). Patients on BSC who continued treatment after progression (n=[redacted]; [redacted]%) continued for an average length of [redacted] days (~[redacted] cycles; median: [redacted] days; range: 1-531 days). Data from the trial show that there is a rapid discontinuation of treatment in the cycles following progression -

see Table 40. For example [redacted]% of regorafenib patients receive some post-progression treatment but 2 cycles after progression only [redacted]% of these patients are still being treated. The economic model uses the trial data as shown in Table 39 and Table 40 to model the proportion of patients who get post-progression treatment and their rate of discontinuation from treatment.

Table 39. Number of patients stratified for timing of discontinuation of treatment relative to time of progression (excludes patients censored for PFS)

Patient groups	Regorafenib	BSC	Total
Stop of treatment before or at progression	[redacted]	[redacted]	193
Continue treatment after progression	[redacted]	[redacted]	281
Total	293	181	474

Table 40. Treatment rate per cycle AFTER progression

Cycle AFTER progressing	Regorafenib	Best supportive care
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]
8	[redacted]	[redacted]
9	[redacted]	[redacted]
10	[redacted]	[redacted]
11	[redacted]	[redacted]
12	[redacted]	[redacted]
13	[redacted]	[redacted]
14	[redacted]	[redacted]
15	[redacted]	[redacted]
16	[redacted]	[redacted]
17	[redacted]	[redacted]
18	[redacted]	[redacted]
19	[redacted]	[redacted]
20	[redacted]	[redacted]
21	[redacted]	[redacted]
22	[redacted]	[redacted]

Dose modification

In the RESORCE study, the average daily dose was reported as 144.1mg for regorafenib. However, this dose was calculated only counting the days where treatment was taken i.e. days where no dose was taken were not included in the calculation of the average.

Patient level data was used to calculate the average dose (including dose interruptions) for patients taking regorafenib both pre and post-progression. The average daily dose of regorafenib prior to progression was [redacted]mg and the average daily dose of regorafenib in patients who had progressed was [redacted]mg. These are the doses used in the cost-effectiveness model.

Calculation of Transition probabilities

Parametric curve fitting is described in 'Clinical inputs' section – page 117. The proportion of patients in each health state over time was based on the area under the curve generated by the curves for Overall Survival and Progression Free Survival.

Transition probabilities over time

Transition probabilities do change over time according to the curve fitted to the clinical data from the RESORCE study. The movement of patients between the 3 health states is based on the parametric curves as described above and the different parametric curves allows for flexibility in the rate of change of the survival functions over time.

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life data from the RESORCE trial

Within the RESORCE trial, both the EQ-5D (3-level) and the FACT-Hep (version 4) were collected. Both instruments were self-administered by the patients at each treatment visit (day 1 of each treatment cycle). Questionnaires were completed at the start of each visit whilst the patient was receiving blinded treatment and before seeing the investigator or any study-related procedures were performed. In addition the questionnaires were also completed at the end of treatment visit. The utility values used in the economic model were calculated from this EQ5D data. The utility values are aligned to the reference case as 1) the EQ-5D is the tool preferred by NICE 2) the values are directly elicited from patients, and 3) the UK tariff was used.

EQ-5D results by treatment arm are presented in the clinical section under 'EQ5D' - page 68. For the model a patient-level data analysis was conducted to estimate the utility values according to the health states used in the model – see 132.

Mapping

No mapping was performed.

Adverse reactions

Based on the RESORCE study, grade 3 or 4 AEs resulting from treatment were considered for inclusion in the model. Only those AEs reported in ≥5% of patients in either the regorafenib or BSC arm were included. This is a standard approach to including TEAEs, as grade 3/4 events are likely to be both costlier and have a greater impact on patient's quality of life than grade 1/2 events. TEAEs included in the model are:

- Anaemia
- Ascites
- Aspartate aminotransferase increase
- Blood bilirubin increase
- Fatigue
- Hypertension

- Hypophosphatemia
- Palmar-plantar erythrodysaesthesia syndrome (Hand Foot Skin reaction – HFSR)

The rate of adverse events for each arm as incorporated in the model is described in 'Adverse events' – page 123. Adverse events could happen in any cycle throughout the model's time horizon. The only factor that could vary the impact of adverse events occurrence at different timepoints (at earlier or later stages of the patient's disease) is the discount rate, which is applied to all costs and outcomes in each cycle, including those related to adverse events.

Health-related quality-of-life studies from the literature

A literature search (see Appendix H) was conducted to locate utility values that were suitable for inclusion in the economic model. Values were required for pre-progression and progressed disease in a population of patients with advanced HCC. Several HRQOL publications reported quality of life values according to different instruments but preference-based utility values were not reported and these are not suitable for the economic model. Economic evaluations were available and the only source of utility values for patients with HCC was based on the SHARP study for sorafenib. The values from the sorafenib submissions to NICE and the SMC report utility values according to the same health states for a comparable population of patients and, having been used before are the only other alternative values for use in the economic model. However, these utility values have a lack of face-validity as the progressed utility value is numerically higher than the pre-progressed utility value. For the purposes of the economic evaluation of regorafenib the preferred values are those derived using the EQ5D collected in the RESORCE study (see Health-related Quality of life data used in the cost-effectiveness analysis - page 132). Although they lack face-validity, the values obtained from the SHARP study for sorafenib have been included in a scenario analysis.

Health-related quality-of-life data used in the cost-effectiveness analysis

Patients with hepatocellular carcinoma are heterogeneous, with a diverse range of underlying causes of cirrhosis, including hepatitis B, hepatitis C, alcoholism and

haemochromatosis. Quality of life is affected by the cancer itself and also the underlying liver disease. The health-related quality-of-life of patients at advanced stages of HCC is affected by pain, fatigue, weight loss, and obstructive syndromes such as ascites and jaundice. It can be expected that such symptoms will worsen as the disease progresses and the harmful effects of the cancer become more manifest.

Within each health state a single utility value is used - with the exception of a disutility which is applied when adverse events are experienced. In the EQ-5D regression analyses all available utility values, captured at each treatment visit, were used and therefore this single figure incorporates quality of life as it changes across the population from cycle to cycle.

The elicitation of the utility values for use in the model is described below.

Exploratory analyses of EQ5D data

To determine whether the EQ5D data would provide suitable data for inclusion in the economic model exploratory analyses were conducted with calculations performed without adjustment. Patients were stratified for pre- and post-progression and utility scores (UK tariff) were averaged for each cycle. This information is presented in Table 41. There is a general pattern of higher pre-progression scores compared to post-progression with the totals confirming the pattern i.e. 0.80 versus 0.77. However, there was considerable variation from cycle to cycle. These results suggested that, with appropriate adjustment for covariates, the data collected from the RESORCE trial would be suitable for inclusion in the economic model and have face-validity..

Table 41. EQ-5D index score per cycle, stratified for progression status (combined across treatment arms)

Cycle	Mean		Std. Dev.		N_{obs}	
	Pre-progression	Post-progression	Pre-progression	Post-progression	Pre-progression	Post-progression
1	0.83	--	0.21	--	531	--
2	0.76	0.56	0.24	0.33	489	4
3	0.80	0.74	0.22	0.25	283	64
4	0.81	0.78	0.19	0.21	228	50
5	0.79	0.76	0.20	0.26	168	60
6	0.80	0.80	0.21	0.23	123	61
7	0.84	0.83	0.20	0.20	98	51
8	0.82	0.80	0.15	0.18	78	48
9	0.82	0.78	0.18	0.23	65	39
10	0.80	0.86	0.21	0.17	53	38
11	0.79	0.84	0.24	0.16	45	37
12	0.86	0.79	0.21	0.24	33	38
13	0.83	0.79	0.15	0.18	31	33
14	0.83	0.77	0.16	0.17	28	24
15	0.84	0.83	0.17	0.17	20	29
16	0.87	0.83	0.20	0.17	17	23
17	0.87	0.79	0.13	0.17	13	20
18	0.86	0.81	0.14	0.18	10	20
19	0.87	0.74	0.16	0.18	10	19
20	0.90	0.81	0.14	0.24	9	16
21	0.88	0.82	0.13	0.13	9	12
22	0.88	0.82	0.14	0.19	9	11
23	0.92	0.82	0.14	0.17	9	11
24	0.91	0.82	0.13	0.17	6	13
25	0.94	0.88	0.13	0.17	5	10
26	0.87	0.89	0.09	0.11	5	7
27	0.90	0.90	0.11	0.13	3	7
28	1.00	0.90	0.14	0.12	2	7
29	n.a.	0.88	n.a.	0.14	1	6
30	--	0.94	--	0.14	--	5
31	--	1.00	--	0.00	--	3
32	--	0.80	--	n.a.	--	1
EOT	0.62	0.66	0.37	0.30	45	243
Total	0.80	0.77	0.22	0.24	2426	1011

EQ5D regression analyses

The EQ5D data were analysed using multiple model types, using both univariate and multivariate model structures. The variables that were considered to be of most interest were 1) treatment 2) progression status 3) Treatment Emergent Adverse Events. It was predetermined that the final model would include the RESORCE trial stratification factors i.e. geographical region, ECOG performance status, AFP level, extrahepatic disease, macrovascular invasion.

The following types of regression model were tested:

- Ordinary Least Squares (OLS) regression
- Tobit regression with repeated measurements
- Mixed model for repeated measurements

A stepwise approach was taken to assess which covariates to include in the final model, resulting in a set of 8 model specifications (see Table 42). Significant coefficients are highlighted with a '*' (significance level of 0.05). In some cases, the estimate based on a certain type of model is significant, while the estimate based on another type of model is not. This difference can be explained by a borderline effect that is sometimes nearly significant and sometimes nearly non-significant. In respect of TEAEs the eight grade 3-4 adverse events presented on page 123 – 'Adverse events' were considered. TEAEs were incorporated in the regression models via a single covariate (yes/no) rather than using a separate covariate for each of the adverse events.

Table 42. Utility models - Analysis results

	OLS	Tobit	Mixed
Model 1			
Treatment arm	-0.011	-0.012	-0.01
Model 2			
Progression status	-0.036*	-0.047*	-0.068*
Model 3			
TEAE	-0.056*	-0.012	-0.011*
Model 4			
Treatment arm	-0.016	-0.016	-0.014
Progression status	-0.037*	-0.047*	-0.068*
Model 5			
Treatment arm	-0.01	-0.012	-0.01
TEAE	-0.056*	-0.012	-0.011
Model 6			
Progression status	-0.039*	-0.048*	-0.069*
TEAE	-0.058*	-0.015*	-0.016
Model 7			
Treatment arm	-0.015	-0.015	-0.014
Progression status	-0.039*	-0.048*	-0.069*
TEAE	-0.057*	-0.015*	-0.016
Model 8			
Progression status	-0.041*	-0.048*	-0.069*
TEAE	-0.051*	-0.014*	-0.015

Treatment arm = regorafenib (BSC is reference); Progression status = post-progression (pre-progression is reference; TEAE = presence (absence is reference); stratification factors serve as a correction to the model estimates, coefficients associated with the stratification factors themselves are not in use; * significance at a level of 0.05

In models 1-7 progression status was always significant; treatment was not significant; and TEAEs (where incorporated) were mostly significant. As treatment arm as a covariate was non-significant in all the model specifications it was dropped going from model 7 to model 8.

Preferred regression model

To allow for a comparison between the 8 model specifications, the adjusted R-squared was derived for the OLS models, and the AIC and BIC estimates for the Tobit and mixed models. For the Tobit and the mixed models no R-squared is available.

Looking at the 8 OLS model specifications (Table 43), none of the specifications fit the data very well, as is shown by the low adjusted R-squared estimates. The adjusted R-squared indicates that model 8 has the best fit to the data. Also, in the case of the Tobit model specifications, AIC and BIC point towards specification 8. For the mixed model, a positive log-likelihood was obtained, resulting in negative AIC and BIC estimates making interpretation difficult. Based on Table 43, model specification 8 was selected as the final model.

In choosing between an OLS, Tobit and mixed model approach, we took the following criterion into account:

- Important to reflect repeated nature of measurements, therefore the OLS model was dropped.
- Smallest difference between the predicted and the observed values:
    - Tobit: mean difference -0.018; mean absolute difference 0.159
    - Mixed: mean difference -0.024; mean absolute difference 0.163
    - Based on this criterion, the Tobit model fits better than the mixed model.
- With the current dataset it is important to allow for skewness. Only the Tobit model takes into account a skewed distribution of the data.

Based on these criteria, the Tobit model (specification 8) was selected as the final model to inform the utility input for the cost-effectiveness model. The utility values used in the model are shown in Table 44.

Table 43. Goodness-of-fit measures for OLS (adjusted R-squared), and Tobit and mixed models (AIC and BIC)

Model	OLS (Adjusted R-squared)	Tobit		Mixed	
		AIC	BIC	AIC	BIC
1. Utility = f (treatment arm)	0.0002	1844.60	1869.28	-2032.13	-2007.45
2. Utility = f (progression status)	0.0052	1684.91	1709.48	-2009.76	-1985.19
3. Utility = f (TEAE)	0.0058	1824.76	1867.43	-2033.05	-2008.37
4. Utility = f (treatment arm, progression status)	0.0059	1685.46	1716.17	-2008.34	-1977.63
5. Utility = f (treatment arm, TEAE)	0.0059	1843.84	1874.69	-2031.36	-2000.51
6. Utility = f (progression status, TEAE)	0.0113	1682.24	1712.95	-2010.49	-1979.78
7. Utility = f (treatment arm, progression status, TEAE)	0.0119	1682.83	1719.68	-2009.05	-1972.19
8. Utility = f (progression status, TEAE, stratification factors)	0.0349	1652.33	1713.75	-2040.21	-1978.79

Table 44. Utility values used in the model, Tobit model

Patient group	Utility estimates
Pre-progression, no TEAE	0.811 (based on average of all observations in this analysis in this patient group)
Post-progression, no TEAE	0.763
Pre-progression, TEAE	0.797 (TEAE-associated disutility = -0.014)
Post-progression, TEAE	0.749 (TEAE-associated disutility = -0.014)

Limitations of the EQ-5D data from the RESORCE study

The EQ-5D questionnaire was completed for those receiving blinded treatment only. This could introduce a bias into the post-progression utility values if patients who continued treatment post-progression were less-ill compared to those who stopped treatment at progression. However, the questionnaire was completed at the end of treatment visits meaning that post-treatment utility was present in the results.

To gain an understanding of the potential for bias we investigated whether there were differences in health parameters at the point of progression between those who went on to continue blinded treatment compared to those who didn't. We first

selected patients whose date of progression was the same as their cycle visit date (at which ECOG performance status and laboratory tests were conducted). However, this provided insufficient patients for analysis i.e. 59 patients who continued treatment and 6 who didn't. Since the subgroup of 6 patients was too small to perform the analyses, we chose to select the subgroup of 'discontinuers' based on date of progression being equal to the end of treatment date - this led to a subgroup of 36 patients, and although the timing of the health parameters wasn't perfectly aligned between the two groups was the best that could be done. In Table 45 health parameters for continuers versus discontinuers is presented.

The information in the table shows that health parameters at the point of progression, of patients who continue blinded treatment after progression, do not differ significantly from the health parameters of patients who stop their treatment at the point of progression. Based on the comparability in health status we conclude that the results of the EQ-5D analyses are appropriate for use in the economic model.

Table 45. Estimates of health parameters at point of progression

Health parameter	**At progression date**	
	Patients no longer on treatment (N=36)	**Patients continue treatment (N=59)**
ECOG performance status (N (%)) **[increased=more diseased]**		
0	16 (44.4%)	33 (55.9%)
1	14 (38.9%)	22 (37.3%)
2	3 (8.3%)	3 (5.1%)
3	2 (5.6%)	1 (1.7%)
4	1 (2.8%)	--
Difference tested with Chi-squared test	ns (0.455)	
Mean alpha-fetoprotein levels in ng/mL **[increased=more diseased]**	25950.0	10370.0
Difference tested with two-sample t-test	ns (0.335)	
Mean haemoglobin ng/dL [decreased=more diseased]	12.16	12.56
Difference tested with two-sample t-test	ns (0.357)	
Mean haematocrit in % [decreased=more diseased]	36.92	38.08
Difference tested with two-sample t-test	ns (0.316)	
Mean platelets in GIGA/L [decreased=more diseased]	198.7	179.2
Difference tested with two-sample t-test	ns (0.257)	
Mean red cell count in T/L [decreased=more diseased]	4.12	4.18
Difference tested with two-sample t-test	ns (0.653)	
Mean white blood cell count in GIGA/L [increased=more diseased]	7.03	6.62
Difference tested with two-sample t-test	ns (0.462)	
Mean aspartate aminotransferase in U/L **[increased=more diseased]**	232.6	73.3
Difference tested with two-sample t-test	ns (0.129)	
Mean alanine aminotransferase in U/L [increased=more diseased]	70.9	59.0
Difference tested with two-sample t-test	ns (0.327)	
Mean bilirubin level in mg/dL [increased=more diseased]	1.52	1.29
Difference tested with two-sample t-test	ns (0.478)	
Mean thyrotropin levels in mU/L [increased=more diseased]	2.83	3.89
Difference tested with two-sample t-test	ns (0.080)	

The utility values used in the economic model are presented in Table 46.

Table 46. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Progression free	0.811	Lower limit (0.590) Upper limit (1.00)	Section B.3.4 Page 135 - 138	EQ-5D data was collected in the RESORCE study and using utilities derived from EQ-5D aligns with the reference case
Progressed disease	0.763	Lower limit (0.520) Upper limit (1.00)	Section B.3.4 Page 135 - 138	EQ-5D data was collected in the RESORCE study and using utilities derived from EQ5D aligns with the reference case
Adverse Reaction i.e. any grade 3 or 4 TEAE occurring in ≥5% of patients	-0.014	Lower limit (-0.011) Upper limit (-0.017)	Section B.3.4 Page 135 - 138	EQ5D data was collected in the RESORCE study and using utilities derived from EQ5D aligns with the reference case
Abbreviations: HS, health state; AR, adverse reaction				

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Appendix I outlines the systematic literature review to search for healthcare resource data. None of the cost and resource use studies located in the literature search provided information from a UK setting. The located publications, being from other healthcare systems, are not generalisable to the UK and are not relevant for the appraisal of regorafenib.

However, as part of the economic evaluations search, several technology assessments of sorafenib were located. As the manufacturer of sorafenib, these technology appraisals were already known to Bayer. Sorafenib has been available for use in advanced HCC since 2008 and consequently physicians have significant

clinical experience and knowledge of the resources used when treating with sorafenib. Conversely, there is no experience in the clinical setting relating to the use of regorafenib in the same disease area.

It has been assumed that the resource units previously used for sorafenib are directly transferable to regorafenib. This is justified as:

- the burden of disease experienced by patients on sorafenib and regorafenib is comparable. Evidence for this comes from the near identical median survival of BSC patients in the SHARP (sorafenib) and RESORCE trials i.e. 7.9 and 7.8 months, respectively
- sorafenib and regorafenib are from the same drug class
- the use of the same resource estimates helps ensure consistency across appraisals
- The economic model used in the appraisal of sorafenib has the same structure as the model for regorafenib

For sorafenib, estimates on the resource use associated with the management of patients with HCC were determined through a resource use survey which was conducted in 2015 with 3 leading clinical experts in the field of oncology in the UK, all of whom were familiar with using sorafenib. A copy of the resource use survey is provided in Appendix O. Appendix P includes the results of the survey. These resource units were assumed to be directly transferable to regorafenib – see Table 47. Resource units were multiplied by unit costs (Table 49) to provide health state costs (Table 50).

Table 47. Application of sorafenib physician survey to regorafenib

Sorafenib resource unit estimates	Application in the regorafenib model
Progression free (treated with sorafenib)	Applied to patients who are progression free and treated with regorafenib
Progression free (treated with BSC)	Applied to patients who are progression free and being treated with BSC alone
Additional resources used at time of progression for sorafenib	Applied to regorafenib patients at time of progression
Post-progression (treated with sorafenib)	Applied to post-progression patients on regorafenib
Post-progression (treated with BSC)	Applied to post-progression patients on BSC

Intervention and comparators' costs and resource use

The drug acquisition cost of regorafenib is based on PAS price per pack i.e. 84 x 40mg tables - [redacted]. The maximum daily dose of regorafenib is 160mg, however, treatment could be interrupted, or the dose reduced, to help manage side effects (see 'Dose modification' - page 34 and page 130). The cost per month (model cycle) is based on the PAS price and the average dosing observed in the RESORCE study. Taking into account treatment interruptions and dose reductions, the progression free average daily dose was [redacted] and the average daily dose post-progression was [redacted].

As the comparator is best supportive care, which excludes active therapies, it was assumed that no drug acquisition costs would apply to this treatment.

Table 48. Drug costs

Regorafenib	**Cost per month cycle (28 days)**	**Source**
Pre-progression average daily dose ([redacted])	[redacted] ([redacted])	Confidential PAS price Data from RESORCE
Post-progression average daily dose [redacted]	[redacted] ([redacted])	Confidential PAS price Data from RESORCE

Health-state unit costs and resource use

Table 49. Unit costs associated with health state resource use

Resource item	Cost (£)	Unit	Source
Medical staff visits			
Oncologist	163.00	Cost per visit	NHS National Schedule of Reference Costs 2015-16 (specialty code 370)
Hepatologist	253.00	Cost per visit	NHS National Schedule of Reference Costs 2015-16 (specialty code 306)
Gastroenterologist	132.00	Cost per visit	NHS National Schedule of Reference Costs 2015-16 (specialty code 301)
Clinical Nurse Specialist	130.00	Cost per visit	PSSRU 2016 (Section 10.7)
Palliative Care Team	131.00	Cost per visit	NHS National Schedule of Reference Costs 2015-16 (specialty code 191)
Macmillian Nurse	73.00	Cost per visit	PSSRU 2016 (Section 10.1)
GP	36.00	Cost per visit	PSSRU 2016 (Section 10.3b)
Nurse	36.00	Cost per visit	PSSRU 2016 (Section 10.2)
Specialist visit	151.12	Cost per visit	NHS National Schedule of Reference Costs 2015-16 (specialty code 370)
Laboratory tests			
AFP test	3.03	Cost per test	Cardiff and Vale Acute Chemistry Repertoire 2016/2017
Liver function test	2.78	Cost per test	Akhtar, W. & Chung, Y. Saving the NHS one blood test at a time. BMJ Qual. Improv. reports 2, (2014)

Biochemistry	1.34	Cost per test	Akhtar, W. & Chung, Y. Saving the NHS one blood test at a time. BMJ Qual. Improv. reports 2, (2014)
Complete blood count	2.65	Cost per test	Akhtar, W. & Chung, Y. Saving the NHS one blood test at a time. BMJ Qual. Improv. reports 2, (2014)
INR	3.43	Cost per test	NHS Standards and Indicators
Radiological tests			
CT scan (abdominal)	121.57	Cost per test	NHS National Schedule of Reference Costs 2015-2016 (code RD22Z)
MRI (abdominal)	238.00	Cost per test	NHS National Schedule of Reference Costs 2015-2016 (code RD03Z)
Hospitalisations			
Acute Care			
General ward	801.00	Cost per day	Response to a Freedom of Information Act request (2012/2013) Average fully absorbed inpatient bed day cost in 2012/13. Inflated to 2015/16 costs using HCHS pay and prices index.
A&E admission	138.00	Cost per admission	NHS National Schedule of Reference Costs 2015-2016 (Table 1 report : FCE based average costs)

Table 50. Health state costs included in the model

Health state	Cost (£)	Lower 95%CI	Upper 95%CI
Regorafenib pre-progression			
Medical staff visits	471.94	330.36	613.52
Laboratory tests	12.24	8.56	15.91
Radiological tests	47.02	32.92	61.13
Hospitalisation	175.82	123.08	228.57
At progression – one-off cost			
Laboratory tests	12.09	8.46	15.71
Radiological tests	80.42	56.29	104.55
Regorafenib – post-progression			
Medical staff visits	303.56	212.49	394.63
Laboratory tests	5.90	4.13	7.67
Radiological tests	19.89	13.93	25.86
Hospitalisation	101.83	71.28	132.38
BSC – pre-progression			
Medical staff visits	598.46	418.92	778.00
Laboratory tests	9.38	6.57	12.20
Radiological tests	19.89	13.93	25.86
Hospitalisation	847.68	593.38	1101.99
BSC – post-progression			
Medical staff visits	314.19	219.93	408.45
Laboratory tests	9.38	6.57	12.20
Radiological tests	19.89	13.93	25.86
Hospitalisation	847.68	593.38	1101.99

Adverse reaction unit costs and resource use

Treatment emergent adverse events in the model are limited to grade 3 or 4 events that occurred in ≥5% of patients in either the regorafenib or BSC arms of the RESORCE trial. The adverse events and costs included in the model are shown in the table overleaf.

Table 51. Resource use and costs associated with adverse events

		Cost	Source
Anaemia		£1,283.67	NHS National Schedule of Reference Cost 2015-2016 (Average HRG codes SA04G-SA04L)
Ascites		£1,667.00	(Average HRG codes GC12G-GC12K)
Aspartate aminotransferase increase		£1,667.00	(Average HRG codes GC12G-GC12K)
Blood bilirubin increase		£1,667.00	(Average HRG codes GC12G-GC12K)
Fatigue		£1,667.00	(Average HRG codes GC12G-GC12K)
Hypertension		£729.87	NHS National Schedule of Reference Cost 2015-2016 (HRG code EB04Z)
Hypophosphataemia		£1,261.96	NHS National Schedule of Reference Cost 2015-2016 (Average HRG codes KC05J-KC05N)
HSFR (hand foot skin reaction)		£873.37	NHS National Schedule of Reference Cost 2015-2016 (HRG code XD57Z)
Weighted cost for an adverse event in the model	**Regorafenib**	£1225.99	
	BSC	£1,492.22	

Miscellaneous unit costs and resource use

None

B.3.6 Summary of base-case analysis inputs and assumptions

Table 52. Summary of variable applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Hazard ratio for PFS	2.08	1.72 to 2.51	
Hazard ratio for OS	1.49	1.20 to 1.83	
Discontinuation rate during PFS	[redacted]	[redacted]	See 'Discontinuation from treatment' page 128
Post-progression treatment – regorafenib*	[redacted]	[redacted]	Table 39
Post-progression treatment – BSC*	[redacted]	[redacted]	Table 39
Adverse event rate – regorafenib	5.55%	4.27% to 6.69%	See 'Adverse events' page 123
Adverse event rate – BSC	5.06%	3.27% to 5.37%	See 'Adverse events' page 123
Average dose in PFS	[redacted]	[redacted]	See 'Intervention and comparators' costs and resource use' page 143
Average dose in PD	[redacted]	[redacted]	See 'Intervention and comparators' costs and resource use' page 143
Utility in PFS	0.81	0.80 to 0.82	Table 44
Utility in PD	0.76	0.75 to 0.78	Table 44
Disutility due to AE	-0.014	-0.0277 to 0.0003	Table 44

Abbreviations: AE, adverse event; BSC, best supportive care; CI, credible interval; PD, progressed disease; PFS, Progression Free Survival; OS, overall survival

*mean percentage of patients on treatment post-progression, for each new cycle the proportion of patients on treatment is adjusted based on this mean value

Assumptions

The key structural and input assumptions incorporated in the model are detailed in Table 53.

Table 53. Key structural and input assumptions

Assumption	Justification	References to section in submission	Sensitivity Analysis
The efficacy data from the multi-national trial (RESORCE) is applicable to the proposed patient population in England.	RESORCE was a multicentre trial with the UK as one of the participating countries. The patient characteristics in England are generally comparable to the characteristics of patients in the RESORCE study and the results are considered generalisable.	Section B.2.13	Sensitivity has been tested by varying the OS hazard ratio
The OS observed in the regorafenib and the BSC group over the trial can be extrapolated to the modeled time horizon using the lognormal distribution.	The lognormal curve was the best fitting curve with good visual and clinical plausibility. Model predictions with the lognormal distribution were closely aligned to clinical trial results.	Clinical inputs – page 117	Different distributions were tested in scenario analyses
Progression free survival is modelled using the unadjusted trial data from RESORCE	The data for progression free survivial was mature		Different parametric distributions were fitted to the PFS data
The proportion of patients receiving treatment after progression is as observed in the RESORCE study	This assumption is conservative as post-progression treatment in England is not expected to be as extensive as in the RESORCE studyl	Section B3.3 - Discontinuation from treatment	Scenario analysis removing post progression treatment
Resource units estimated for sorafenib and based on a physician survey are directly transferable to regorafenib	The resource units used for sorafenib are considered to be transferable to regorafenib. This is justified as: • the burden of disease experienced by patients on sorafenib and regorafenib is comparable as demonstrated by the near identical median survival of BSC patients in SHARP (sorafenib Phase III RCT) and RESORCE (regorafenib) studies i.e. 7.9 and 7.8 months, respectively • the patient populations are similar i.e. patients in the RESORCE study have comparable characteristics to	B3.5.	Values tested in the OWSA and PSA

	patients receiving sorafenib in England • both sorafenib and regorafenib are from the same drug class • the use of the same resource estimates helps ensure consistency across appraisals • The economic model used in the appraisal of sorafenib has the same structure as the model for regorafenib		
Only grade 3 / 4 TEAEs occurring in at least ≥5% of the regorafenib or BSC arms are included.	This is common practice for modelling adverse events and it is these events that can be considered to have a cost and quality of life impact		Values tested in the OWSA and PSA
Time horizon	Lifetime horizon (15 years). This time horizon is appropriate for a condition where a survival difference is shown.		Varying time horizons are tested in the scenario analysis
Average dose data for regorafenib from the RESORCE study is used in the model	The RESORCE study included dose reductions and treatment interruptions to manage adverse events. This treatment approach is in keeping with clinical practice where dose reductions/interruptions are a standard part of patient care. Note that the efficacy results in RESORCE were obtained with dose reductions/interruptions.		Excluding dose reductions/interruptions is tested in a scenario analysis

OWSA – one-way sensitivity analysis; PSA – probabilistic sensitivity analysis

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

A summary of the base-case cost-effectiveness results is in provided in Table 54. Regorafenib is a cost-effective treatment option when compared to BSC at a willingness to pay threshold of £50,000 per QALY.

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Table 54. Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER versus baseline (£/QALY)
Regorafenib	[redacted]	1.340	1.044	12,262	0.467	0.367	33,437
BSC	[redacted]	0.874	0.677	-	-	-	-
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

See appendix J for clinical outcomes from the model and disaggregated results.

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis (PSA)

The PSA is based on a willingness to pay threshold of £50,000. The PSA was conducted using 1,000 simulations. A scatter plot and cost-effectiveness acceptability curve (CEAC) are presented overleaf.

Probabilistic sensitivity analysis was conducted to simultaneously take into account the uncertainty associated with parameter values. The implementation of PSA involved assigning specific parametric distributions and repeatedly sampling mean parameter values. Sampling was based on point estimates used in the deterministic analysis and where standard errors were not avaliable, a default of 30% of the mean (point estimate) was used.

Each group of samples from all of the parameters included in the PSA generated an estimate for total costs and effects.

Variables and statistical distributions used in the probabilistic sensitivity analyses are reported in Table 55.

Table 55. Variable included in the probabilistic analysis

Input	Mean	Distribution type
Hazard Ratio for PFS	2.08	Normal (14.7, 5.4)
Hazard Ratio for OS	1.49	Normal (7.8, 11.9)
Adverse events for regorafenib	5.6%	Beta (23.6, 400.9)
Adverse events for BSC	5.1%	Beta (23.7, 444.4)
Utility PFS	0.81	Beta (5873.92, 1368.89)
Disutility progression	0.05	Beta (87.69, 1739.15, 276.78)
Disutility adverse event	0.014	Beta (3.93, 276.78)
Hospitalisation costs – regorafenib (progression free)	£176	Gamma (25; 7.47)
Medical Staff visits costs - regorafenib (progression free)	£472	Gamma (25; 12.76)
Lab tests costs - regorafenib (progression free)	£12	Gamma (25; 0.47)
Radiological tests costs - regorafenib (progression free)	£47	Gamma (25; 1.93)
Hospitalisation costs - regorafenib (progressed disease)	£102	Gamma (25; 4.64)
Medical Staff visits costs - regorafenib (progressed disease)	£304	Gamma (25; 8.34)
Lab tests costs - regorafenib (progressed disease)	£6	Gamma (25; 0.22)
Radiological tests costs - regorafenib (progressed disease)	£20	Gamma (25; 0.72)
Hospitalisation costs – BSC (progression free)	£848	Gamma (25; 35.03)
Medical Staff visits costs - BSC (progression free)	£598	Gamma (25; 17.32)
Lab tests costs - BSC (progression free)	£9	Gamma (25; 0.36)
Radiological tests costs - BSC (progression free)	£20	Gamma (25; 0.72)
Hospitalisation costs - BSC (progressed disease)	£848	Gamma (25; 35.03)
Medical Staff visits costs - BSC (progressed disease)	£314	Gamma (25; 7.04)
Lab tests costs - BSC (progressed disease)	£9	Gamma (25; 0.32)
Radiological tests costs - BSC (progressed disease)	£20	Gamma (25; 0.72)
Average dose per cycle for PFS	[redacted]	Gamma [redacted]
Average dose per cycle for PD	[redacted]	Gamma [redacted]

PSA outputs are represented graphically by:

1. Plotting incremental cost and QALY pairs on the cost effectiveness plane (CE scatter plot)

2. Presenting the likelihood of regorafenib being cost-effective at a willingness-to-pay (WTP) threshold of £50,000 per QALY.

A table of the results, scatter plot and CEAC are presented below. Regorafenib is associated with a probability of 100% of being cost-effective at a WTP threshold of £50,000 per QALY and a 21% probability of being cost-effective at a WTP of £30,000.

Table 56. PSA results

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER versus baseline (£/QALY)
Regorafenib	[redacted]	1.045	£12,311	0.369	33,335
BSC	[redacted]	0.676	-	-	-
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; CI, credible interval					

Figure 16. PSA Scatterplot

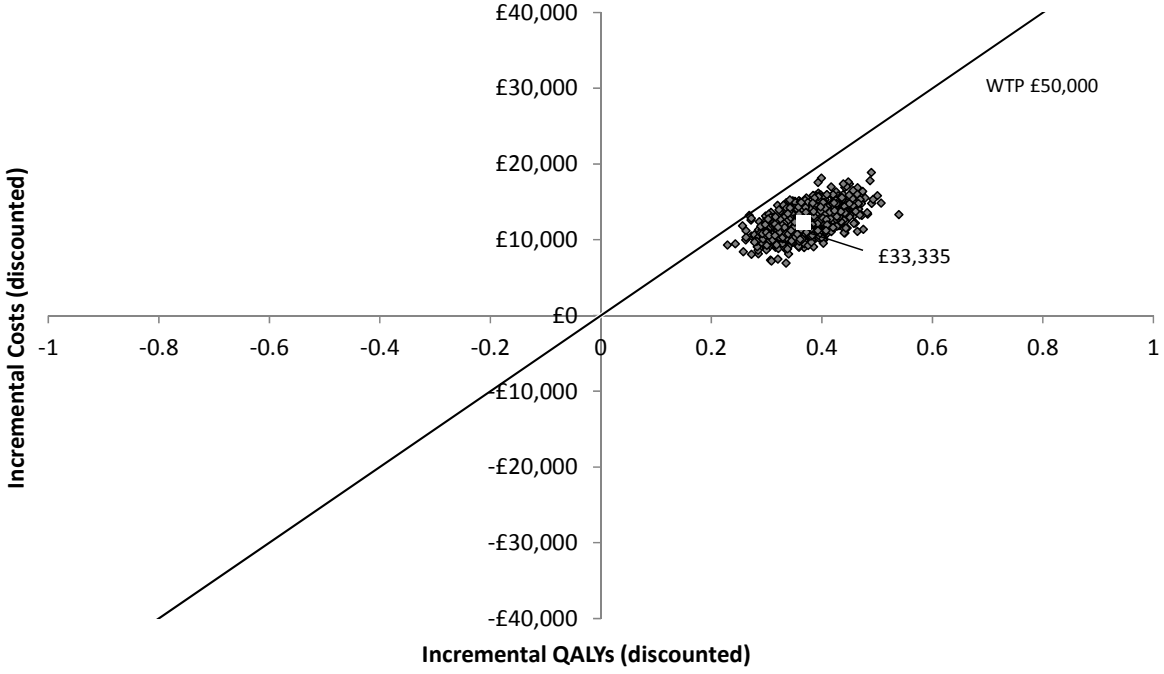
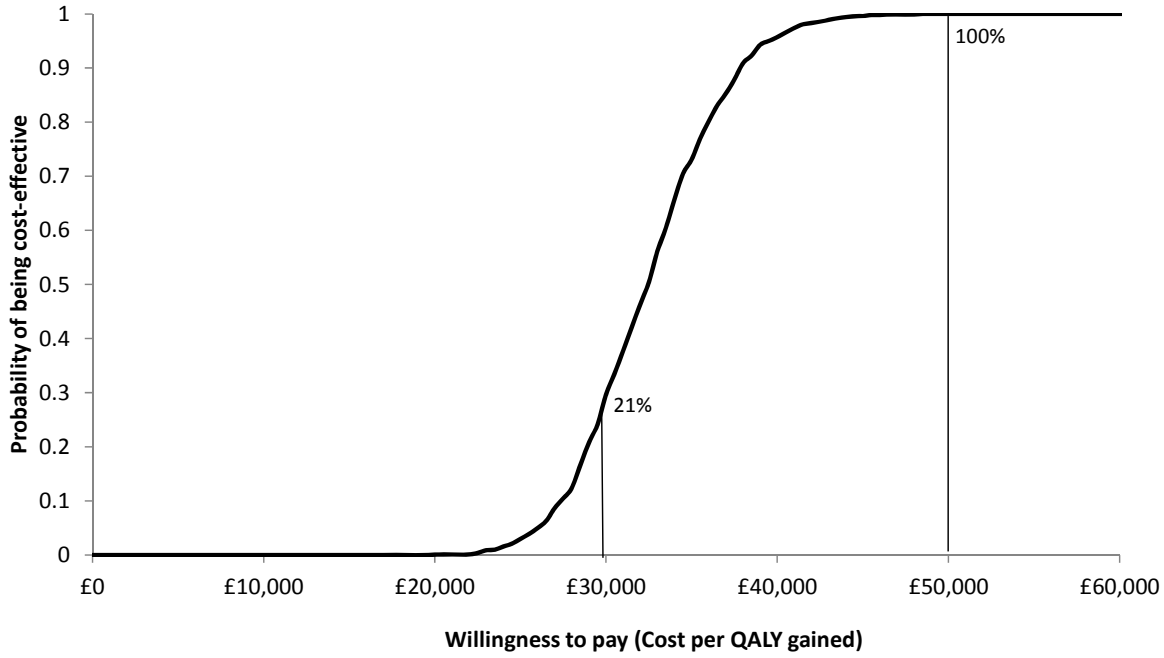


Figure 17. Cost effectiveness acceptability curve



Deterministic sensitivity analysis

Table 57 provides the inputs and results of the deterministic sensitive analysis. Figure 18 shows a tornado plot for the top 10 most sensitive parameters. The tornado plot is based on a willingness to pay of £50,000 per QALY. Decreasing the hazard ratio for overall survival for regorafenib had the greatest negative impact on cost-effectiveness. However, even in this sensitivity analysis regorafenib remained cost-effective.

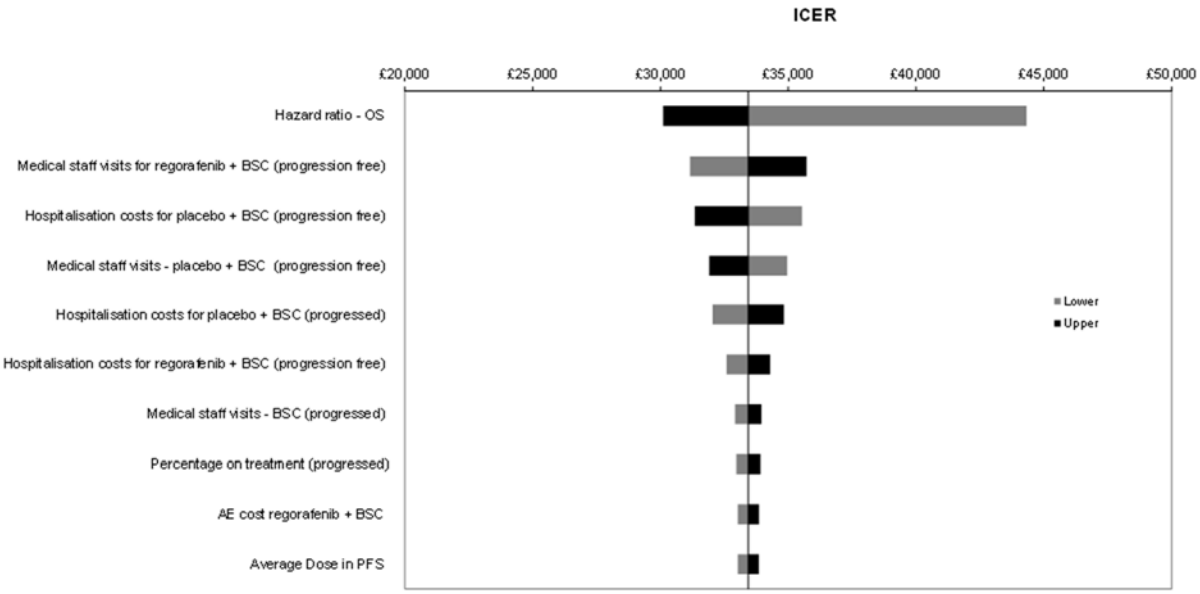
Table 57. Deterministic sensitivity analysis results

Variable	Source	Low variation			High variation		
		Incr Cost (£)	Incr QALYs	ICER (£/ QALY)	Incr Cost (£)	Incr QALYs	ICER (£/ QALY)
Percentage off treatment in Progression Free Survival (PFS) [redacted]	95% CI	£12,284	0.367	£33,497	£12,240	0.367	£33,376
Percentage on treatment in Progressed disease (PD) ([redacted]	+/-30%	£12,090	0.367	£32,967	£12,434	0.367	£33,908
Hazard Ratio OS (1.20; 1.83)	95% CI	£8,888	0.202	£44,322	£14,790	0.491	£30,110
Utility values PFS (0.80; 0.82)	95% CI	£12,262	0.365	£33,624	£12,262	0.369	£33,252
Utility values PD (0.75; 0.78)	95% CI	£12,262	0.364	£33,732	£12,262	0.370	£33,148
Adverse event disutility (-0.0277; -0.0003)	95% CI	£12,262	0.367	£33,455	£12,262	0.367	£33,419
Monthly Adverse event rate for regorafenib (4.3%; 6.7%)	95% CI	£12,162	0.367	£33,156	£12,352	0.367	£33,689
Monthly Adverse event rate for BSC (3.3%; 5.4%)	95% CI	£12,356	0.367	£33,700	£12,246	0.367	£33,392
AE cost regorafenib (£858; £1,594)	+/-30%	£12,109	0.367	£33,020	£12,415	0.367	£33,855
AE cost BSC (£1,045; £1,940)	+/-30%	£12,364	0.367	£33,716	£12,160	0.367	£33,159
Hospitalisation costs – regorafenib (progression free) (£123; £229)	+/-30%	£11,950	0.367	£32,587	£12,574	0.367	£34,288
Medical Staff visits– regorafenib (progression free) (£330; £614)	+/-30%	£11,425	0.367	£31,155	£13,099	0.367	£35,719
Lab tests – regorafenib (progression free) (£9; £16)	+/-30%	£12,241	0.367	£33,378	£12,284	0.367	£33,497

Radiological tests– regorafenib (progression free) (£33; £61)	+/-30%	£12,179	0.367	£33,210	£12,346	0.367	£33,665
Hospitalisations – regorafenib (progressed disease) (£71; £132)	+/-30%	£13,031	0.367	£33,345	£12,296	0.367	£33,530
Medical Staff visits– regorafenib (progressed disease) (£212; £395)	+/-30%	£12,821	0.367	£33,161	£12,364	0.367	£33,714
Lab tests – regorafenib (progressed disease) (£4; £8)	+/-30%	£12,271	0.367	£33,432	£12,264	0.367	£33,443
Radiological tests– regorafenib (progressed disease) (£14; £26)	+/-30%	£12,280	0.367	£33,419	£12,269	0.367	£33,456
Hospitalisations – BSC (progression free) (£593; £1,102)	+/-30%	£11,751	0.367	£35,534	£11,493	0.367	£31,341
Medical Staff visits – BSC (progression free) (£419; £778)	+/-30%	£12,073	0.367	£34,962	£11,703	0.367	£31,913
Lab tests – BSC (progression free) (£7; £12)	+/-30%	£12,257	0.367	£33,461	£12,254	0.367	£33,414
Radiological tests – BSC (progression free) (£12; £26)	+/-30%	£12,250	0.367	£33,487	£12,244	0.367	£33,388
Hospitalisations – BSC (progressed disease*) (£593; £1,102)	+/-30%	£12,110	0.367	£32,043	£12,774	0.367	£34,832
Medical Staff visits – BSC (progressed disease*) (£220; £408)	+/-30%	£12,236	0.367	£32,921	£12,452	0.367	£33,954
Lab tests – BSC (progressed disease*) (£7; £12)	+/-30%	£12,299	0.367	£33,422	£12,268	0.367	£33,453
Radiological tests – BSC (progressed disease*) (£14; £26)	+/-30%	£12,293	0.367	£33,405	£12,274	0.367	£33,470
Average dose per cycle for PFS [redacted]	95% CI	£12,153	0.367	£33,023	£12,413	0.367	£33,848

Average dose per cycle for PD health states ([redacted])	95% CI	£12,279	0.367	£33,367	£12,288	0.367	£33,508
*Changes both regorafenib and BSC arms because when patients progress they receive BSC, therefore changes in progressed for BSC affect both arms.							

Figure 18. Tornado diagram: one-way sensitivity analysis results



Scenario analysis

A number of scnerio analyses were conducted - the results of which are shown in Table 58. There was a low sensitivity of the ICER to different extrapolations of PFS and OS with the cost per QALY often being lower than the base case. As described in Section B3.3, the loglogistic curve was found to be a plausible extrapolation for overall survival and a possible alternative to the lognormal curve – when this curve was used the cost per QALY was £32,379.

The ICER was sensitive to reduced time horizons, however regorafenib remained cost-effective when using a 3-year time horizon.

In the RESORCE study patients had dose reductions and treatment interruptions if required and the overall survival benefit observed was with these treatment modifications. The scenario using the cost of 160mg daily is therefore likely to be a large overestimation of treatment cost. However, at a cost per QALY of £41,206 regorafenib remained cost-effective in this scenario.

The scenarios where post-progression treatment was removed or limited to 3 cycles resulted in an improved cost-effectiveness estimate.

Table 58. Scenario analysis results

	Incr costs (£)	Incr QALYs	ICER (£/QALYs)
Base case	**12,262**	**0.367**	**33,437**
PFS – different extrapolations			
Lognormal	11,796	0.365	32,302
Loglogistic	11,915	0.366	32,571
Weibull	12,007	0.366	32,842
Exponential	12,257	0.367	33,410
Gamma	11,842	0.365	32,456
Gompertz	12,414	0.368	33,775
OS – different extrapolations			
Loglogistic	12,755	0.395	32,379
Weibull	5,747	0.223	25,726
Exponential	7,885	0.301	26,212
Gamma	9,692	0.246	39,466
Gompertz	6,768	0.245	27,587
Utilities			
Nexavar pre and post-progression utility values (pre 0.6885; post 0.7111)	12,262	0.327	37,554
Progression disutility doubled.	12,262	0.355	34,524
Daily average dose of Regorafenib			
160mg i.e. no dose reductions or treatment interruptions	15,111	0.367	41,206
Post progression treatment			
None	10,913	0.367	29,731
Maximum of 3 cycles	11,949	0.367	32,582
Time horizon			
3 years	9,647	0.238	40,555
5 years	11,004	0.305	36,112
10 years	12,029	0.355	33,862

Summary of sensitivity analyses results

A comprehensive set of sensitivity and scenario analyses were completed. The incremental cost per QALY for regorafenib remained below £50,000 in all analyses confirming the robustness of the base case results.

The main driver of cost-effectiveness was the relative OS efficacy of regorafenib relative to BSC alone. However, even when the most conservative efficacy estimates from the RESORCE trial were applied regorafenib remained cost-effective at a WTP threshold of £50,000 per QALY.

B.3.9 Subgroup analysis

No subgroup analyses were conducted.

B.3.10 Validation

Validation of cost-effectiveness analysis

Median PFS and OS from the model were compared with the results from the RESORCE trial. The technical validity of the model was tested at two modelling agencies to ensure that calculations were correct and that the results were logical and consistent - this was conducted by examining formulae and conducting one and two-way sensitivity analyses to ensure results were logical.

B.3.11 Interpretation and conclusions of economic evidence

There are no published economic evaluations (see Appendix G) of regorafenib in HCC to compare to the analyses presented in this submission. However, the structure of the model used in this appraisal is common to the oncology area and accepted modelling methods were used. The predictions of the model aligned closely to the clinical results from the RESORCE study (see Appendix J) and the base case cost-effectiveness results show regorafenib to be well within the threshold of £50,000 per QALY. Regorafenib remained below the £50,000 threshold in a range of sensitivity and scenario analyses providing confidence that regorafenib represents a good use of NHS resources.

The characteristics of patients in the RESORCE trial are sufficiently comparable to patients in England who might be expected to be treated with regorafenib to have confidence in the generalisability of the results (see section B.2.13).

The main weakness of the economic evaluation was the need to extrapolate treatment beyond the duration of the trial, however this is common to the majority of

analyses of oncology products. Extrapolation of survival beyond the trial period was conducted using the standard parametric distributions. Regorafenib remained cost-effective irrespective of the method of extrapolation. The conclusion that regorafenib is cost-effectiveness is strengthened by the positive results of the wide range of sensitivity and scenario analyses.

B.4 References

1. Huynh H, Nguyen TT, Chow KH, Tan PH, Soo KC, Tran E. Over-expression of the mitogen-activated protein kinase (MAPK) kinase (MEK)-MAPK in hepatocellular carcinoma: its role in tumor progression and apoptosis. BMC Gastroenterol. 2003;3:19.

2. Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schutz G, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer. 2011;129(1):245-55.

3. Chen J, Gao J. Advances in the study of molecularly targeted agents to treat hepatocellular carcinoma. Drug Discov Ther. 2014;8(4):154-64.

4. Bruix J, Tak WY, Gasbarrini A, Santoro A, Colombo M, Lim HY, et al. Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. Eur J Cancer. 2013;49(16):3412-9.

5. Ravi S, Singal AK. Regorafenib: an evidence-based review of its potential in patients with advanced liver cancer. Core Evid. 2014;9:81-7.

6. National Cancer Intelligence Network. Trends in incidence of primary liver cancer subtypes. 2012 February 2012.

7. International Agency for Research on Cancer (IARC). Cancer Fact Sheets: Liver Cancer in 2012. 2016.

8. Cancer Research UK. Liver Cancer Statistics in the UK2017 18/01/2017. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer#heading-Zero.

9. International Agency for Research on Cancer (IARC). Population Fact Sheets: World. 2012.

10. Office for National Statistics. Cancer Registration Statistics England for 2014. 2016.

11. Welsh Cancer Intelligrnce and Surveillance Unit. Incidence of liver cancer (C22) and liver cell carcinomas (C22.0) in Wales for 2014. Data were provided on request. 2016.

12. Information Services Division (ISD) Scotland. Cancer of the Liver. Trends in Incidence (ICD-10 C22). C22.0 data provided on request. 2016.

13. N. Ireland Cancer Registry. Incidence, prevalence and survival statistics for Liver & Intrahepatic Bile Duct Cancer 1993-2014. Liver cell carcinom ICD-10 C22.0 data provided on request. 2016.

14. European Association For The Study Of The Liver and European Organisation For Research Treatment Of Cancer (EASL-EORTC). EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908-43.

15. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003;362(9399):1907-17.

16. Ryder SD, British Society of G. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut. 2003;52 Suppl 3:iii1-8.

17. Health Protection Agency. Hepatitis C in the UK. 2011 July 2011.

18. Verslype C, Rosmorduc O, Rougier P, Group EGW. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23 Suppl 7:vii41-8.

19. Scottish HepatoPancreatoBiliary (HPB) Managed Clinical Network (MCN). Guideline for the management of hepatocellular carcinoma (HCC) - updated June 2010. 2010.

20. Bruix J, Sherman M, American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-2.

21. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial (including supplementary material in appendices). Lancet. 2017;389(10064):56-66.

22. Bayer HealthCare AG. Clinical Study Report: A randomized, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib. 2016 19th September 2016. Report No.: PH-38451.

23. Bruix J, Merle P, Granito A, Huang Y, Bodoky G, Yokosuka O, et al. Efficacy, safety, and health-related quality of life (HRQoL) of regorafenib in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: Results of the international, double-blind phase 3 RESORCE trial (poster). Annals of Oncology. 2016;27(suppl 6):LBA28.

24. Bayer HealthCare. Statistical Analysis Plan: A randomized, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib. Patients with hepatocellular carcinoma treated with regorafenib or placebo after failure of sorafenib. 2015. Contract No.: v1.3 for Protocol No.: BAY 73-4506/15982.

25. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30(1):52-60.

26. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

27. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90.

28. Reig M, Darnell A, Forner A, Rimola J, Ayuso C, Bruix J. Systemic therapy for hepatocellular carcinoma: the issue of treatment stage migration and registration of progression using the BCLC-refined RECIST. Semin Liver Dis. 2014;34(4):444-55.

29. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11(3):570-9.

30. Heffernan N, Cella D, Webster K, Odom L, Martone M, Passik S, et al. Measuring health-related quality of life in patients with hepatobiliary cancers: the functional assessment of cancer therapy-hepatobiliary questionnaire. J Clin Oncol. 2002;20(9):2229-39.

31. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100(10):698-711.

32. Steel JL, Eton DT, Cella D, Olek MC, Carr BI. Clinically meaningful changes in health-related quality of life in patients diagnosed with hepatobiliary carcinoma. Ann Oncol. 2006;17(2):304-12.

33. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.

34. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-12.

35. Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295-302.

36. Demetri GD. Differential properties of current tyrosine kinase inhibitors in gastrointestinal stromal tumors. Semin Oncol. 2011;38 Suppl 1:S10-9.

37. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006;368(9544):1329-38.

38. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors.

European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92(3):205-16.

39. King J, Palmer DH, Johnson P, Ross P, Hubner RA, Sumpter K, et al. Sorafenib for the Treatment of Advanced Hepatocellular Cancer - a UK Audit. Clin Oncol (R Coll Radiol). 2017;29(4):256-62.

40. National Cancer Institute (NCI). Levels of Evidence for Adult and Pediatric Cancer Treatment Studies (PDQ®)–Health Professional Version2015 21st November 2016. Available from: https://www.cancer.gov/publications/pdq/levels-evidence/treatment#section/_30.

41. Hubert MM, Karellis A, Sherman M, Gill S, Beecroft R, Sampalis JS. Beyond budget silos: budget impact analysis of transarterial radioembolization with yittrium-90 glass micrsospheres for hepatocellular carcinoma from a hospital perspective. Value in Health. 2016;19(3):A308.

42. Chan A, Leung H. Cost Effectiveness of Sorafenib Versus SBRT for Advanced Hepatocellular Carcinoma. Value in Health. 2016;19(3):A152.

43. Leung HW, Liu C-F, Chan AL. Cost-effectiveness of sorafenib versus SBRT for unresectable advanced hepatocellular carcinoma. Radiation Oncology. 2016;11(1):69.

44. Parikh N, Marshall VD, Singal A, editors. Cost-effectiveness of sorafenib therapy for advanced hepatocellular carcinoma: An analysis of the SEER-Medicare database2016 2016.

45. Parikh ND, Marshall VD, Singal AG, Nathan H, Lok AS, Balkrishnan R, et al. Survival and cost-effectiveness of sorafenib therapy in advanced hepatocellular carcinoma: An analysis of the SEER-Medicare database. Hepatology. 2017;65(1):122-33.

46. Zhang P, Wen F, Li Q. Oxaliplatin plus fluorouracil/leucovorin or sorafneib as first-line treatments for advanced hepatocellular carcinoma: a cost-effectiveness analysis. J Clin Oncol. 2016;34:e18270-e.

47. Zhang P, Wen F, Li Q. FOLFOX4 or sorafenib as the first-line treatments for advanced hepatocellular carcinoma: A cost-effectiveness analysis. Digestive and Liver Disease. 2016;48(12):1492-7.

48. Cammà C, Cabibbo G, Petta S, Enea M, Iavarone M, Grieco A, et al. Cost-effectiveness of sorafenib treatment in field practice for patients with hepatocellular carcinoma. Hepatology. 2013;57(3):1046-54.

49. Carr BI, Carroll S, Muszbek N, Gondek K. Economic evaluation of sorafenib in unresectable hepatocellular carcinoma. Journal of gastroenterology and hepatology. 2010;25(11):1739-46.

50. Chaplin S, Taylor M, Lapon J, White J. Economic evaluation of glass yttrium-90 microspheres versus sorafenib for the treatment of advanced hepatocellular carcinoma : Cost effectiveness analysis in the United Kingdom. CardioVascular and Interventional Radiology. 2015;38(3):S279-S80.

51. Muszbeck N, Munir U, Vioix H, Schiola A, Valderrama A, Teich V. PCN64 Cost-effectiveness analysis of sorafenib versus best supportive care (BSC) in advanced hepatocellular carcinoma (AHCC): the public health care system perspective in Brazil. Value in Health. 2010;13(3):A35.

52. Muszbeck N, Vioix H, Munir U, Schiola A, Valderrama A, Teich V. PCN68 Cost-effectiveness analysis of sorafenib versus best supportive care (BSC) in advanced hepatocellular carcinoma (AHCC): the private health care system perspective in Brazil. Value in Health. 2010;13(3):A36.

53. Muszbek N, Shah S, Carroll S, McDonald H, Dale P, Maroun J, et al. Economic evaluation of sorafenib in the treatment of hepatocellular carcinoma in Canada. Current medical research and opinion. 2008;24(12):3559-69.

54. National Institute for Health and Care Excellence. Sorafenib for the treatment of advanced hepatocellular carcinoma (TA189) 2010 [Available from: https://www.nice.org.uk/guidance/ta189.

55. Scottish Medicines Consortium. Sorafenib (Nexavar) re-submission 2011 [Available from: https://www.scottishmedicines.org.uk/SMC_Advice/Advice/482_08_sorafenib__Nexavar_/sorafenib_Nexavar_Resubmission

56. Scottish Medicines Consortium. Sorafenib (Nexavar) 2nd re-submission 2015 [Available from: https://www.scottishmedicines.org.uk/SMC_Advice/Advice/482_08_sorafenib__Nexavar_/sorafenib_Nexavar_2nd_Resubmission

57. Zhang P, Yang Y, Wen F, He X, Tang R, Du Z, et al. Cost-effectiveness of sorafenib as a first-line treatment for advanced hepatocellular carcinoma. European journal of gastroenterology & hepatology. 2015;27(7):853-9.

58. Qin SK, Kruger E, Tan SC, Cheng SQ, Yao XX, Liang J. Cost-Effectiveness Analysis of Oxaliplatin Plus Fluorouracil/Leucovorin (Folfox4) Compared to Sorafenib for Treatment of Advanced Hepatocellular Carcinoma Patients in China. Value in Health. 2016;19(7):A889-A.

59. Rognoni C, Ciani O, Sommariva S, Tarricone R. Real-World Data for the Evaluation of Transarterial Radioembolization versus Sorafenib in Hepatocellular Carcinoma: A Cost-Effectiveness Analysis. Value in Health. 2017;20(3):336-44.

60. Zhang P, Yang Y, Wen F, Wheeler J, Fu P, Li Q. Cost-effectiveness analysis of antiviral therapy in patients with advanced hepatitis B virus-related hepatocellular carcinoma treated with sorafenib. Journal of Gastroenterology and Hepatology. 2016;31(12):1978-85.

61. Connock M, Round J, Bayliss S, Tubeuf S, Greenheld W, Moore D. Sorafenib for the treatment of advanced hepatocellular carcinoma. Health Technology Assessment Database. 2010.

62. Scottish Medicines Consortium. Sorafenib (Nexavar) full submission 2008 [Available from: https://www.scottishmedicines.org.uk/SMC_Advice/Advice/482_08_sorafenib__Nexavar_/sorafenib__Nexavar_

63. Lockart I, Coppock J, Roy S, Levy M, Davison S. Sorafenib treatment patterns and estimated cost in a real world setting. Journal of Gastroenterology and Hepatology (Australia). 2016;31(Supplement 2):109-.

64. Bruix J, Merle P, Granito A, Huang YH, Bodoky G, Yokosuka O, et al. Efficacy, safety, and health-related quality of life (HRQoL) of regorafenib in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: Results of the international, double-blind phase 3 RESORCE trial. Annals of Oncology. 2016;27(suppl_6):LBA28-LBA.

65. Bruix J, Merle P, Granito A, Huang YH, Bodoky G, Yokosuka O, et al. LBA-03Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: results of the international, randomized phase 3 RESORCE trial. Annals of Oncology. 2016;27(suppl_2):ii140-ii1.

66. US National Institutes of Health. Study of Regorafenib After Sorafenib in Patients With Hepatocellular Carcinoma (RESORCE) NCT01774344. ClinicalTrialsgov. 2016.

67. Bolondi L, Tak WY, Gasbarrini A, Santoro A, Colombo M, Lim HY, et al. 6576 POSTER Phase II Safety Study of the Oral Multikinase Inhibitor Regorafenib (BAY 73-4506) as Second-line Therapy in Patients With Hepatocellular Carcinoma. European Journal of Cancer. 2011;47:S464.

68. Bruix J, Merle P, Granito A, Huang YH, Bodoky G, Yokosuka O, et al. LBA-03 Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: results of the international, randomized phase 3 RESORCE trial (abstract). Annals of Oncology. 2016;27(suppl_2):ii140-ii1.

69. Yu L, Su R, Wang B, Zhang L, Zou Y, Zhang J, et al. Prediction of novel drugs for hepatocellular carcinoma based on multi-source random walk. IEEE/ACM transactions on computational biology and bioinformatics. 2016.

70. Cheng A-L, Finn RS, Kudo M, Llovet JM, Qin S, Le Berre M-A, et al., editors. Regorafenib (REG) in patients with hepatocellular carcinoma (HCC) progressing following sorafenib: An ongoing randomized, double-blind, phase III trial. American Society Clinical Oncology; 2013: J Clin Oncol.

71. Bruix J, Finn RS, Kudo M, Llovet JM, Qin S, Le Berre M-A, et al., editors. RESORCE: An ongoing randomized, double-blind, phase III trial of regorafenib (REG) in patients with hepatocellular carcinoma (HCC) progressing on sorafenib

(SOR). Journal of Clinical Oncology; 2014: Amer Soc Clinical Oncology 2318 Mill Road, STE 800, Alexandria, VA 22314 USA.

72. Ribeiro de Souza A, Reig M, Bruix J. Systemic treatment for advanced hepatocellular carcinoma: the search of new agents to join sorafenib in the effective therapeutic armamentarium. Expert Opinion on Pharmacotherapy. 2016;17(14):1923-36.

73. Woo HY, Yoo SY, Heo J. New chemical treatment options in second-line hepatocellular carcinoma: what to do when sorafenib fails? Expert Opinion on Pharmacotherapy. 2017;18(1):35-44.

74. Trojan J, Waidmann O. Role of regorafenib as second-line therapy and landscape of investigational treatment options in advanced hepatocellular carcinoma. Journal of Hepatocellular Carcinoma. 2016;3:31.

75. von Felden J, Schulze K, Gil-Ibanez I, Werner T, Wege H. First-and second-line targeted systemic therapy in hepatocellular carcinoma—An update on patient selection and response evaluation. Diagnostics. 2016;6(4):44.

76. Bruix J. Regorafenib and the RESORCE trial: a new second-line option for hepatocellular carcinoma patients. 2016.

77. Kudo M. Recent advancement in HCC treatment. Liver Cancer. 2016;5:1.

78. Abou-Alfa G. An odyssey from doxorubicin to nivolumab with sorafenib and regorafenib in between. Liver Cancer. 2016;5:43.

79. Killock D. Liver cancer: Regorafenib a new RESORCE in HCC. Nature Reviews Clinical Oncology. 2016.

80. Finn RS. Highlights on targeted therapy for HCC. Liver Cancer. 2016;5:7.

81. US National Institutes of Health. Safety Study of BAY73-4506 in Patients With Hepatocellular Carcinoma (NCT01003015). ClinicalTrialsgov. 2015.

82. Colombo GL, Cammà C, Attili AF, Ganga R, Gaeta GB, Brancaccio G, et al. Intermediate and Advanced Hepatocellular Carcinoma Management in four Italian Centers: Patterns of Treatment and Costs. Value in Health. 2015;18(7):A451-A2.

83. Li IF, Tasy S-L, Bair MJ, Wang T-E. Fear of progression and quality of life in patients with hepatocellular carcinoma. Psycho-Oncology. 2015;24:104-357.

84. Brunocilla PR, Gaia S, Carucci P, Rolle E, Castiglione A, Rizzetto M, et al. Sorafenib In Advanced Hepatocellular Carcinoma (hcc): A Prospective Observational Study On Side Effects And Quality Of Life. Hepatology. 2011;54(4):1396A.

85. Barone C, Brandi G, Daniele B, Villa E, Leo S, Di Fabio F, et al. L03Ramucirumab (RAM) as Second-Line Treatment in Patients with Advanced Hepatocellular Carcinoma (HCC) Following First-Line Therapy with Sorafenib:

Analyses from the Randomized Phase III REACH Study. Annals of Oncology. 2015;26(suppl_6):vi-vi.

86. Koeberle D, Dufour J-F, Demeter G, Samaras P, Saletti P, Li Q, et al. Sorafenib with or without everolimus in patients with unresectable hepatocellular carcinoma (HCC): A randomized multicenter phase II trial (SAKK 77/08 and SASL 29). J Clin Oncol. 2014;32(suppl 5s):abstr 4099.

87. Palmer DH, Hussain SA, Smith AJ, Hargreaves S, Ma YT, Hull D, et al. Sorafenib for advanced hepatocellular carcinoma (HCC): impact of rationing in the United Kingdom. Br J Cancer. 2013;109(4):888-90.

88. Shaya FT, Breunig IM, Seal B, Mullins CD, Chirikov VV, Hanna N. Comparative and cost effectiveness of treatment modalities for hepatocellular carcinoma in SEER-Medicare. Pharmacoeconomics. 2014;32(1):63-74.

89. Palmer D, Hussain S, Smith A, Hull D, Johnson P. Sorafenib for advanced hepatocellular carcinoma (HCC): Impact of rationing in the United Kingdom. Journal of Clinical Oncology. 2010;28(15_suppl):e14516-e.

90. Smith A, Hussain S, Hull D, Johnson P, Palmer D. Sorafenib for advanced Hepatocellular Carcinoma (HCC): Impact of rationing in the United Kingdom. Annals of Oncology. 2010;21(suppl_6):vi95.

91. Abou-Alfa GK, Cheng A-L, Meyer T, El-Khoueiry AB, Ikeda M, Chun HG, et al. Phase 3 randomized, double-blind, controlled study of cabozantinib (XL184) versus placebo in subjects with hepatocellular carcinoma who have received prior sorafenib (CELESTIAL; NCT01908426). American Society of Clinical Oncology; 2014.

92. Koeberle D, Dufour JF, Demeter G, Li Q, Ribi K, Samaras P, et al. Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29). Ann Oncol. 2016;27(5):856-61.

93. Mantovani G, Massa E, Spiga C, Chessa L, Madeddu C, Zolfino T, et al. Efficacy, safety and impact on quality of life of sorafenib in elderly patients with advaced hepatocellular carcinoma. Preliminary results of a phase II study. Journal of Hepatology. 2009;50:S294.

94. Patel AA, Walling AM, Saab S, Wenger N. Palliative care and resource utilization at the end of life in advanced liver disease. Journal of General Internal Medicine. 2016;31(2):321.

95. Imai Y, Hiraoka A, Shiraishi A, Tatsukawa H, Yamago H, Azemoto N, et al. Antibiotic prophylaxis in transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma. Acta Hepatologica Japonica 2013;51(10):713-5.

96. Xing M, Prajapati HJ, Webber GR, Kim HS. Staged Doxorubicin Eluting Bead Transarterial Chemo-embolization Therapy for Unresectable Hepatocellular Carcinoma Confers to Survival Advantage with Preservation of Quality of Life. Hepatology. 2014;60:875A.

97. Rifayi M, Lavanya G, Nithiyanantham K, Sirohi B, Gopalakrishnan G, Krishnatry R. Impact on quality of life with stereotactic RT in advanced hepatocellular carcinoma : Initial institutional experience. European Journal of Cancer. 2016;54:S4.

98. Shomura M, Kagawa T, Shiraishi K, Hirose S, Arase Y, Tsuruya K, et al. Longitudinal alteration in health-related quality of life and its impact on clinical course in patients with advanced hepatocellular carcinoma who received sorafenib treatment. Hepatology. 2015;62:370A-1A.

99. Bai M, Reynolds NR, McCorkle R. The promise of clinical interventions for hepatocellular carcinoma from the west to mainland China. Palliative and Supportive Care. 2013;11(06):503-22.

100. Kallini J, Gabr A, Hickey R, Desai K, Thornburg B, Lewandowski R, et al. Palliative trans-arterial locoregional therapy for hepatocellular carcinoma: a cost analysis using the 2015 American Society of Clinical Oncology value of cancer framework. Journal of Vascular and Interventional Radiology. 2016;3(27):S66.

101. Megias Vericat JE, Garcia Marcos R, Lopez Briz E, Gomez Munoz F, Ramos Ruiz J, Martinez Rodrigo JJ, et al. Trans-arterial chemoembolization with doxorubicin-eluting particles versus conventional trans-arterial chemoembolization in unresectable hepatocellular carcinoma: A study of effectiveness, safety and costs. Radiologia. 2015;57(6):496-504.

102. Palozzo A, Trojniack MP, Paganelli F, Faoro S, Bertipaglia C. Sorafenib in hepatocarcinoma : A model to evaluate effectiveness and appropriateness of drugs using the Italian RFOM registry. Journal of Oncology Pharmacy Practice 2010(2):17.

103. Zhou M, Ng KF. Cancer treatment in China: How are policy and practice in tier 1 versus tier 2/3 cities impacting patient access to high-cost therapies. Value in Health. 2014;17(7):A739.

104. Shaya FT, Breunig IM, Hanna N, Chirikov V, Seal BS, Mullins CD. The cost-effectiveness of transarterial chemoembolization treatments. American Society of Clinical Oncology; 2012.

105. Gilbertsen P, Coffey S, Gonda E, Karp J, Marshall K, Memon K, et al. Abstract No. 182: Quality of life assessment of patients treated with Yttrium-90 or transarterial chemoembolization: A comparative study using the fact-hep. Journal of Vascular and Interventional Radiology. 2011;22(3):S79.

106. N/A. Sorafenib for advanced hepatocellular carcinoma (HCC): horizon scanning review (Structured abstract). Health Technology Assessment Database. 2006.

107. Canadian Agency for Drugs and Technologies in Health. Yttrium-90 microspheres (TheraSphere (TM) and SIR-Spheres (TM)) for the treatment of unresectable hepatocellular carcinoma (Structured abstract). Health Technology Assessment Database. 2007.

108. NSHC. Erlotinib (Tarceva) in combination with sorafenib (Nexavar) for unresectable, advanced or metastatic hepatocellular carcinoma? first line (Structured abstract). Health Technology Assessment Database. 2011.

109. N/A. Sorafenib for the treatment of advanced hepatocellular carcinoma (Structured abstract). Health Technology Assessment Database;. 2010.

110. Belinson S, Yang Y, Chopra R, Shankaran V, Samson D, Aronson N. Local therapies for unresectable primary hepatocellular carcinoma (Structured abstract). Health Technology Assessment Database. 2013.

111. Uka K, Aikata H, Takaki S, Miki D, Jeong SC, Hiramatsu A, et al. Similar effects of recombinant interferon-alpha-2b and natural interferon-alpha when combined with intra-arterial 5-fluorouracil for the treatment of advanced hepatocellular carcinoma (Provisional abstract). Liver International. 2007.

112. National Institute for Health and Care Excellence. Hepatocellular carcinoma (advanced and metastatic) - sorafenib (first line) (review of TA189) [ID1012] - CDF rapid reconsideration process.

113. Scottish Medicines Consortium. Briefing Note - sorafenib (Nexavar). 2008.

114. Scottish Medicines Consortium. Briefing note: sorafenib Nexavar (Resubmission). 2011.

115. Scottish Medicines Consortium. Briefing note: sorafenib Nexavar (2nd resubmission). 2015.

116. Canadian Agency for Drugs and Technologies in Health. Yttrium-90 Microsphere Radioembolization for the Treatment of Primary or Secondary Liver Cancer: Clinical Effectiveness, Cost-Effectiveness, and Guidelines. 2016.

117. Canadian Agency for Drugs and Technologies in Health. Yttrium-90 Microspheres for Cancer Patients with Primary or Secondary Liver Tumors: Clinical and Cost-Effectiveness. 2011.

118. Haute Autorité de santé. NEXAVAR. 2008.

119. Gemeinsamer Bundesausschuss. Protonentherapie beim inoperablen hepatozellulären Karzinom 2015.

120. Zhu AX, Galle PR, Kudo M, Finn R, Yang L, Abada P, et al. A randomized, double-blind, placebo-controlled phase III study of ramucirumab versus placebo as second-line treatment in patients with hepatocellular carcinoma and elevated baseline alpha-fetoprotein following first-line sorafenib (REACH-2). Annals of Oncology. 2016;27(suppl 6):710TiP.

121. Mutsaers A, Greenspoon J, Walker-Dilks C, Swaminath A. Systematic Review of Patient-Reported Quality of Life Following Stereotactic Ablative Body Radiation Therapy for Primary and Metastatic Liver Cancer. International Journal of Radiation Oncology• Biology• Physics. 2016;96(2):E536-E7.

122. Lawrie TA, Bryant A, Cameron A, Gray E, Morrison J. Pegylated liposomal doxorubicin for relapsed epithelial ovarian cancer. The Cochrane Library. 2013.

123. Zeghari-Squalli N. Stereotactic Radiation Therapy for Liver Tumours France: HAS; 2016.

124. Sanoff HK, Chang Y, Lund JL, O'Neil BH, Dusetzina SB. Sorafenib Effectiveness in Advanced Hepatocellular Carcinoma. Oncologist. 2016;21(9):1113-20.

125. D.E. K, editor Up-titration of sorafenib for hepatocellular carcinoma: Impact on duration of exposure and cost. ASCO; 2017.

126. Intaraprasong P, Siramolpiwat S, Vilaichone RK. Advances in Management of Hepatocellular Carcinoma. Asian Pac J Cancer Prev. 2016;17(8):3697-703.

127. Bonnetain F, Paoletti X, Collette S, Doffoel M, Bouché O, Raoul JL, et al. Quality of life as a prognostic factor of overall survival in patients with advanced hepatocellular carcinoma: results from two French clinical trials. Quality of Life Research. 2008;17(6):831.

128. Diouf M, Filleron T, Barbare J-C, Fin L, Picard C, Bouché O, et al. The added value of quality of life (QoL) for prognosis of overall survival in patients with palliative hepatocellular carcinoma. Journal of hepatology. 2013;58(3):509-21.

129. Gill ML, Atiq M, Sattar S, Khokhar N. Treatment outcomes with long acting octreotide in inoperable hepatocellular carcinoma: a local experience and review of literature. Appetite. 2005;2(4):0.003.

130. Li YY, Sha WH, Zhou YJ, Nie YQ. Short and long term efficacy of high intensity focused ultrasound therapy for advanced hepatocellular carcinoma. Journal of gastroenterology and hepatology. 2007;22(12):2148-54.

131. Phillips R, Gandhi M, Cheung YB, Findlay MP, Win KM, Hai HH, et al. Summary scores captured changes in subjects' QoL as measured by the multiple scales of the EORTC QLQ-C30. Journal of clinical epidemiology. 2015;68(8):895-902.

132. Xing M, Kokabi N, Camacho JC, Spivey JR, Hanish SI, El-Rayes B, et al. Longitudinal quality of life assessment in patients with unresectable advanced infiltrative hepatocellular carcinoma with portal vein thrombosis post yittrium-90 radioembolization. Journal of Vascular and Interventional Radiology. 2013;24(5):759.e3.

133. Xing M, Webber G, Prajapati HJ, Chen Z, El-Rayes B, Spivey JR, et al. Preservation of quality of life with doxorubicin drug-eluting bead transarterial chemoembolization for unresectable hepatocellular carcinoma: Longitudinal prospective study. Journal of gastroenterology and hepatology. 2015;30(7):1167-74.

134. Yau T, Cheng PN, Chan P, Chen L, Yuen J, Pang R, et al. Preliminary efficacy, safety, pharmacokinetics, pharmacodynamics and quality of life study of

pegylated recombinant human arginase 1 in patients with advanced hepatocellular carcinoma. Investigational new drugs. 2015;33(2):496-504.

135. Yeo W, Mo F, Koh J, Chan A, Leung T, Hui P, et al. Quality of life is predictive of survival in patients with unresectable hepatocellular carcinoma. Annals of oncology. 2006;17(7):1083-9.

136. Yau TC, Paul N-MC, Pierre C, Roberta P, Ronnie TPP. Preliminary efficacy, safety, pharmacokinetics, pharmacodynamics, and quality of life study of pegylated recombinant human arginase 1 in patients with advanced hepatocellular carcinoma. J Clin Oncol 2014;32((suppl; abstr e15137)).

137. Rognoni C, Ciani O, Sommariva S, Tarricone R. Real-World Data for the Evaluation of Transarterial Radioembolization versus Sorafenib in Hepatocellular Carcinoma: A Cost-Effectiveness Analysis. Value in Health. 2016.

138. Shomura M, Kagawa T, Okabe H, Shiraishi K, Hirose S, Arase Y, et al. Longitudinal alterations in health-related quality of life and its impact on the clinical course of patients with advanced hepatocellular carcinoma receiving sorafenib treatment. BMC cancer. 2016;16(1):878.

139. Hulstaert F, Schwierz C, Nevens F, Thiry N, Gamil M, Colle I, et al. Should chronic hepatitis B be treated as early as possible? International journal of technology assessment in health care. 2013;29(01):35-41.

140. Tanaka H, Iijima H, Nouso K, Aoki N, Iwai T, Takashima T, et al. Cost-effectiveness analysis on the surveillance for hepatocellular carcinoma in liver cirrhosis patients using contrast-enhanced ultrasonography. Hepatology Research. 2012;42(4):376-84.

141. Liu S, Schwarzinger M, Carrat F, Goldhaber-Fiebert JD. Cost effectiveness of fibrosis assessment prior to treatment for chronic hepatitis C patients. PLoS One. 2011;6(12):e26783.

142. Lee KK, Wu DBC, Chow PY, Lee VWY, Li H. Economic analysis between entecavir and lamivudine for the treatment of chronic hepatitis B in Hong Kong. Journal of gastroenterology and hepatology. 2012;27(7):1167-74.

143. Ruggeri M, Cicchetti A, Gasbarrini A. The cost-effectiveness of alternative strategies against HBV in Italy. Health Policy. 2011;102(1):72-80.

144. Dakin H, Bentley A, Dusheiko G. Cost–utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B. Value in Health. 2010;13(8):922-33.

145. Saab S, Hunt DR, Stone MA, McClune A, Tong MJ. Timing of hepatitis C antiviral therapy in patients with advanced liver disease: a decision analysis model. Liver Transplantation. 2010;16(6):748-59.

146. Yuan Y, Iloeje UH, Hay J, Saab S. Evaluation of the cost-effectiveness of entecavir versus lamivudine in hepatitis BeAg-positive chronic hepatitis B patients. Journal of Managed Care Pharmacy. 2008;14(1):21-33.

147. Barros FM, Cheinquer H, Tsuchiya CT, Santos EA. Cost-effectiveness analysis of treatment with peginterferon-alfa-2a versus peginterferon-alfa-2b for patients with chronic hepatitis C under the public payer perspective in Brazil. Cost Effectiveness and Resource Allocation. 2013;11(1):25.

148. Kuan RK, Janssen R, Heyward W, Bennett S, Nordyke R. Cost-effectiveness of hepatitis B vaccination using HEPLISAV™ in selected adult populations compared to Engerix-B® vaccine. Vaccine. 2013;31(37):4024-32.

149. Wiens A, Lenzi L, Venson R, Pedroso MLA, Correr CJ, Pontarolo R. Economic evaluation of treatments for chronic hepatitis B. The Brazilian Journal of Infectious Diseases. 2013;17(4):418-26.

150. Cammà C, Petta S, Cabibbo G, Ruggeri M, Enea M, Bruno R, et al. Cost-effectiveness of boceprevir or telaprevir for previously treated patients with genotype 1 chronic hepatitis C. Journal of hepatology. 2013;59(4):658-66.

151. Hutton DW, So SK, Brandeau ML. Cost-effectiveness of nationwide hepatitis B catch-up vaccination among children and adolescents in China. Hepatology. 2010;51(2):405-14.

152. Hutton DW, Tan D, So SK, Brandeau ML. Cost-effectiveness of screening and vaccinating Asian and Pacific Islander adults for hepatitis B. Annals of Internal Medicine. 2007;147(7):460-9.

153. Cucchetti A, Trevisani F, Cescon M, Ercolani G, Farinati F, Del Poggio P, et al. Cost-effectiveness of semi-annual surveillance for hepatocellular carcinoma in cirrhotic patients of the Italian Liver Cancer population. Journal of hepatology. 2012;56(5):1089-96.

154. Canavan C, Eisenburg J, Meng L, Corey K, Hur C. Ultrasound elastography for fibrosis surveillance is cost effective in patients with chronic hepatitis C virus in the UK. Digestive diseases and sciences. 2013;58(9):2691-704.

155. Wells C, Murrill W, Arguedas M. Comparison of Health-Related Quality of Life Preferences Between Physicians and Cirrhotic Patients: Implications for Cost–Utility Analyses in Chronic Liver Disease. Digestive diseases and sciences. 2004;49(3):453-8.

156. Grishchenko M, Grieve RD, Sweeting MJ, De Angelis D, Thomson BJ, Ryder SD, et al. Cost-effectiveness of pegylated interferon and ribavirin for patients with chronic hepatitis C treated in routine clinical practice. International journal of technology assessment in health care. 2009;25(02):171-80.

157. Landman MP, Feurer ID, Pinson CW, Moore DE. Which is more cost-effective under the MELD system: primary liver transplantation, or salvage transplantation after hepatic resection or after loco-regional therapy for hepatocellular carcinoma within Milan criteria? HPB. 2011;13(11):783-91.

158. Vitale A, Volk ML, Pastorelli D, Lonardi S, Farinati F, Burra P, et al. Use of sorafenib in patients with hepatocellular carcinoma before liver transplantation: A cost-benefit analysis while awaiting data on sorafenib safety. Hepatology. 2010;51(1):165-73.

159. National Institute for Health and Care Excellence. Specification for manufacturer/sponsor submission of evidence. 2012.

160. National Institute for Health and Care Excellence. Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma. 2009.

161. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in advanced hepatocellular carcinoma. New England journal of medicine. 2008;359(4):378-90.

162. Cheng A-L, Kang Y-K, Chen Z, Tsao C-J, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. The lancet oncology. 2009;10(1):25-34.

163. Beheshti MV, Meek J. Calculation of operating expenses for conventional transarterial chemoembolization in an academic medical center: a step toward defining the value of transarterial chemoembolization. Journal of Vascular and Interventional Radiology. 2014;25(4):567-74.

164. Colombo GL, Camma C, Attili AF, Ganga R, Gaeta GB, Brancaccio G, et al. Patterns of treatment and costs of intermediate and advanced hepatocellular carcinoma management in four Italian centers. Therapeutics and clinical risk management. 2015;11:1603-12.

165. Hidajat N, Griesshaber V, Hildebrandt B, Hosten N, Schröder R-J, Felix R. Repetitive transarterial chemoembolization (rTACE) of hepatocellular carcinoma: comparisons between an arterial port system and conventional angiographic technique. European journal of radiology. 2004;51(1):6-11.

166. Hwang S-J, Chang H-T, Hwang I-H, Wu C-Y, Yang W-H, Li C-P. Hospice offers more palliative care but costs less than usual care for terminal geriatric hepatocellular carcinoma patients: a nationwide study. Journal of palliative medicine. 2013;16(7):780-5.

167. Liepa AM, Candrilli, Sean D. , D'yachkova, Yulia , Taipale, Kaisa , Kaye, James A. Economic burden of advanced hepatocellular carcinoma (HCC) in Spain among patients discontinuing first-line sorafenib. Journal of Clinical Oncology. 2014;32(3).

168. Malbranche C, Boulin M, Guiu B, Pernot C, Cercueil J-P, Serge AL, et al. Economic impact of transarterial chemoembolization with drug eluting beads in the treatment of hepatocellular carcinoma. Bulletin du cancer. 2011;98(6):671-8.

169. McGhan AA, Kaplan, David E. Costs of palliative treatments of intermediate and advanced stage hepatocellular carcinoma may exceed usually accepted limits of cost effectiveness. Hepatology. 2012;56:1097A.

170. Nani R, De Giorgio, M. , Virotta, G. , Lucà, M.G. , Bianchi, C. , Baldan, A. , Fagiuoli, S. , Agazzi, R. A single-centre cost analysis in treatment of advanced hepatocellular carcinoma : TARE versus sorafenib. CardioVascular and Interventional Radiology. 2015;38(3):S260-S1.

171. Stokes M, Liepa A, Chuang C-C, D'yachkova Y, Wang A, Boulanger L, et al. US treatment patterns and costs for patients with hepatocellular cancer who received sorafenib as first-line treatment. Ann Oncol. 2012;23(suppl 4):58.

172. Tan JYC, Crest, P. , Roberts, S. , Kemp, W. Health care costs associated with hepatocellular carcinoma management in an australian teritary care institiution. Journal of Gastroenterology and Hepatology. 2013;28:77.

173. Tang C, Shen J, Feng W, Bao Y, Dong X, Dai Y, et al. Combination therapy of radiofrequency ablation and transarterial chemoembolization for unresectable hepatocellular carcinoma: a retrospective study. Medicine. 2016;95(20).

174. Vadot L, Boulin M, Malbranche C, Guiu B, Aho S, Musat A, et al. Result and cost of hepatic chemoembolisation with drug eluting beads in 21 patients. Diagnostic and interventional imaging. 2013;94(1):53-9.

175. Besur S, Walters AL, Lincourt A, Levi DM, Russo MW. P579 Operative and Nonoperative utilization in inpatients with hepatocellular carcinoma from 2000-2010 in the United States. Journal of Hepatology. 2014;60(1):S262-S.

176. Hunter N, Potosek JE, Miksad RA. Hepatocellular carcinoma and end-of-life care. J Clin Oncol. 2014;32(30).

177. Liepa AM, Candrilli SD, D'Yachkova Y, Taipale K, Kaye JA. Economic burden of advanced hepatocellular carcinoma (HCC) in Spain among patients discontinuing first-line sorafenib. Journal of Clinical Oncology. 2014;32(3 suppl 1):324.

178. Liu A, Do A. Palliative Care Utilization is Associated with Reduced Costs and Reduced Procedures in the Setting of Hepatocellular Carcinoma with Mortality: A Study of the National Inpatient Sample. Hepatology. 2016;64(1):719A-20A.

179. Pollom EL, Lee K, Durkee BY, Grade M, Mokhtari DA, Wahl DR, et al. Cost-effectiveness of Stereotactic Body Radiation Therapy versus Radiofrequency Ablation for Hepatocellular Carcinoma: A Markov Modeling Study. Radiology. 2017;283(2):460-8.

180. Bolondi L, Cillo U, Colombo M, Craxì A, Farinati F, Giannini EG, et al. Position paper of the Italian Association for the Study of the Liver (AISF): The multidisciplinary clinical approach to hepatocellular carcinoma. Digestive and Liver Disease. 2013;45(9):712-23.

181. Thomson Healthcare. RED BOOK™ for Windows®. 2007.

182. Centers Medicare and Medicaid Services. Clinical Laboratory Fee. 2010.

183. Elsevier HS. DRG Expert 2007: A Comprehensive Guidebook to the DRG Classification System. 2006.

184. Conferenza delle Regioni e Provincie Autonome. Tariffa Unica Concezionale per le prestazioni di assistenza ospedaliera. Regole e tariffe valide per il 2006. 2005.

185. Munari L PA. Recombinant interferon alfa-2b therapy for chronic hepatitis C in Italy: an economic analysis. FORUM Trends Exp Clin Med 1996;6:347-53.

186. Ministry of Health and Long term care. Ontario Drug benefit formulary 2006.

187. Ministry of Health and Long term care. Ontario Schedule of Benefits for PHysicians under the Health Insurance Act. 2007.

188. Ministry of Health and Long term care. Hospital participating in the Ontario Case Costing Project. 2007.

189. Ministry of Health British Colombia. British Columbia Medical Services Commission Payment Schedule. 2007.

190. University Health Network Toronto. 2006.

191. National Health Insurance research database. 2015.

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Single technology appraisal

Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]

Dear [redacted]

The Evidence Review Group, ScHARR-TAG, and the technical team at NICE have looked at the submission received on 10 July 2017 from Bayer. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **15 August 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals NICE Docs.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Sana Khan, Technical Lead (Sana.Khan@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (Stephanie.Yates@nice.org.uk)

Yours sincerely

Alexandra Filby
Technical Adviser– Appraisals

On behalf of:
Dr. Frances Sutcliffe
Associate Director – Appraisals

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Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

Systematic literature review

A1. Please confirm if data extraction and quality assessment were undertaken independently by a minimum of two reviewers for the clinical effectiveness reviews. If this was not done, please explain why.

A2. Please clarify why the abstract Bruix et al. (2016) (reference number 23 in the company submission) was excluded. Appendix D1.1, Table 65 (page 190 of the company submission), suggests that the reason for exclusion was 'study design'. However, this paper is an abstract reporting findings from the RESORCE RCT and is also cited and used in the company submission, section B2.3 (page 28).

A3. Appendix D1.3, Table 67 (page 196 of the company submission): Please specify the critical appraisal tool used.

A4. Appendix D1.3, Table 67 (page 196 of the company submission): In response to the question, "Is there any evidence to suggest that the authors measured more outcomes than they reported?", the answer given is "no because results of all pre-specified outcomes are reported in full". However, this has not been demonstrated within the company submission. Please provide a list of all of the intended outcomes to be assessed in the RESORCE trial and indicate with data or page numbers in the company submission or clinical study report (CSR) that all of these outcomes were indeed reported.

A5. The footnote in Table 16 (page 50 of the company submission) states that five patients in the regorafenib group and one from the placebo group did not receive the study drug. Please provide the reasons for this.

Clinical trial design

A6. **Priority question:** Please clarify whether the marketing authorisation for regorafenib as stated in the company submission (Table 2, page 17): "adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib" will **include** the following groups, who were all excluded from the RESORCE trial.

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a. **Patients who are intolerant to sorafenib (not contraindicated) in the trial**: Table 6 in the company submission (page 31) reports the exclusion criteria of the RESORCE trial to be: 'Permanent discontinuation of prior sorafenib therapy due to sorafenib related toxicity'. The company submission acknowledges that the safety and efficacy of regorafenib in this group is 'unknown' (page 85) and states that the 'anticipated licence' will not include this group. This is different from Table 2 (page 17 in the company submission) which states that the marketing authorisation is for: "adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib". Please clarify whether the marketing authorisation for regorafenib will or will not include patients who are intolerant to sorafenib.

b. **Patients with Child-Pugh class B**: Table 30 (page 86 of the company submission) indicates that 16% of 448 sorafenib-treated patients in the UK are Child-Pugh class B. It is also noted in a footnote for Table 15 (page 49 of the company submission) that a small number of Child-Pugh B patients were included in the RESORCE trial for whom there is no relevant evidence on the efficacy or safety of regorafenib. However, page 88 of the company submission acknowledges that this group is absent from the RESORCE trial.

c. **Patients with ECOG performance status of 2**: Table 30 (page 86 of the company submission) indicates that 21% of 448 sorafenib-treated patients in the UK are ECOG performance status 2. However, page 88 of the company submission acknowledges that this group is absent from the RESORCE trial.

A7. Appendix D1.3, Table 67 (page 196 of the company submission) notes that, 'no imputation was performed for missing lesion assessment and tumour response (in the RESORCE trial). For example, if a patient missed a scan visit and progressive disease (PD) was documented at the next available scan visit, the actual visit date of the first documented PD was used to calculate progression free survival (PFS) and time to progression (TTP). Please clarify whether this means that the recorded date of progression might be later than when progression actually occurred. Also, please indicate how many patients in each arm of the RESORCE trial might be affected by this.

A8. Please provide the RESORCE trial protocol, listed in the CSR as being in Section 16.1.1 (this section has not been made available).

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Section B: Clarification on cost-effectiveness data

Extrapolation of survival outcomes

B1. **Priority question.** Page 28 of the company submission states that "After the primary endpoint of the study was reached (overall survival [OS]; 29th February 2016) and the results supported a positive benefit / risk assessment for regorafenib, patients on placebo at that time were offered the opportunity of receiving regorafenib through open-label treatment and patients randomised to regorafenib could continue open-label regorafenib. Data presented in this submission relates to the double-blind period only." Furthermore, page 54 of the company submission states that "This submission presents the study results from the clinical database released on 5th August 2016." There is a potential for the different dates (29th February 2016 and 5th August 2016) to cause confusion and uncertainty in the results reported:

a. Please clarify if results included in the company submission and the company model, report data from the clinical database released on the 5 August 2016 and include data from patients after the primary endpoint of the trial was reached on 29 February 2016 and treatment switching had occurred.

b. If data after treatment switching is reported please provide an additional analysis of the trial data up to the August 2016 datalock which includes appropriate consideration of statistical adjustments for treatment switching.

B2. **Priority question.** Page 119 of the company submission states that "Coupled with the largely parallel log cumulative hazard curves, this result suggests that the proportional hazards assumption is plausible, so survival was modelled using dependent survival curves."

a. Given that the log cumulative hazard curves presented in Figure 14 (page 119 of company submission) cross, please explain why it was considered appropriate to assume proportional hazards.

b. Please provide a separate analysis in which independent models are fitted to the overall survival data for each treatment group (that is, not including a treatment covariate). Please also include independent generalised gamma models. Please provide results for statistical fit and an updated Table 36 in the company submission (including generalised gamma).

c. Given that the lognormal distribution was selected for overall survival, please clarify why a hazard ratio has been applied to this model rather than an acceleration factor. Please provide the acceleration factor associated with this joint model.

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d. The section on “Clinical Validity” (page 121 of the company submission) discusses the difference between the observed and predicted overall survival cumulative survival probabilities at cycle 35 (within the observed period of the RESORCE trial). Please explain how the clinical plausibility of the extrapolated curves was considered in the model selection exercise.

e. Please comment on the selection of 35 cycles as a comparison point in Table 36 (page 123 of the company submission). Additionally, please add the cycle which corresponds to the last data point on the Kaplan-Meier curves (cycle 36?) to Table 36.

B3. Please provide the empirical hazard function plot for both progression free survival and overall survival.

B4. Table 55 (page 153 of the company submission): A hazard ratio for progression free survival is reported in the table, however, the model uses the observed Kaplan-Meier progression free survival curves directly rather than a selected parametric function. Please explain how and why was this hazard ratio was included in the probabilistic sensitivity analysis?

B5. In the probabilistic sensitivity analysis (PSA), the baseline treatment group (regorafenib group) was treated as fixed in both overall survival and progression free survival. Please provide an updated PSA including uncertainty in the baseline treatment group.

Time on Treatment

B6. **Priority Question:** Please clarify why a time to treatment discontinuation curve was not fitted and used, similar to the technology appraisal for sorafenib? This approach would remove the need for assumptions to be made regarding discontinuation of treatment before progression and treatment beyond progression. Please implement in the model if possible.

B7. Table 40 (page 129 of company submission): The table indicates that some patients are still receiving post-progression treatment more than 22 cycles after progression. Please comment on whether it is assumed that no patients remain on treatment 22 cycles beyond progression in the model.

B8. Please provide the observed Kaplan-Meier curve for time to treatment discontinuation or death for the regorafenib group over the entire trial duration (irrespective of mRECIST progression status).

Utility Data

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B9. **Priority question.** A published paper has been identified after the cut-off date of the company review (Chau et al. (2017); http://dx.doi.org/10.1016/j.ejca.2017.05.001). Please comment on the relevance of the utility values reported in this paper, noting that there appears to be a sizeable difference in the values between baseline and end of treatment values. End of treatment appears to be a proxy for progression (79% of patients ended treatment due to progression). Please perform a sensitivity analyses incorporating this information.

B10. **Priority question.** Table 41 (page 134 in the company submission): Please provide the proportion of patients alive who completed the EQ-5D at each cycle. Please also provide clarification on why the end of treatment value in Table 41 for pre-progression is lower than all values for cycles 1-32. Similarly, clarify why the end of treatment pre-progression value and end of treatment post-progression value is lower than all bar one value within cycles 1-32.

B11. Please comment on the face validity of the small difference in mean utility values used in the model for those in a progression-free state and those that have progressed (difference = 0.048).

B12. Page 137 of the company submission states: "The Tobit model (specification 8) was selected as the final model to inform the utility input for the cost-effectiveness model". Utility values reported in Table 44 (page 138 of the company submission) are estimates after adjusting for stratification factors. Please clarify how this adjustment was reflected in the submitted health economic model. If stratification factors were not incorporated in the economic model, then please use a statistical model for utility without stratification factors.

B13. Please provide more details on the models fitted to the utility data. What were the final parameterisations of the models, and which software was used to fit these models?

Resource use and costs

B14. **Priority question.** Please clarify why the resource use estimated from three clinicians (page 142 of the company submission) was used instead of the committee preferred approach used in the assessment of sorafenib. Please provide an analysis using the values preferred by the NICE CDF committee.

B15. Please clarify why arbitrary standard errors equal to 30% of the mean have been used for costs when a preferable standard error could be calculated from NHS Reference Cost data.

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B16. Please comment whether the cost of the Palliative Care Team (currently costed to be £131 in Table 49, page 145 of the company submission) would be more appropriately costed as HRG CODE SD04A (cost £136)

Previous cost-effectiveness publications

B17. A published cost-effectiveness analysis has been identified after the cut-off date of the company review. (Parikh et al. (2017) DOI: 10.1002/cncr.30863). Please comment on the relevance and limitations of this study.

Adverse events

B18. Please comment on the apparent discrepancy in adverse event rates per cycle used in the model and the data reported from RESORCE. The adverse event rates reported in Table 37, page 125 of the company submission as 5.55% for regorafenib and 5.06% for best supportive care (BSC). However, drug-related treatment emergent adverse events (TEAEs) from the RESORCE study reported on page 77 of the company submission are: (hand-foot skin reaction, diarrhoea (33% vs. 9%), decreased appetite (24% vs. 6%), hypertension (23% vs. 5%) and fatigue (21.1% vs. 13.5%).

B19. The proportions of TEAEs do not appear to follow a constant rate (Table 38, page 126-127 of company submission). Please comment on the following:

a. The appropriateness of applying a fixed TEAE probability during each model cycle. Why are the observed time-dependent probabilities not applied directly in the model during each cycle?

b. Why the total number of TEAEs for regorafenib predicted from the model (Sheet “Pat_cohort”, sum of AEs in column Z = 42%) is less than the number of grade 3/4 TEAEs in Table 28, page 75-76 of the company submission (66.31%).

Model implementation

B20. **Priority Question** Worksheets “NewlyDiagnosedReg” and “NewlyDiagnosedPlacebo.”, please clarify:

a. What these calculations are intending to reflect
b. How the data presented in Table 40, page 129 of the company submission have been calculated

B21. Please clarify how uncertainty surrounding progression free survival has been included in the PSA. Bootstrapping appears to have been included in the model but is not discussed in the company submission.

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B22. Sheets “QALYs”, cell H26: Why are the state utilities divided by 13 rather than 365.25/28?

B23. Worksheet “Effect extrapolation”, please clarify:

a. Overall survival :
   i. Why the estimate for the rate parameter in the Gamma distribution in the model was negative
   ii. The estimate for model parameters in Gompertz distribution were both zero and,
   iii. The rate parameter in the exponential distribution was zero
b. Progression free survival:
   i. Why the estimate for the rate parameter in the Gamma distribution in the model was negative and,
   ii. The estimate for the shape parameters in Gompertz distribution was zero.

B24. Please confirm if there is an error in Pat_cohort (AN29:AN270) and if these cells should reference C78 rather than C77.

Section C: Textual clarifications and additional points

C1. Page 68 of the company submission: Please confirm whether the minimally important difference for EQ-5D VAS is 10 (as shown in table 27) or 7 (as shown in the text)

C2. Page 94 of the company submission: Please clarify how the assumption of [redacted] of patients progressing on sorafenib receiving regorafenib was estimated.

C3. Table 38, pages 126-127 of the company submission: Please clarify whether the data presented in the table are percentages relating to the number of patients receiving treatment. If not, please provide further details.

C4. Table 42, page 136 of the company submission: Please clarify whether there is a typo in the table. Should Model 8 include stratification factors as suggested in Table 43 (page 138 of company submission)?

C5. Please clarify when the EQ-5D was filled out. Was it at ‘the end of treatment visits’ (page 138 of the company submission) or day 1 of each treatment cycle (page 131)? Please clarify if these are the same or different time-points.

C6. Table 55, page 153 of the company submission: Normal distributions were assumed for the hazard ratios for progression free survival and overall survival. Please clarify whether these are log normal distributions instead of normal distributions.

Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]: Clarification questions received 1 August 2017

Section A: Clarification on effectiveness data

Systematic literature review

A1. Please confirm if data extraction and quality assessment were undertaken independently by a minimum of two reviewers for the clinical effectiveness reviews. If this was not done, please explain why.

The selection of articles (based on title/abstract and full-text) was done according to NICE requirements with two reviewers implementing the screening process in parallel. In cases where the reviewers could not find agreement on the selection of papers, a third reviewer was consulted.

The initial data extraction was conducted by one reviewer and focused on full evidence extraction; a second reviewer performed a thorough quality check of all the collected evidence.

A2. Please clarify why the abstract Bruix et al. (2016) (reference number 23 in the company submission) was excluded. Appendix D1.1, Table 65 (page 190 of the company submission), suggests that the reason for exclusion was 'study design'. However, this paper is an abstract reporting findings from the RESORCE RCT and is also cited and used in the company submission, section B2.3 (page 28).

The article by Bruix (reference number 23) was cited in the clinical section but has been incorrectly categorised has having been removed in the systematic literature review. Figure 19 of appendix B should report 5 publications relating to one clinical trial. We apologise for the error.

A3. Appendix D1.3, Table 67 (page 196 of the company submission): Please specify the critical appraisal tool used.

Each of the questions outlined in section 2.5.1 of the 'User guide for company evidence submission template' (updated April 2017) was answered. In the company submission the last row of table 67, which identified the source of the questions, was deleted. The study appraisal was 'Adapted from Centre for Reviews and Dissemination' as suggested in the NICE User Guide.

A4. Appendix D1.3, Table 67 (page 196 of the company submission): In response to the question, "Is there any evidence to suggest that the authors measured more outcomes than they reported?, the answer given is "no because results of all pre-specified outcomes are reported in full". However, this has not been demonstrated within the company submission. Please provide a list of all of the intended outcomes to be assessed in the RESORCE trial and indicate with data or page numbers in the company submission or clinical study report (CSR) that all of these outcomes were indeed reported.

The prespecified endpoints from the RESORCE study have been listed in table 14 (page 44) of the company submission and reproduced below. Listed in this table is the location of the outcome for each endpoint in the company submission or CSR.

Table 1. (Table 14 from company submission) – Relevant endpoints and measures in the RESORCE study

Endpoint	Definition & timing of assessment / measure	Location within the company submission (CS) or Clinical Study Report (CSR)
Primary Endpoints		
Overall Survival (OS)	Measured from the date of randomisation until the date of death due to any cause. After the last dose of study medication and the 'end of treatment' visit, all patients entered a follow-up period during which information on survival status was collected.	CS – page 56
Secondary Endpoints		
Time to Progression (TTP)	Defined as the time (days) from randomisation to radiological or clinical disease progression. Disease progression was based on RECIST 1.1 criteria and the mRECIST criteria for HCC regarding the definition of Progressive Disease (25). Radiological tumor assessment (CT / MRI scans of chest, abdomen and pelvis) using the RECIST Version 1.1 and modified RECIST criteria for HCC was performed at screening, every 6 weeks during treatment for the first 8 cycles, and every 12 weeks thereafter.	CS – page 59-61
Progression-free survival (PFS)	Time (days) from date of randomisation to date of disease progression (radiological or clinical) or death due to any cause, if death occurs before progression is documented.	CS – page 58-59

Objective tumour response rate (ORR)	Tumour response and disease progression were evaluated based on RECIST 1.1 criteria and the mRECIST criteria for HCC regarding the definition of Progressive Disease (25). Radiological tumor assessment (CT / MRI scans of chest, abdomen and pelvis) using the RECIST Version 1.1 and modified RECIST criteria for HCC was performed at screening, every 6 weeks during treatment for the first 8 cycles, and every 12 weeks thereafter. Objective tumour response rate (ORR) was defined as the rate of patients with complete response (CR) or partial response (PR) over all randomised patients. Patients prematurely discontinuing the study without an assessment were considered non-responders for the analysis.	CS – page 61-64
Disease Control Rate (DCR)	The rate of subjects, whose best response was not progressive disease compared to all treated subjects (i.e. complete response, partial response or stable disease). In order to be counted as a responder in DCR stable disease had to be maintained for at least 6 weeks.	CS – page 61-64
Tertiary endpoints		
Duration of response	For CR or PR - Measured from the date of first documented response (CR or PR) to date of disease progression or death (if death occurred before disease progression). Evaluated using both mRECIST and RECIST 1.1 criteria (25).	CS – page 65
Duration of stable disease	The time (days) from randomisation to date that disease progression or death (if death occurred before progression) was first documented. Only calculated for patients who failed to achieve a best response of CR or PR. Evaluated using both mRECIST and RECIST 1.1 criteria (25).	CS – page 65
Exploratory endpoint		
Overall survival measured from the start of prior sorafenib therapy	Measured from the beginning of prior sorafenib treatment until the date of death due to any cause.	CS – page 66-67

Health Related Quality of Life (HRQoL): **FACT-Hep (version 4)** **EuroQol – 5 Dimension (EQ-5D)**	The FACT-Hep and EQ-5D were both self-administrated by the patient before seeing the physician at baseline, day 1 of each cycle, and at end-of-treatment visit. FACT-Hep is a disease-specific module of the FACT questionnaire, used extensively in oncology clinical trials. The FACT-Hep is a 45-item questionnaire developed to measure the quality of life HRQoL in patients with hepatobiliary cancers, including metastatic colorectal cancer, HCC, pancreatic cancer, and cancers of the gallbladder and bile duct (29, 30). FACT-Hep consists of five subscales: (1) physical well-being (PWB); (2) social/family well-being (SWB); (3) emotional well-being (EWB); (4) functional well-being (FWB); and the hepatobiliary cancer subscale (HCS). The HCS includes 18 items that assess specific symptoms of hepatobiliary carcinoma and side-effects of its treatment. Aggregate scores can also be formed. The PWB, FWB, SWB and EWB are summed to form the FACT-General (FACT-G) total score. The FACT-G and HCS score are summed to form the FACT-Hep total score (FACT-Hep = FACT-G + HCS) (range 0 to 180). The Trial Outcome Index (TOI) consists of the summation of the PWB, FWB and HCS subscales. The TOI has been demonstrated to be a sensitive indicator of clinical outcome in other disease types. All FACT items are rated on 5-point scales ranging from 0 = not at all to 4 = very much. Higher scores on all scales of the FACT-Hep reflect better quality of life or fewer symptoms. The MID for the respective scores are: (FACT-G) subscales = 2–3; FACT-G total score = 6–7; HCS = 5–6; FACT-Hep total score = 8–9; TOI = 7–8. The EQ-5D is a generic quality of life preference based instrument which has been validated in cancer populations to measure both utility and health status. The EQ-5D contains a descriptive system measuring 5 health dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension contains 3 levels of response: no problem (level 1), some problems (level 2), and extreme problems (level 3). The five health dimensions are summarised into the EQ-5D index score (ranges -0.59 to 1 with higher scores representing better health states). The EQ-5D also contains a visual analog scale (EQ-visual analog scale [VAS]), which records the respondent's self-rated health status on a vertical graduated visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). On average, it took less than 5 minutes to complete the questionnaire.	CS – page 67-71

OTHER ENDPOINTS		
Safety	Adverse event (AE) assessment occurred at every visit until 30 days after last study treatment (excluding survival assessment). AEs were classified by seriousness, intensity and causal relationship. Adverse events were classified using NCI-CTCAE version 4.03 guidelines Laboratory, haematology, biochemistry, urinalysis, and PT/PT-INR/PTT measures were assessed at screening, on day 1 and day 15 of every treatment cycle and at the end of treatment visit. Alfa fetoprotein (AFP) was not assessed on day 15 visits. Liver function (ALT, AST, and bilirubin) & blood pressure was monitored every week in cycles 1 and 2. Physical and Vital signs (Body weight/height, temperature, blood pressure (BP), and heart rate) examination occurred at every visit. ECG – measured at screening, day 1 of each cycle and then at 'end of treatment' visit. Adverse event = *any untoward medical occurrence in a patient after providing written informed consent for participation in the study.* Serious adverse event = *an adverse event that results in death, is life threatening, or requires hospitalisation or prolongation of existing hospitalisation, results in a persistent or significant disability or incapacity, or a congenital anomaly or birth defect, or is determined by the investigator to be a medically important event.*	CS – page 73-81 and Appendix F

A5. The footnote in Table 16 (page 50 of the company submission) states that five patients in the regorafenib group and one from the placebo group did not receive the study drug. Please provide the reasons for this.

The individual reasons for patients not receiving study drug are presented below.

Regorafenib
Patient was randomised in error. Patient could not be scanned by MRI due to pacemaker.
Adverse Event Not Associated With Clinical Disease Progression
Screening Failure - Patient was randomised but later found not to meet inclusion criteria
Patient labs outside of study requirements on cycle 1 day 1.
Screening failure - ECG showed a possible anterior myocardial infarction without any symptom. Cardiologist review could not exclude that MI had occurred within the past 6 months
Best supportive care
Patient was randomised but before treatment experienced an adverse event which led to a worsening of liver function to Child-Pugh B i.e. outside of study requirements

Clinical trial design

A6. Priority question: Please clarify whether the marketing authorisation for regorafenib as stated in the company submission (Table 2, page 17): "adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib" will include the following groups, who were all excluded from the RESORCE trial.

a. ***Patients who are intolerant to sorafenib (not contraindicated) in the trial****: Table 6 in the company submission (page 31) reports the exclusion criteria of the RESORCE trial to be: 'Permanent discontinuation of prior sorafenib therapy due to sorafenib related toxicity'. The company submission acknowledges that the safety and efficacy of regorafenib in this group is 'unknown' (page 85) and states that the 'anticipated licence' will not include this group. This is different from Table 2 (page 17 in the company submission) which states that the marketing authorisation is for: "adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib". Please clarify whether the marketing authorisation for regorafenib will or will not include patients who are intolerant to sorafenib.*

We cannot find any statement in the company submission indicating that the licence will not include patients who were unable to tolerate sorafenib (the inclusion criteria in the RESORCE study stipulated tolerability of prior treatment with sorafenib defined as not less than 20 days at a minimum daily dose of 400 mg QD (every day) within the last 28 days prior to withdrawal). The SmPC does not exclude these patients from the licence, however, section 4.4 states

"There is insufficient data on patients who discontinued sorafenib therapy due to sorafenib-related toxicity or only tolerated a low dose (< 400 mg daily) of sorafenib. The tolerability of Stivarga in these patients has not been established"

b. ***Patients with Child-Pugh class B****: Table 30 (page 86 of the company submission) indicates that 16% of 448 sorafenib-treated patients in the UK are Child-Pugh class B. It is also noted in a footnote for Table 15 (page 49 of the company submission) that a small number of Child-Pugh B patients were included in the RESORCE trial for whom there is no relevant evidence on the efficacy or safety of regorafenib. However, page 88 of the company submission acknowledges that this group is absent from the RESORCE trial.*

The inclusion criteria for the RESORCE study included Child-Pugh A status only. However, there were 11 patients with Child-Pugh B enrolled in the study (5 for regorafenib and 6 in the BSC arm) – therefore the statement on page 88 of the company submission is not correct – we

apologise for the error. The number of patients enrolled with Child-Pugh B status is too small to draw conclusions about safety and efficacy in this group.

The license is not restricted to Child-Pugh A patients and therefore, according to the licence patients with Child-Pugh B status could receive treatment with regorafenib.

It is not possible to define a patient based on single clinical parameters in isolation and we anticipate that clinicians will use their clinical judgement to determine whether individual patients might benefit from treatment.

c. ***Patients with ECOG performance status of 2****: Table 30 (page 86 of the company submission) indicates that 21% of 448 sorafenib-treated patients in the UK are ECOG performance status 2. However, page 88 of the company submission acknowledges that this group is absent from the RESORCE trial.*

The license is not restricted to patients with ECOG PS 0 or 1. We anticipate that clinicians will consider multiple parameters when assessing the potential to benefit from treatment rather than basing a treatment decision solely on a single clinical parameter such as ECOG status.

A7. Appendix D1.3, Table 67 (page 196 of the company submission) notes that, 'no imputation was performed for missing lesion assessment and tumour response (in the RESORCE trial). For example, if a patient missed a scan visit and progressive disease (PD) was documented at the next available scan visit, the actual visit date of the first documented PD was used to calculate progression free survival (PFS) and time to progression (TTP). Please clarify whether this means that the recorded date of progression might be later than when progression actually occurred. Also, please indicate how many patients in each arm of the RESORCE trial might be affected by this.

Table 2 shows the number (%) of patients for whom a scan was missed and progression recorded at their next scan.

It is possible that in these instances progression had occurred before the missed scan, however, it is also possible that progression had not occurred until after the missed scan. As the number of patients affected is small it is likely to be of no consequence.

Table 2. Subjects with PD (mRECIST) identified after a missed scan (FAS)

	Regorafenib N=379 (100%)	**Best Supportive Care N=194 (100%)**
Subjects with progression after a missed scan	23 (6.1%)	7 (3.6%)

A8. Please provide the RESORCE trial protocol, listed in the CSR as being in Section 16.1.1 (this section has not been made available).

This has been uploaded as a separate document.

Section B: Clarification on cost-effectiveness data

Extrapolation of survival outcomes

B1. Priority question. Page 28 of the company submission states that "After the primary endpoint of the study was reached (overall survival [OS]; 29th February 2016) and the results supported a positive benefit / risk assessment for regorafenib, patients on placebo at that time were offered the opportunity of receiving regorafenib through open-label treatment and patients randomised to regorafenib could continue open-label regorafenib. Data presented in this submission relates to the double-blind period only." Furthermore, page 54 of the company submission states that "This submission presents the study results from the clinical database released on 5th August 2016." There is a potential for the different dates (29th February 2016 and 5th August 2016) to cause confusion and uncertainty in the results reported:

a. Please clarify if results included in the company submission and the company model, report data from the clinical database released on the 5 August 2016 and include data from patients after the primary endpoint of the trial was reached on 29 February 2016 and treatment switching had occurred.

The clinical database release on the 5th August relate to the double-blind period only i.e. up to 29 February. There was no cross-over during the double-blind trial period.

A CSR was released earlier but the database was reopened following the identification of a small number of errors. The August CSR corrected the errors identified in the first CSR and was the one used in the submission.

b. If data after treatment switching is reported please provide an additional analysis of the trial data up to the August 2016 datalock which includes appropriate consideration of statistical adjustments for treatment switching.

To be provided on 18th August 2017.

B2. Priority question. Page 119 of the company submission states that "Coupled with the largely parallel log cumulative hazard curves, this result suggests that the proportional hazards assumption is plausible, so survival was modelled using dependent survival curves."

a. Given that the log cumulative hazard curves presented in Figure 14 (page 119 of company submission) cross, please explain why it was considered appropriate to assume proportional hazards.

In the context of a disease area where deaths can be expected very early on, it would seem reasonable to assume that the very early crossing of the arms can be attributed to randomness in a small number of early events. We don't believe that this early crossing indicates non-proportionality. Further to the parallel plots (from about day 15) the Grambsch and Therneau's correlation test between Schoenfeld residuals and the log of time resulted in a p-value of 0.331 - as this value is not statistically significant the proportional hazards assumption is not violated.

b. Please provide a separate analysis in which independent models are fitted to the overall survival data for each treatment group (that is, not including a treatment covariate). Please also include independent generalised gamma models. Please provide results for statistical fit and an updated Table 36 in the company submission (including generalised gamma).

Independent models have been fitted to the OS data as requested. The statistical fits for each parametric distribution are presented in Table 3 and Table 4. An equivalent to table 36 from the company submission is provided below - Table 5. Figure 1 show the independent parametric curves fitted to the KM data. The cost-effectiveness results are presented in Table 6. Regorafenib was cost-effectiveness irrespective of the independent curve selected.

Table 3. Statistical fit of independent OS parametric curves - BSC

Distribution	*AIC*	*BIC*
Loglogistic	1885.867	1892.403
Lognormal	1885.879	1892.415
Generalised Gamma	1886.313	1896.117
Gompertz	1900.373	1906.908
Exponential	1901.015	1904.283
Weibull	1891.882	1898.417

Table 4. Statistical fit of independent OS parametric curves - Regorafenib

Distribution	*AIC*	*BIC*
Lognormal	3312.354	3320.229
Generalised Gamma	3314.032	3325.845
Loglogistic	3314.643	3322.518
Weibull	3328.78	3336.655
Exponential	3338.979	3342.917
Gompertz	3339.502	3347.377

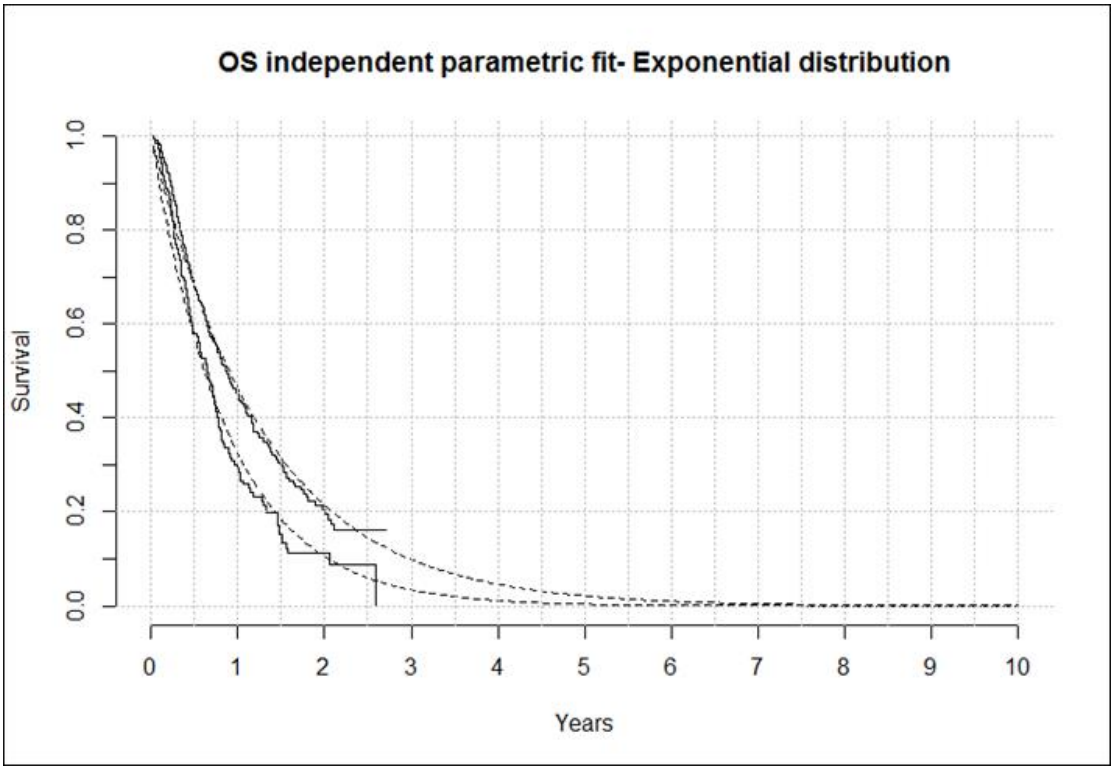
Table 5. Overall survival probabilities (independent curves)

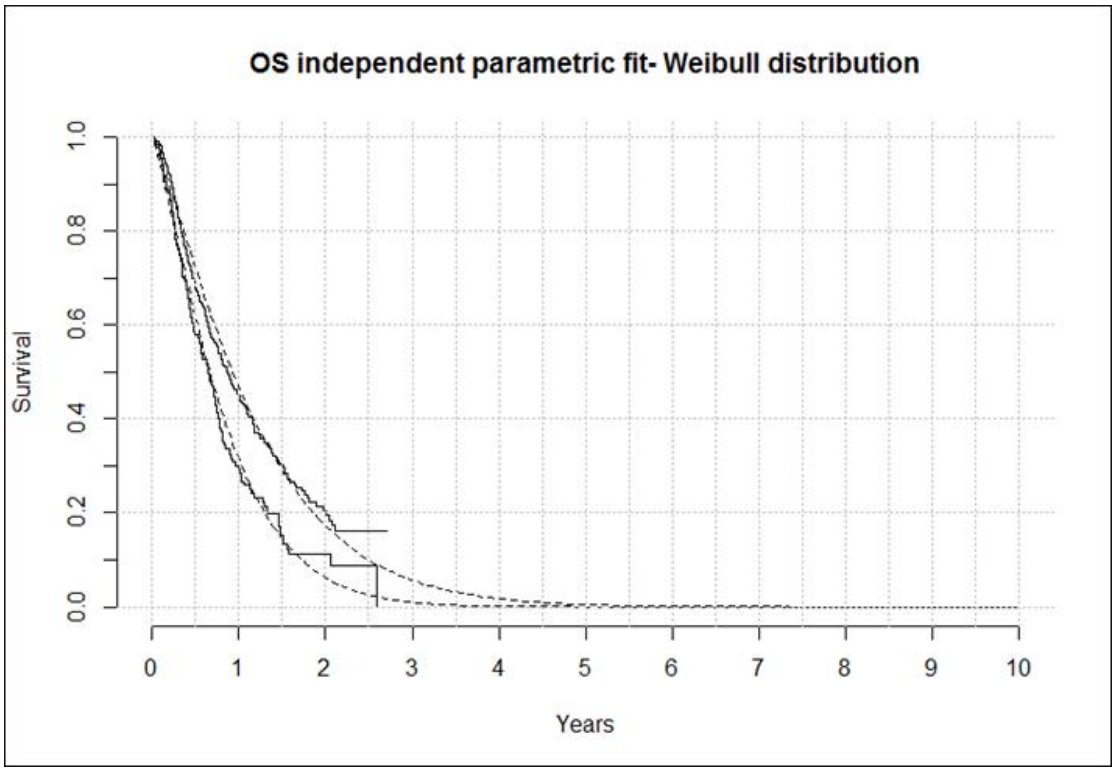
	Kaplan -Meier	Loglogistic	Weibull	Lognormal	Gompertz	Exponential	Generalised Gamma
Regorafenib							
2 years	0.21	0.20	0.17	0.21	0.20	0.21	0.21
35 cycles	0.16	0.13	0.08	0.14	0.10	0.13	0.13
5 years		0.05	0	0.05	0.01	0.02	0.04
10 years		0.02	0	0.01	0	0	0.01
BSC							
2 years	0.11	0.11	0.06	0.11	0.08	0.11	0.09
35 cycles	0.09	0.07	0.02	0.06	0.02	0.05	0.04
5 years		0.02	0	0.01	0	0	0.01
10 years		0.01	0	0	0	0	0.00
Difference: regorafenib minus BSC							
2 years	0.11	0.09	0.11	0.1	0.12	0.1	0.12
35 cycles	0.07	0.06	0.06	0.08	0.08	0.08	0.09
5 years		0.03	0	0.04	0.01	0.02	0.04
10 years		0.01	0	0.01	0	0	0.01

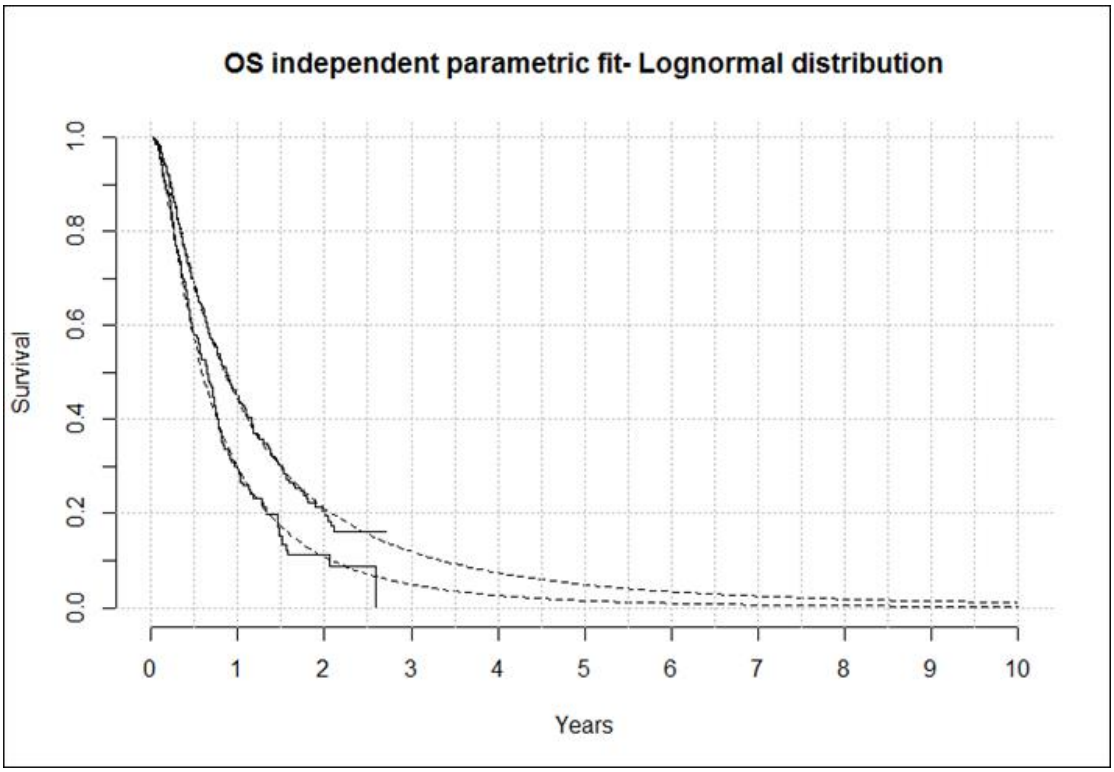
Table 6. Cost-effectiveness results: independently fitted parametric curves for OS data

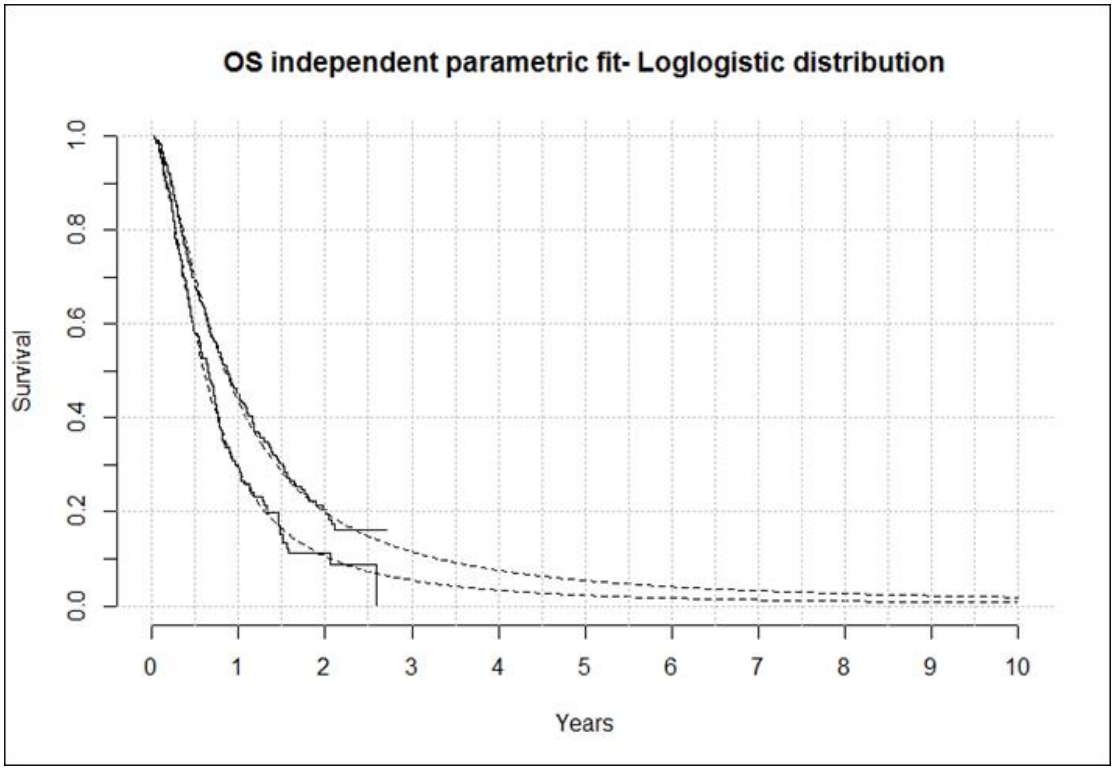
	Incr costs (£)	Incr QALYs	ICER (£/QALYs)
Base case (company submission)	[redacted]	**0.367**	**33,437**
Loglogistic	[redacted]	0.360	33,463
Lognormal	[redacted]	0.368	33,334
Weibull	[redacted]	0.244	25,248
Exponential	[redacted]	0.290	26,428
Generalised Gamma	[redacted]	0.377	33,028
Gompertz	[redacted]	0.265	27,033

Figure 1. Independent parametric fits (overall survival)




OS independent parametric fit- Weibull distribution
Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
9
10
Years


OS independent parametric fit- Lognormal distribution
Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
9
10
Years


OS independent parametric fit- Loglogistic distribution
Survival
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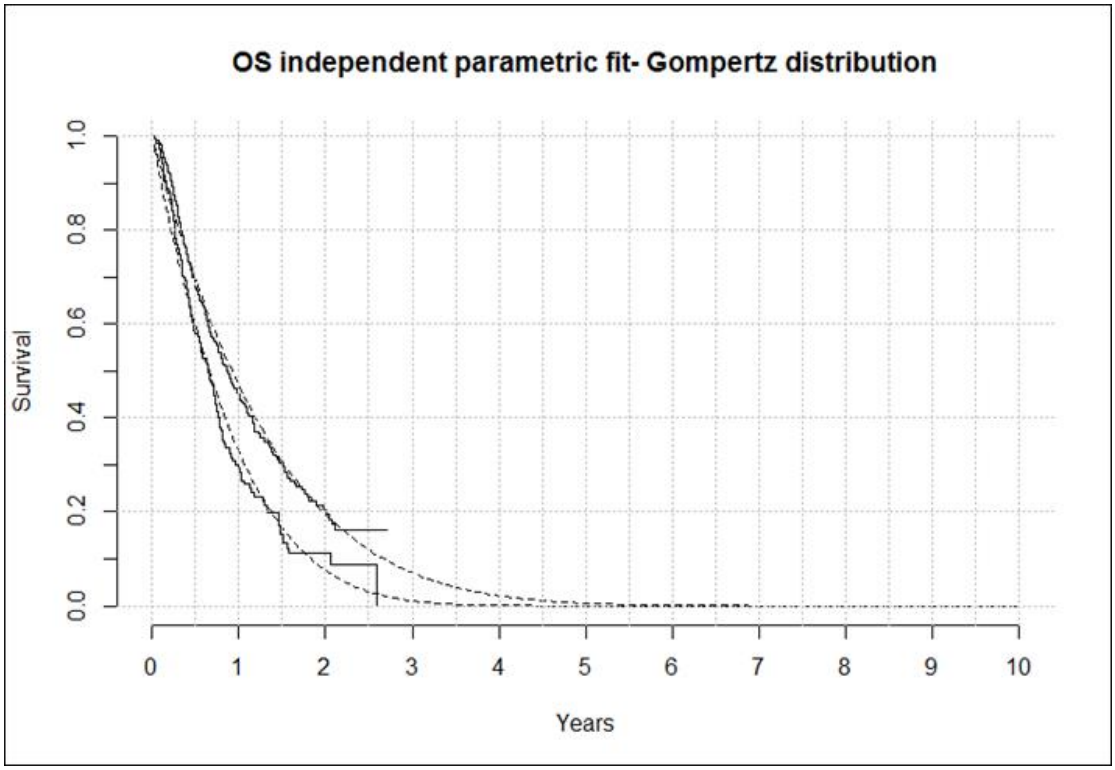
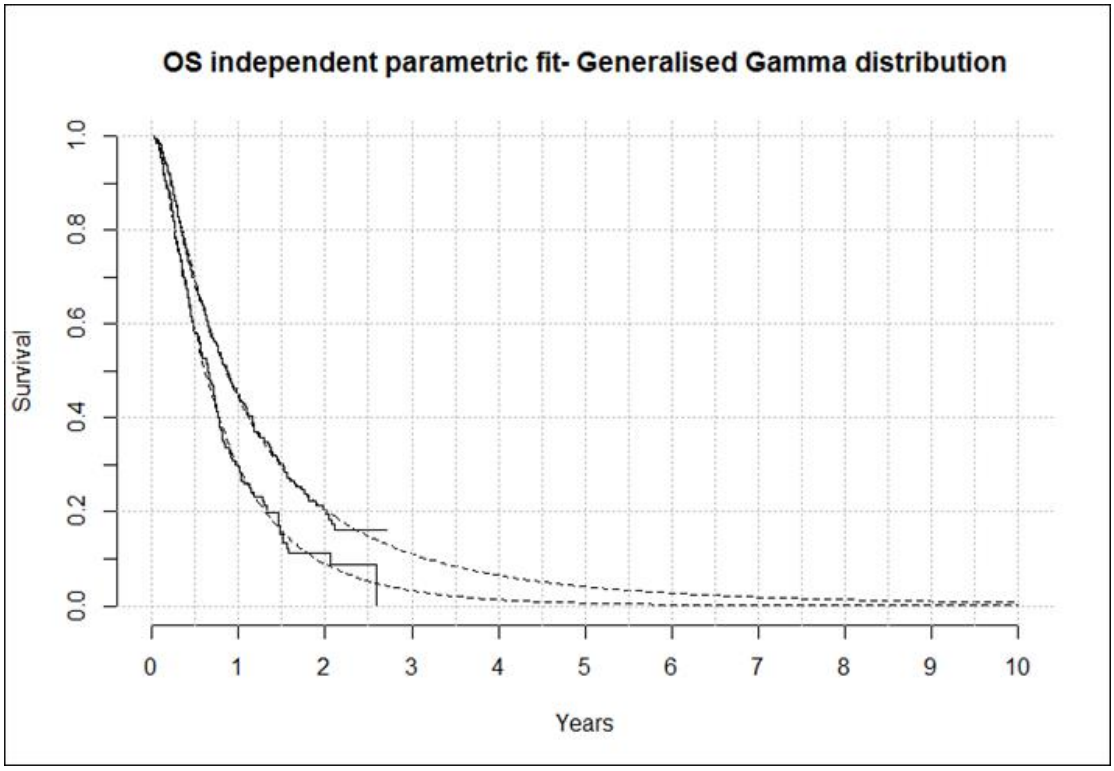
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
9
10
Years


OS independent parametric fit- Gompertz distribution
Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
9
10
Years



c. Given that the lognormal distribution was selected for overall survival, please clarify why a hazard ratio has been applied to this model rather than an acceleration factor. Please provide the acceleration factor associated with this joint model.

For the dependent models the approach taken was firstly to implement the curve for the regorafenib arm in the model. Subsequently the curve for the BSC arm was obtained via the Cox hazard ratio. The Cox hazard ratio was chosen as it is independent of which parametric model is chosen i.e. no parametric distribution assumption is underlying this HR. The approach was guided by the NICE DSU technical support document (no. 14) – this document indicates that proportional hazard models are appropriate in the case of parallel lines in the log cumulative hazard plot together with proportionality not being statistically rejected (Grambsch and Therneau's correlation test between Schoenfeld residuals). In section 2.9 of the DSU document it says that in accelerated failure time models, the treatment effect is an acceleration factor. As per your request we have therefore implemented the approach via the treatment coefficient. The model attached with this response has a dropdown 'treatment effect' where the user can select either i) hazard ratio ii) treatment coefficient.

The cost-effectiveness result using the treatment coefficient is shown Table 7.

Table 7. Cost-effectiveness result

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER versus baseline (£/QALY)
Regorafenib	[redacted]	1.340	1.044	10,612	0.360	0.285	37,239
BSC	[redacted]	0.981	0.759				
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

d. The section on "Clinical Validity" (page 121 of the company submission) discusses the difference between the observed and predicted overall survival cumulative survival probabilities at cycle 35 (within the observed period of the RESORCE trial). Please explain how the clinical plausibility of the extrapolated curves was considered in the model selection exercise.

In respect of comparing the clinical plausibility of the different parametric fits we endeavored to be as logical as possible. The ultimate selection of a base case curve was decided not on clinical plausibility alone but on a combination of clinical plausibility, statistical fit and visual inspect of the curves. Ultimately however we acknowledge the selection of the most appropriate curve is uncertain.

Firstly, the prediction of each parametric curve at the 35 cycle timepoint (the point of database lock) was compared with the observed KM data – those curves with predictions that were furthest from the observed data were considered clinically implausible on the basis of failing to closely predict known outcomes from the RESORCE study. The Weibull, Gompertz and Gamma curves were considered to be clinically implausible as they overestimated the probability of dying significantly. Of the remaining curves the exponential curve predicted the observed data at the 35-cycle timepoint equally as well as the lognormal and loglogistic curves. However, in respect of BSC it underestimated survival relative to the other two curves and therefore, relative to these curves, was biased against the BSC arm.

We felt that the remaining curves (lognormal and loglogistic) could both be considered clinically plausible and were better fitted to observed data than the rejected curves. Beyond the observed data it becomes very difficult. Broadly speaking we considered the survival at 5 and 10 years in the context of an advanced disease with a median survival of <12 months. Of the two remaining curves we felt that the curve that would be most reflective of the condition would be the one that predicted a lower chance of survival in the outer years. On this basis the lognormal curve was considered to be more plausible than the loglogistic curve. As stated in the submission we feel that the both the loglogistic curve demonstrated a good degree of clinical plausibility.

e. Please comment on the selection of 35 cycles as a comparison point in Table 36 (page 123 of the company submission). Additionally, please add the cycle which corresponds to the last data point on the Kaplan-Meier curves (cycle 36?) to Table 36.

Cycle 35 was the latest point for which there was observed data from the trial and the point at most events had taken place. It seems an appropriate point for comparison in table 36. From the dataset used in the submission there are no later points that could have been included in table 36. Question B1 (answer due 18th August) uses data from a later dataset (i.e. beyond the primary endpoint of the trial). Please see here for KM data at the latest available timepoint.

The labelling of '35' might be a bit confusing, but it indeed represents a time span of 36 cycles. The labelling means that at the end of the time span between 35 and 36 cycles, patients in the regorafenib arm have a 0.16 probability of being alive, which is the last data point available from the originally submitted data.

B3. Please provide the empirical hazard function plot for both progression free survival and overall survival.

Please find the information requested in Figure 2 and Figure 3.

Figure 2. Overall survival – Empirical Hazard Functions

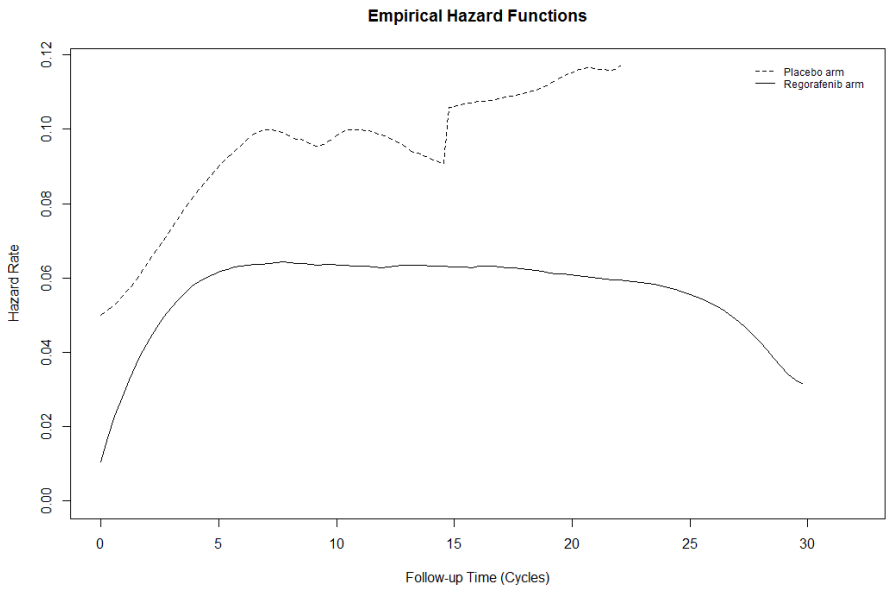
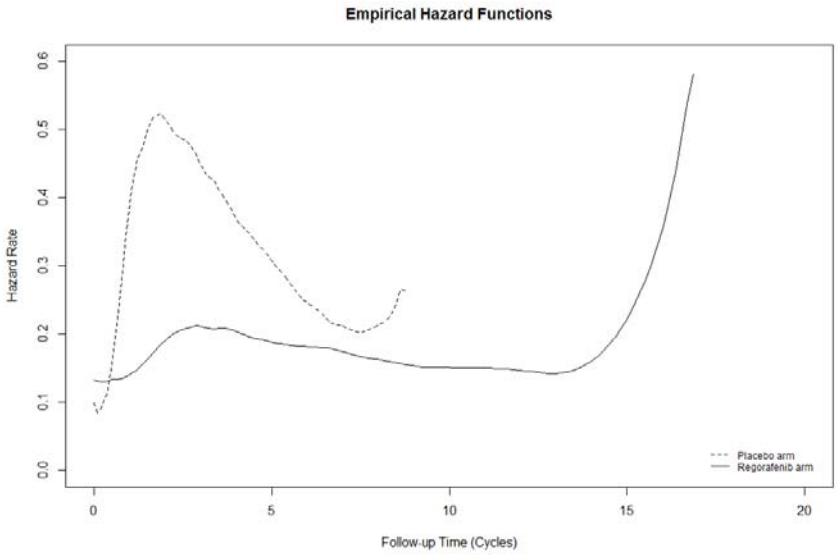


Figure 3. Progression Free Survival – Empirical Hazard Functions



B4. Table 55 (page 153 of the company submission): A hazard ratio for progression free survival is reported in the table, however, the model uses the observed Kaplan-Meier progression free survival curves directly rather than a selected parametric function. Please explain how and why was this hazard ratio was included in the probabilistic sensitivity analysis?

In our submission we used the observed Kaplan-Meier data for PFS directly and uncertainty around PFS was not captured in the PSA presented. It would have been clearer had the hazard ratio not been presented in table 55 as it was not applicable to the PSA conducted – we apologise for any confusion.

B5. In the probabilistic sensitivity analysis (PSA), the baseline treatment group (regorafenib group) was treated as fixed in both overall survival and progression free survival. Please provide an updated PSA including uncertainty in the baseline treatment group.

The model has been modified to include uncertainty in the regorafenib group for OS and PFS. The values used to implement the probabilistic analysis were the standard error of each KM data-point (for PFS - Table 8) and the variance/covariance matrix for the lognormal distribution (for OS). Cost-effectiveness results are shown in table 9

Table 9. Figure 4 and Figure 5 show the PSA scatterplot and CEAC curve respectively.

Table 8. PFS – Standard errors by cycle

	Regorafenib		Best Supportive Care	
Cycle	**PFS**	**SE**	**PFS**	**SE**
0	1.000	0.000	1.000	0.000
1	0.973	0.008	0.979	0.010
2	0.692	0.025	0.906	0.021
3	0.618	0.026	0.858	0.025
4	0.473	0.027	0.755	0.031
5	0.392	0.027	0.693	0.034
6	0.354	0.027	0.611	0.036
7	0.275	0.025	0.574	0.037
8	0.229	0.024	0.529	0.038
9	0.205	0.024	0.476	0.038
10	0.165	0.022	0.409	0.038
11	0.143	0.021	0.338	0.038
12	0.143	0.021	0.316	0.037
13	0.125	0.020	0.293	0.037
14	0.105	0.019	0.259	0.036
15	0.088	0.019	0.242	0.036
16	0.082	0.018	0.233	0.036
17	0.082	0.018	0.215	0.035
18	0.053	0.016	0.215	0.035
19	0.053	0.016	0.197	0.034
20	0.053	0.016	0.130	0.031
21	0.053	0.016	0.130	0.031
22	0.053	0.016	0.108	0.029
23	0.039	0.014	0.108	0.029
24	0.039	0.014	0.108	0.029
25	0.031	0.013	0.108	0.029
26	0.031	0.013	0.108	0.029
27	0.031	0.013	0.087	0.030
28	0.031	0.013	0.087	0.030
29	0.031	0.013	0.087	0.030

Table 9.

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER versus baseline (£/QALY)
Regorafenib	[redacted]	1.044	12,107	0.367	32,983
BSC	[redacted]	0.677	-	-	-

Figure 4. PSA Scatterplot

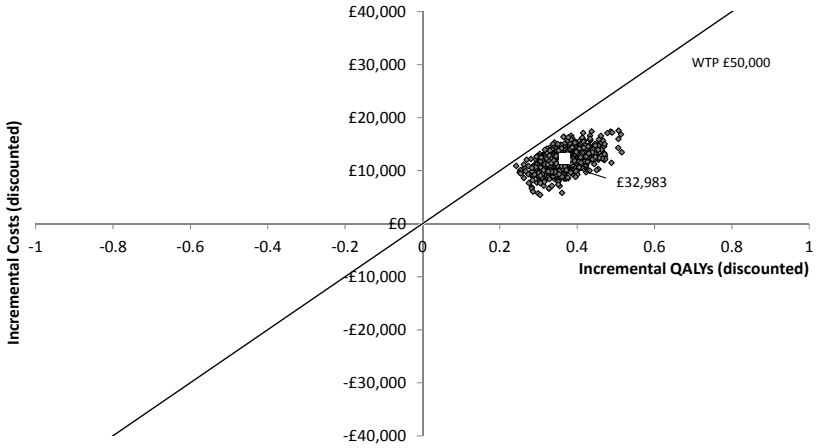
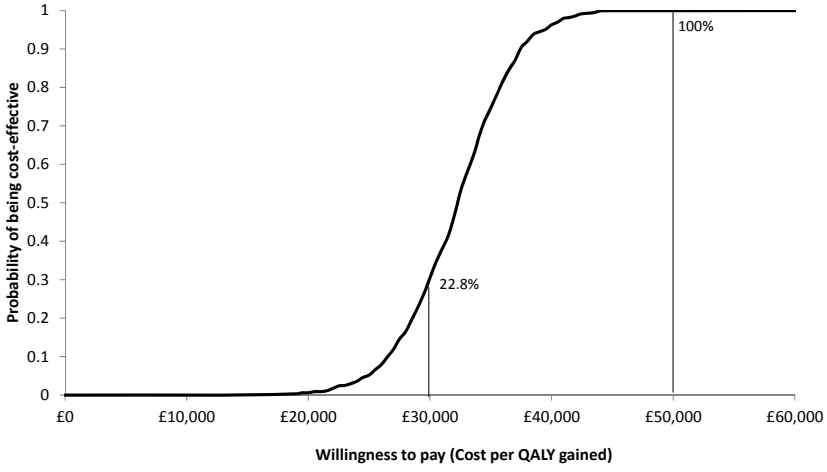


Figure 5. Cost-effectiveness Acceptability Curve



Time on Treatment

B6. ***Priority Question:*** *Please clarify why a time to treatment discontinuation curve was not fitted and used, similar to the technology appraisal for sorafenib? This approach would remove the need for assumptions to be made regarding discontinuation of treatment before progression and treatment beyond progression. Please implement in the model if possible.*

In respect of treatment costs, the submitted model accurately predicted the treatment costs compared to the amount of treatment received in the RESORCE study. In the trial the mean total dose of treatment received was [redacted] i.e. equivalent to [redacted] packs. At a cost of [redacted] per pack this equates to [redacted]. The submitted model predicted a cost of [redacted] over the period of the trial.

In the company submission it was assumed that patients did not continue treatment beyond the 29th February cut-off. The time on treatment curve using the same assumption is presented in in B8 (Figure 6). This curve leads to estimated costs of [redacted]. When this cost is implemented directly in the model the ICER is £34,039 (Table 10). We have also calculated a time on treatment KM curve where patients on treatment on the 29th February were censored rather than assuming treatment discontinuation (Figure 8). This curve leads to estimated treatment costs of £[redacted] and an ICER of £38,906 (Table 11).

Table 10.

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER versus baseline (£/QALY)
Regorafenib	[redacted]	1.044	12,483	0.367	34,039
BSC	[redacted]	0.677	-	-	-

Table 11

Technologies	Total costs (£)	Total QALYs	Incr costs (£)	Incr QALYs	ICER versus baseline (£/QALY)
Regorafenib	[redacted]	1.044	14,268	0.367	38,906
BSC	[redacted]	0.677	-	-	-

Parametric distributions were fitted to both time to treatment discontinuation KM curves. Table 12 and Table 13 show the statistical fit of each model and Figure 7 and Figure 9 (question B8) show how well each curve fits the data visually. Table 14 and Table 15 show the ICER when each curve is implemented in the model.

Table 12. AIC and BIC – time on treatment distribution (patients assumed to discontinue treatment at 29 February cut-off)

Distribution	AIC	BIC
Lognormal	1149.66	1157.51
Loglogistic	1150.41	1158.26
Weibull	1144.26	1152.11
Gompertz	1144.24	1152.09
Exponential	1142.60	1157.51

Table 13. AIC and BIC – time on treatment distribution (patients on treatment at cut-off censored)

Distribution	AIC	BIC
Lognormal	1148.23	1156.07
Loglogistic	1145.59	1153.44
Weibull	1176.79	1184.63
Gompertz	1159.86	1167.70
Exponential	1179.11	1183.03

Table 14. Cost-effectiveness results with different treatment extrapolations (patients assumed to discontinue treatment at 29 February cut-off)

	Incremental costs (£)	ICER (£/QALY)
Original base case	[redacted]	33,437
Raw KM treatment data	[redacted]	34,460
Lognormal	[redacted]	34,150
Loglogistic	[redacted]	34,627
Weibull	[redacted]	34,456
Exponential	[redacted]	34,388
Gompertz	[redacted]	34,271

Table 15. Cost-effectiveness results with different treatment extrapolations (patients on treatment at cut-off censored)

	Incremental costs (£)	ICER (£/QALY)
Original base case	[redacted]	33,437
Raw KM treatment data	[redacted]	38,906
Lognormal	[redacted]	39,207
Loglogistic	[redacted]	38,741
Weibull	[redacted]	38,985
Exponential	[redacted]	38,905
Gompertz	[redacted]	39,060

B7. ***Table 40 (page 129 of company submission): The table indicates that some patients are still receiving post-progression treatment more than 22 cycles after progression. Please comment on whether it is assumed that no patients remain on treatment 22 cycles beyond progression in the model.***

In the submitted basecase it was assumed that no patients are on regorafenib from cycle 23 after progression. In clinical practice in England we anticipate that clinicians will not treat as many patients post-progression as they did in the RESORCE study. We also anticipate that post-progression treatment would be limited in duration relative to what was observed in the RESORCE study.

B8. Please provide the observed Kaplan-Meier curve for time to treatment discontinuation or death for the regorafenib group over the entire trial duration (irrespective of mRECIST progression status).

Please see below the Kaplan-Meier curves for time to treatment discontinuation or death for the regorafenib group.

Figure 6. KM curve for time on treatment (patients assumed to discontinue treatment at 29 February cut-off)

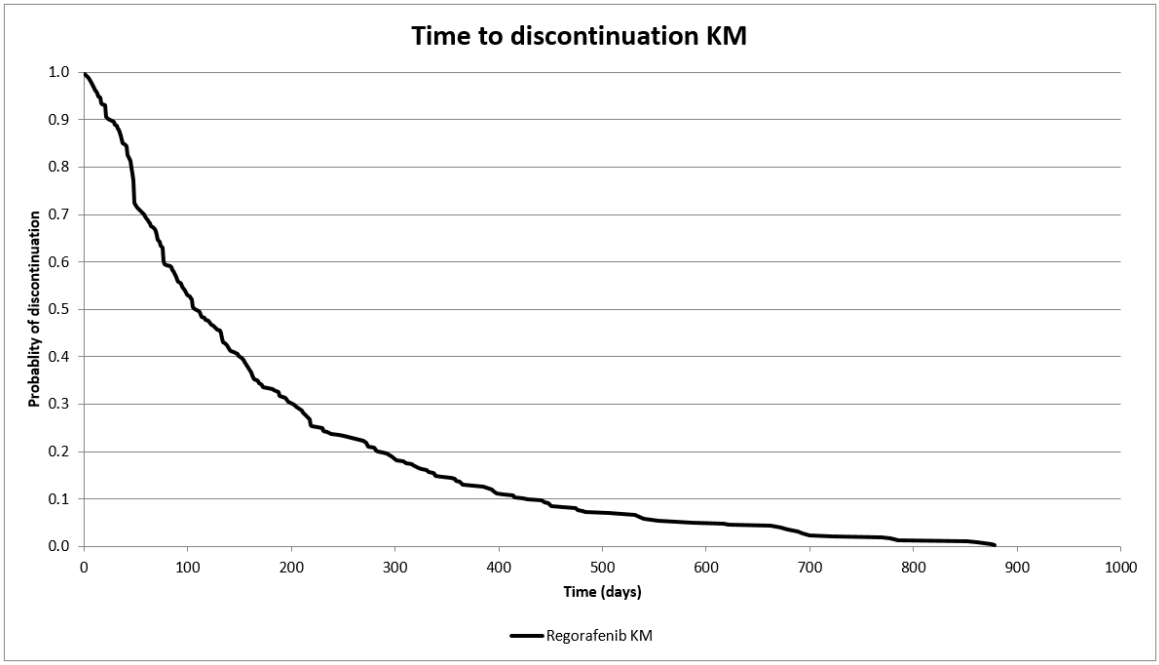


Figure 7. Parametric fits - time on treatment (patients assumed to discontinue treatment at 29 February cut-off)

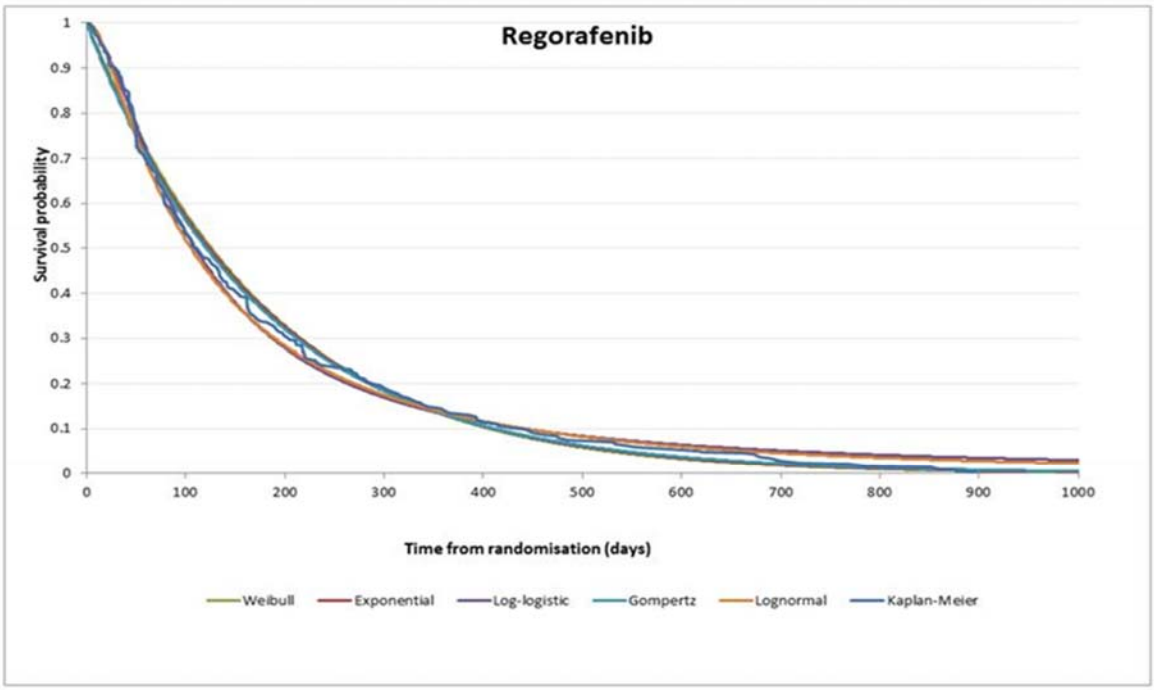


Figure 8. KM curve for time on treatment (patients on treatment on 29th February censored)

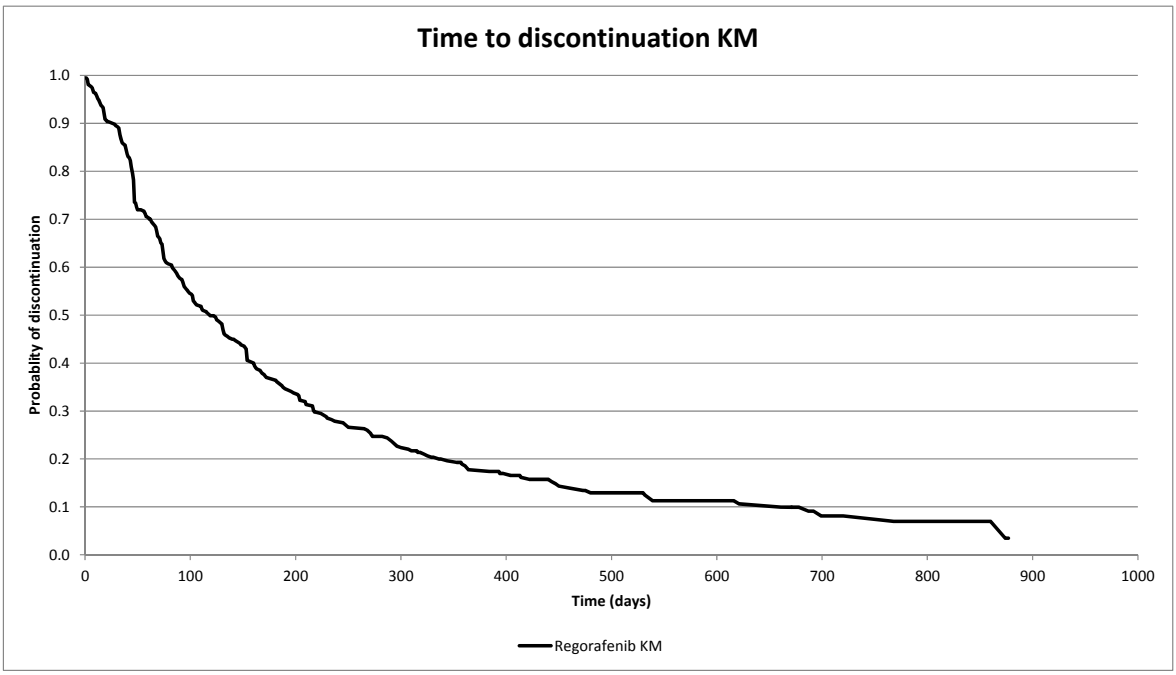
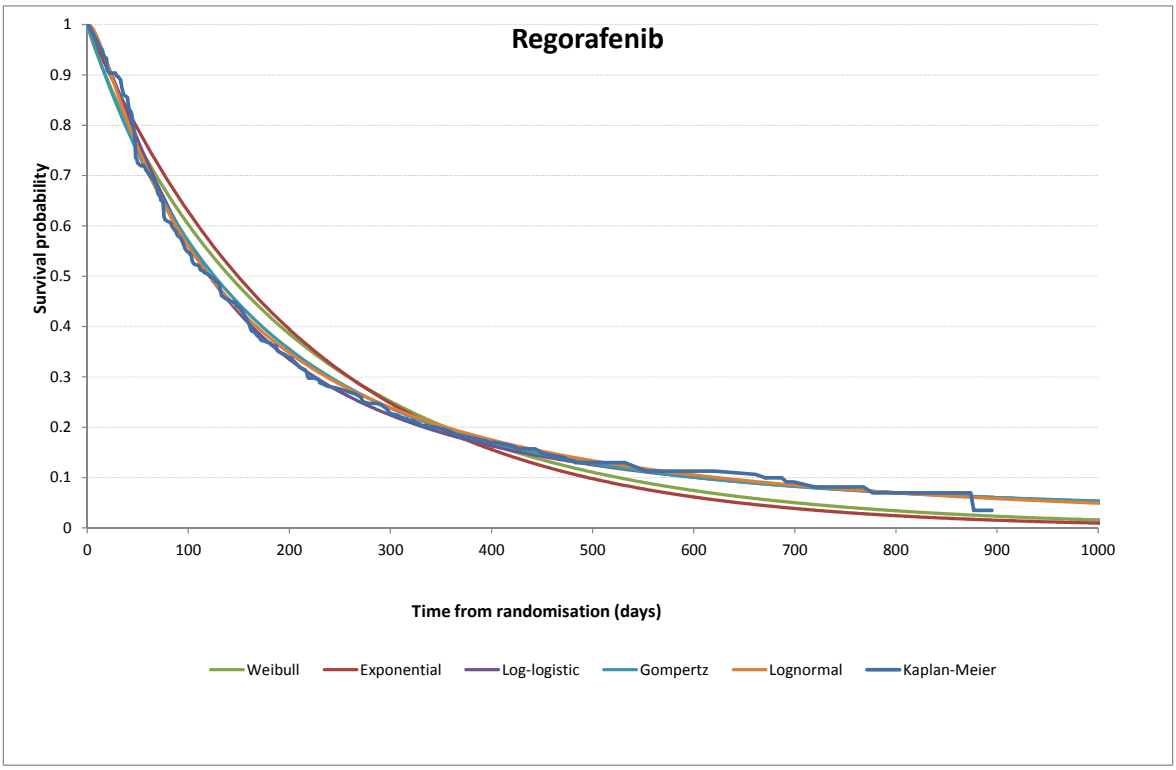


Figure 9: Parametric fits (time on treatment) (patients on treatment on 29th February censored)



Utility data

B9. ***Priority question.*** *A published paper has been identified after the cut-off date of the company review (Chau et al. (2017); http://dx.doi.org/10.1016/j.ejca.2017.05.001). Please comment on the relevance of the utility values reported in this paper, noting that there appears to be a sizeable difference in the values between baseline and end of treatment values. End of treatment appears to be a proxy for progression (79% of patients ended treatment due to progression). Please perform a sensitivity analyse incorporating this information.*

The utility values that are most appropriate to this technology appraisal are those from the EQ-5D data from the RESORCE study. In this study EQ-5D was administered at each treatment cycle and at the end of treatment visit. In our analysis we used patient level data to stratify patients according to progression status. Please note that the EOT visit could have occurred at any treatment cycle for individual patients but for ease of presentation is included at the end of table 41.

In table 41 of our submission it can be seen that the EOT visit utility values (from RESORCE) are lower than utility values in any other cycle. This is because at the point of discontinuing treatment the patient might have experienced an intolerable adverse event or a large drop in ECOG performance status for example. The EOT utility therefore tends to capture the patient's quality of life at its lowest point. This EOT utility value therefore is not a proxy for the progression health state.

Within the progressed state there are a range of patients i.e. some who have recently progressed (and are relatively well) through to those who are sicker. Using an average utility value better represents the spectrum of health of these patients.

As the EOT utility value from RESORCE is not a suitable proxy for progression, similarly the EOT utility value from Chau et al is not a suitable proxy for progression. We believe that assuming the EOT utility value is a proxy for progression is not correct and for this reason have not incorporated the values in a sensitivity analysis.

B10. Priority question. Table 41 (page 134 in the company submission): Please provide the proportion of patients alive who completed the EQ-5D at each cycle. Please also provide clarification on why the end of treatment value in Table 41 for pre-progression is lower than all values for cycles 1-32. Similarly, clarify why the end of treatment pre-progression value and end of treatment post-progression value is lower than all bar one value within cycles 1-32.

Please find the information requested in Table 16. Please see B9 for an explanation to the second part of this question.

Table 16. EQ-5D response per cycle stratified by progression status

	Pre-progression			Post-progression		
Cycle	Completed EQ-5D	Alive	Percentage	Completed EQ-5D	Alive	Percentage
1	531	573	93%		0	
2	489	518	94%	4	44	9%
3	283	297	95%	64	224	29%
4	228	255	89%	50	226	22%
5	168	181	93%	60	250	24%
6	123	136	90%	61	248	25%
7	98	118	83%	51	215	24%
8	78	85	92%	48	219	22%
9	65	66	98%	39	211	18%
10	53	56	95%	38	191	20%
11	45	46	98%	37	177	21%
12	33	36	92%	38	159	24%
13	31	31	100%	33	146	23%
14	28	29	97%	24	128	19%
15	20	20	100%	29	116	25%
16	17	20	85%	23	97	24%
17	13	16	81%	20	88	23%
18	10	16	63%	20	79	25%
19	10	10	100%	19	77	25%
20	9	10	90%	16	72	22%
21	9	10	90%	12	54	22%
22	9	10	90%	11	43	26%
23	9	9	100%	11	40	28%
24	6	6	100%	13	35	37%
25	5	6	83%	10	29	34%
26	5	5	100%	7	23	30%
27	3	5	60%	7	20	35%
28	2	3	67%	7	18	39%
29	1	2	50%	6	14	43%

30				5	13	38%
31				3	11	27%
32				1	9	11%

B11. Please comment on the face validity of the small difference in mean utility values used in the model for those in a progression-free state and those that have progressed (difference = 0.048).

It would be expected that patients who have progressed would have worse utility relative to those who haven't progressed. This is shown in the lower utility value for progressed patients from the RESORCE study. We consider the values derived from the RESORCE study to be face-valid.

In a scenario analysis (table 38 of the company submission) we presented results where the utility decrement associated with progression was doubled. The cost-effectiveness of regorafenib was found to be relatively insensitive to this change.

B12. Page 137 of the company submission states: "The Tobit model (specification 8) was selected as the final model to inform the utility input for the cost-effectiveness model". Utility values reported in Table 44 (page 138 of the company submission) are estimates after adjusting for stratification factors. Please clarify how this adjustment was reflected in the submitted health economic model. If stratification factors were not incorporated in the economic model, then please use a statistical model for utility without stratification factors.

The regression model used in the base case included stratification factors. These stratification factors were included in the event utilities were required to be adjusted for very specific populations which differed significantly from the trial population. As the population included in the economic model was the RESORCE study population, strictly speaking, inclusion of these stratification factors was not necessary. The submitted model only included the utilities from the regression model that were related to pre-progression, post-progression and adverse events.

As requested, the results of the regression model with and without stratification factors has been provided below. The results of both regressions, in respect of the utility values used in the economic model, are virtually identical.

Regression model (with stratification factors included) – As used in the company submission

Random-effects tobit regression	Number of obs	=	3437
Group variable: SUBJIDN	Number of groups	=	543
Random effects u_i ~ Gaussian	Obs per group: min	=	1
	avg	=	6.3
	max	=	32
	Wald chi2(7)	=	137.56
Log likelihood = -816.162	Prob > chi2	=	0

	Coef.	Std. Err.	z	P>z	[95% Conf	Interval]
Progressed	-0.099	0.010	-9.73	0	-0.119	-0.079
With TEAE	-0.029	0.014	-2	0.046	-0.057	-0.001
Geographical region	0.084	0.025	3.31	0.001	0.034	0.134
ECOG	-0.096	0.026	-3.7	0	-0.147	-0.045
AFP level	-0.051	0.025	-2.05	0.04	-0.099	-0.002
Extrahepatic disease	-0.038	0.026	-1.47	0.142	-0.088	0.013
Macrovascular invasi	-0.063	0.026	-2.4	0.016	-0.115	-0.012
Constant	0.931	0.027	35.05	0	0.879	0.983
/sigma_u	0.254	0.010	24.56	0	0.234	0.274
/sigma_e	0.206	0.004	58.67	0	0.199	0.213
rho	0.602	0.021	0.560918	0.642781	0.561	0.643

Likelihood-ratio test of sigma_u=0: chibar2(01)= 1520.04 Prob>=chibar2 = 0.000

Observation summary:	0	left-censored	observations
	2222	uncensored	observations
	1215	right-censored	observations

		Delta-method				
	dy/dx	Std. Err.	z	P>z	[95% Conf	Interval]
Progressed	-0.048	0.005	-9.5	0	-0.058	-0.038
With TEAE	-0.014	0.007	-2	0.046	-0.028	0.000
Geographical region	0.041	0.012	3.28	0.001	0.016	0.065
ECOG	-0.046	0.012	-3.72	0	-0.071	-0.022
AFP level	-0.025	0.012	-2.06	0.039	-0.048	-0.001
Extrahepatic disease	-0.018	0.012	-1.47	0.142	-0.043	0.006
Macrovascular invasi	-0.031	0.013	-2.4	0.016	-0.056	-0.006

Regression model (without stratification factors)

Random-effects tobit regression	Number of obs	=	3437
Group variable: SUBJIDN	Number of groups	=	543
Random effects u_i ~ Gaussian	Obs per group: min	=	1
	avg	=	6.3
	max	=	32
	Wald chi2(2)	=	96.18
Log likelihood = -836.11882	Prob > chi2	=	0

	Coef.	Std. Err.	z	P>z	[95% Conf	Interval]
Progressed	-0.099	0.010	-9.67	0	-0.119	-0.079
With TEAE	-0.031	0.014	-2.16	0.031	-0.060	-0.003
Contant	0.865	0.013	66.198	0	0.839	0.890
/sigma_u	0.265	0.011	24.71	0	0.244	0.286
/sigma_e	0.207	0.004	58.61	0	0.200	0.213
rho	0.622	0.020			0.582	0.662

Likelihood-ratio test of sigma_u=0: chibar2(01)= 1580.89Prob>=chibar2 = 0.000

Observation summary:	0	left-censored	observations
	2222	uncensored	observations
	1215	right-censored	observations

	dy/dx	Delta-method Std. Err.	z	P>z	[95% Conf	Interval]
Progressed	-0.048	0.005	-9.44	0	-0.058	-0.038
With TEAE	-0.015	0.007	-2.16	0.031	-0.029	-0.001

B13. Please provide more details on the models fitted to the utility data. What were the final parameterisations of the models, and which software was used to fit these models?

More detail on the models is provided in the answer to question B12. Stata 12 was the statistical software used.

Resource use and costs

B14. Priority question. Please clarify why the resource use estimated from three clinicians (page 142 of the company submission) was used instead of the committee preferred approach used in the assessment of sorafenib. Please provide an analysis using the values preferred by the NICE CDF committee.

The resource estimates included in the sorafenib CDF reappraisal pooled those obtained in 2015 with those collected in 2007. The estimates from 2007 were included for sorafenib as they were used in the original technology appraisal for sorafenib; however, they are not appropriate for this appraisal. 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. We consider that the 2015 estimates should be used without pooling with those obtained from 2007. However, as requested, the cost-effectiveness results using the pooled resource use estimates are presented in Table 17.

Table 17. Cost-effectiveness results: pooled resource use estimates

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER versus baseline (£/QALY)
Regorafenib	[redacted]	1.340	1.044	16,099	0.520	0.367	43,900
BSC	[redacted]	0.874	0.677	-	-	-	-

B15. Please clarify why arbitrary standard errors equal to 30% of the mean have been used for costs when a preferable standard error could be calculated from NHS Reference Cost data.

We estimate the standard errors from the NHS Reference costs to be in the range of 2-15%. Our use of 30% as a standard error therefore includes a greater range of uncertainty.

B16. Please comment whether the cost of the Palliative Care Team (currently costed to be £131 in Table 49, page 145 of the company submission) would be more appropriately costed as HRG CODE SD04A (cost £136)

We agree with the ERG and this has now been implemented into the model. Updated base case results are in the table below. There is a small (less than £10) increase in the ICER.

Table 18. Cost-effectiveness results – palliative care costs of £136

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER versus baseline (£/QALY)
Regorafenib	[redacted]	1.340	1.044	[redacted]	0.467	0.367	33,345
BSC	[redacted]	0.874	0.677	-	-	-	-

Previous cost-effectiveness publication

B17. A published cost-effectiveness analysis has been identified after the cut-off date of the company review. (Parikh et al. (2017) DOI: 10.1002/cncr.30863). Please comment on the relevance and limitations of this study.

We consider that the publication by Parikh et al is of little relevance for the following reasons:

- The analyses conducted appear to be restricted to a time horizon matching the length of the RESORCE study – no extrapolation beyond the trial has been conducted. This reduces the overall survival benefit and the QALY's gained
- Regorafenib costs are based on US prices and are not reflective of the submitted PAS price for the regorafenib appraisal
- The perspective is that of a different healthcare system

Adverse events

B18. Please comment on the apparent discrepancy in adverse event rates per cycle used in the model and the data reported from RESORCE. The adverse event rates reported in Table 37, page 125 of the company submission as 5.55% for regorafenib and 5.06% for best supportive care (BSC). However, drug-related treatment emergent adverse events (TEAEs) from the RESORCE study reported on page 77 of the company submission are: (hand-foot skin reaction, diarrhoea (33% vs. 9%), decreased appetite (24% vs. 6%), hypertension (23% vs. 5%) and fatigue (21.1% vs. 13.5%).

The adverse events reported on page 77 of the company submission represent the frequency of events that occurred over the entire double-blind period of the trial. For the economic model patient-level data was used to estimate that probability of experiencing any of 8 grade 3/4 adverse events per 28-day cycle. There is no discrepancy between the values reported in the clinical section of the submission and those used in the cost-effectiveness model.

B19. The proportions of TEAEs do not appear to follow a constant rate (Table 38, page 126-127 of company submission). Please comment on the following:

a. The appropriateness of applying a fixed TEAE probability during each model cycle. Why are the observed time-dependent probabilities not applied directly in the model during each cycle?

Considering the 8 adverse events in the model, within table 38 various different patterns of occurrence over time can be observed. As examples: anaemia tends to increase over time whereas hypertension and HFSR increase and decreases over time. In contrast there were spikes in incidence for hypophosphataemia (regorafenib cycle 28). As a modelling simplification we calculated the overall average of TEAEs per treatment arm and assumed a constant rate per treatment cycle. We believe that incorporation of observed time-dependent probabilities and the approach we took are both valid modelling approaches.

b. Why the total number of TEAEs for regorafenib predicted from the model (Sheet "Pat_cohort", sum of AEs in column Z = 42%) is less than the number of grade 3/4 TEAEs in Table 28, page 75-76 of the company submission (66.31%).

The difference is attributable to table 28 considering AEs with an incidence of at least 1% in either arm. Adverse events were considered in the model if they occurred at an incidence of 5% or greater in either arm – this is a standard modelling approach and reduces complexity.

Model implementation

B20. Priority Question Worksheets "NewlyDiagnosedReg" and "NewlyDiagnosedPlacebo.", please clarify:

a. What these calculations are intending to reflect

In retrospect the names given to these worksheets are confusing as it is not newly diagnosed patients to which the worksheets refer but rather newly progressed patients. In table 40 of the company submission the proportion of patients remaining on regorafenib in the cycles following progression is presented. In simple terms, the purpose of the named worksheets is to enable the model to estimate (at a cycle level) the proportion of patients receiving treatment. In order to do this the information presented in table 40 of the submission needs to be applied taking account of the cycle in which progression happens. A more detailed description of the calculations in these worksheets is provided below.

The calculations in the tab “NewlyDiagnosedReg” and “NewlyDiagnosedPlacebo” are where a ‘cycle-cohort simulation’ is performed on newly progressed patients for both the regorafenib and placebo arms. In each cycle of the model, the number of progressed patients is calculated using the following formula: PFS(n-1)-PFS(n)*Prob(dying in cycle n). That is, newly progressed patients are those patients who are no longer in PFS and are still alive.

The cycle-cohort of newly progressed patients can then be followed from the cycle they entered the progressed health state to determine how many patients are still on treatment based on the time to treatment discontinuation curve. The table below shows an example of how this works.

Table 19. Cycle-cohort simulation

		Cycle	1	2	3	4
Cycle	New progressed patients each cycle	Total progressed at each cycle	[redacted]			
1	0.00826	0.00826				
2	0.12938	0.13394				
3	0.10308	0.26551				
4	0.05692	0.28940				

The second column in the table above shows the newly progressed patients in each cycle in the model. From this, the number of patients on treatment each cycle after progression is calculated. For example, in cycle 1 of the model [redacted] patients enter the progressed health state, and [redacted] of those patients are on treatment ([redacted]). For this cycle cohort, in the 2nd cycle after progression, [redacted] are on treatment ([redacted] patients), and so on for cycles 3 and 4, etc. In cycle 2 of model, there are also an additional 0.12938 newly progressed patients, and [redacted]% of these patients are on treatment ([redacted] patients), and so on for cycles 2, 3 and 4, etc.

From this analysis, the total number of progressed patients on treatment at each cycle can be calculated to give an overall weighted percentage on treatment in the model. For regorafenib patients, this weighted percentage is used to calculate the following costs in the model for progressed patients:

- Drug
- Adverse events
- Hospitalisations
- Medical staff visits
- Laboratory tests
- Radiological tests

For placebo patients, this weighted percentage is used to calculate adverse event costs only.

b. How the data presented in Table 40, page 129 of the company submission have been calculated

To associate treatment costs to patients still on treatment after disease progression, a time-to-event analysis was performed using treatment discontinuation as the event variable and the number of days on treatment post progression as the time variable. For clarity, the PFS variable and the mRECIST progression criteria are used to form this group of patients.

The variables necessary for a time-to-event analysis are time to the event and an indicator of whether a patient truly experienced the event of interest or not (censoring). The source of the variables used in this analysis are described below:

- **Time:** the days from disease progression to treatment discontinuation. The difference between the progression event date and the recorded end of treatment date gives the number of days between progression and treatment discontinuation.
- **Censoring:** whether a patient truly discontinued treatment or not. Observations were marked as censored if the reported reason for treatment discontinuation was death, withdrawal by subject, or was not recorded (end of trial or lost to follow-up).

All other recorded reasons indicated true treatment discontinuation. The time-to-event analysis estimated the probability of a patient being on treatment x cycles after disease progression. The same analysis is performed for patients in the placebo arm.

B21. Please clarify how uncertainty surrounding progression free survival has been included in the PSA. Bootstrapping appears to have been included in the model but is not discussed in the company submission.

Please see our response to question B5 for an explanation.

B22. Sheets "QALYs", cell H26: Why are the state utilities divided by 13 rather than 365.25/28?

We agree with the ERG and this has now been implemented into the model. Updated base case results can be found in the table below. This has been corrected in the other tabs as well (Pat_cohort, Model_cost and Model_QALYs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER versus baseline (£/QALY)
Regorafenib	[redacted]	1.340	1.048	[redacted]	0.467	0.368	33,395
BSC	[redacted]	0.874	0.680	-	-	-	-

B23. Worksheet "Effect extrapolation", please clarify:

a. *Overall survival :*
   i. *Why the estimate for the rate parameter in the Gamma distribution in the model was negative*
   ii. *The estimate for model parameters in Gompertz distribution were both zero and,*
   iii. *The rate parameter in the exponential distribution was zero*
b. *Progression free survival:*
   i. *Why the estimate for the rate parameter in the Gamma distribution in the model was negative and,*
   ii. *The estimate for the shape parameters in Gompertz distribution was zero.*

The coefficients generated in R are sometimes transformed using the natural log before their implementation in the Excel model, due to differences between the parameterization in R and the formulas used in Excel. For example, for the dependent Generalised Gamma distribution, sigma is equal to 0.9951 in R, and the parameter value seen in the model is LN(0.9951)= -0.00491. Additionally, the coefficients seen in the model represent the regorafenib arm, so they have been adjusted for the effect of the treatment ('Tx'). For example, for the dependent Generalised Gamma distribution, mu is equal to 5.48 in R, and the parameter value seen in the model is 5.48+0.34=5.82 (=mu+Tx). It is because of these transformations that some values seen in the model are negative. The coefficients that appear to be zero in the model are simply rounded to the second decimal but are non-zero.

The transformations to the parameters along with the formula used to generate the adjusted coefficients as seen in the model are shown below. Please note that some additional transformations were made directly in the model; these can be seen in the survival formulas for the different distributions.

Original coefficients generated in R

	Treatment	Rate	Shape	Scale	meanlog	Sdlog
Loglogistic	**0.33**		1.67	221.76		
Weibull	**0.34**		1.23	324.79		
Lognormal	**0.33**				5.39	1.04
Gompertz	**-0.40**	0.00278	0.00053			
Exponential	**-0.38**	0.00308				
Gamma	**-0.34**	0.00	1.44			
		mu	sigma	q		
Generalised Gamma	**0.34**	5.48	1.00	0.21		

Transformations performed

	Rate	Shape	Scale	meanlog	Sdlog
Loglogistic		N.A.	LN		
Weibull		N.A.	LN		
Lognormal				N.A.	N.A.
Gompertz	LN	N.A.			
Exponential	LN				
Gamma	LN	LN			
	Mu	sigma	q		
Generalised Gamma	N.A.	LN	N.A.		

Adjustment of parameters to derive the regorafenib arm using the treatment coefficient (Tx)

	Rate	Shape	Scale	meanlog	Sdlog
Loglogistic		N.A.	EXP(LN(Scale)+Tx)		
Weibull		N.A.	EXP(LN(Scale)+Tx)		
Lognormal				meanlog+Tx	N.A.
Gompertz	EXP(LN(Rate)+Tx)	N.A.			
Exponential	EXP(LN(Rate)+Tx)				
Gamma	LN(Rate)+Tx	N.A.			
	Mu	sigma	q		
Generalised Gamma	mu+Tx	N.A.	N.A.		

Parameters seen in the model (regorafenib arm)

	Rate	Shape	Scale	meanlog	Sdlog
Loglogistic		1.67	307.98		
Weibull		1.23	458.46		
Lognormal				5.73	1.04
Gompertz	0.00	0.00053			
Exponential	0.00				
Gamma	-5.70	0.37			
	Mu	sigma	q		
Generalised Gamma	5.82	0.00	0.31		

Example R output for the lognormal model

```
> lognorm1<- flexsurvreg(Surv(time,event) ~ 1, dist="lognormal")
> print(lognorm1)
Call:
flexsurvreg(formula = Surv(time, event) ~ 1, dist = "lognormal")

Estimates:
         est     L95%    U95%    se
meanlog  5.3803  5.2316  5.5291  0.0759
sdlog    0.9802  0.8700  1.1043  0.0596

N = 194,  Events: 140,  Censored: 54
Total time at risk: 45426
Log-likelihood = -940.9394, df = 2
AIC = 1885.879
```

B24. Please confirm if there is an error in Pat_cohort (AN29:AN270) and if these cells should reference C78 rather than C77.

The manufacturer confirms this was a mistake and it has now been rectified into the model. Updated base case results are in the table below.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER versus baseline (£/QALY)
Regorafenib	[redacted]	1.340	1.044	12,269	0.467	0.367	33,456
BSC	[redacted]	0.874	0.677	-	-	-	-

Section C: Textual clarifications and additional points

C1. Page 68 of the company submission: Please confirm whether the minimally important difference for EQ-5D VAS is 10 (as shown in table 27) or 7 (as shown in the text)

The minimally important difference for EQ-5D VAS in the table is incorrect and should be 7 as it is in the text. We apologise for the error.

C2. Page 94 of the company submission: Please clarify how the assumption of [redacted] of patients progressing on sorafenib receiving regorafenib was estimated.

We took a simplified approach to estimating patient numbers i.e. [redacted] of patients who begin treatment with sorafenib receive second-line treatment with regorafenib (n = [redacted] patients). The figure of [redacted] takes account of the fact that not all patients would be able to receive regorafenib and was an internal forecasting assumption.

After being asked a similar question by the group responsible for estimating budget impact we think that a more transparent approach would have involved an intermediate step (outlined below). However, our estimate of the number of patients who will receive regorafenib remains the same.

- According to CDF figures there were 538 notifications for sorafenib in HCC in 2015. As the licence for regorafenib is for patients who have been previously treated with sorafenib, this 538 patients constitutes the potential eligible population for regorafenib
- A publication by Reig et al. (2013) suggests that 50% (43/85) of people were eligible for second line treatment following progression on sorafenib. Applying this to the number of people who received sorafenib in England in 2015 would give 269 people eligible for second-line treatment.
- We would assume that the majority of eligible patients (i.e. [redacted]%) would receive treatment with regorafenib i.e. [redacted]% x 269 = [redacted]

Reference
Reig M et al. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. Hepatology 2013 (Dec); 2023-2031

C3. Table 38, pages 126-127 of the company submission: Please clarify whether the data presented in the table are percentages relating to the number of patients receiving treatment. If not, please provide further details.

The title of the table is incorrect and should read as percentages rather than proportions.

C4. Table 42, page 136 of the company submission: Please clarify whether there is a typo in the table. Should Model 8 include stratification factors as suggested in Table 43 (page 138 of company submission)?

We can confirm that model 8 does contain stratification factors. Please see our response to B12 for more detail.

C5. Please clarify when the EQ-5D was filled out. Was it at 'the end of treatment visits' (page 138 of the company submission) or day 1 of each treatment cycle (page 131)? Please clarify if these are the same or different time-points.

These are different timepoints. The EQ-5D was completed on day 1 of each treatment cycle whilst the patient was receiving study treatment. It was also completed at the 'End of Treatment' visit which was within 14 days of stopping study treatment.

The EQ-5D was self-administered by the subject at the start of the visit, before the subject saw the investigator and before any study related procedures were done, so that any interaction between the subjects and investigator or other health care provider would not influence the responses to the questionnaires.

C6. Table 55, page 153 of the company submission: Normal distributions were assumed for the hazard ratios for progression free survival and overall survival. Please clarify whether these are log normal distributions instead of normal distributions.

The manufacturer confirms that a log normal distribution was applied. What is currently reported in table 55 is not correct.

Section B: Clarification on cost-effectiveness data

Extrapolation of survival outcomes

B1. Priority question. Page 28 of the company submission states that "After the primary endpoint of the study was reached (overall survival [OS]; 29th February 2016) and the results supported a positive benefit / risk assessment for regorafenib, patients on placebo at that time were offered the opportunity of receiving regorafenib through open-label treatment and patients randomised to regorafenib could continue open-label regorafenib. Data presented in this submission relates to the double-blind period only." Furthermore, page 54 of the company submission states that "This submission presents the study results from the clinical database released on 5th August 2016." There is a potential for the different dates (29th February 2016 and 5th August 2016) to cause confusion and uncertainty in the results reported:

a. Please clarify if results included in the company submission and the company model, report data from the clinical database released on the 5 August 2016 and include data from patients after the primary endpoint of the trial was reached on 29 February 2016 and treatment switching had occurred.

The clinical database release on the 5th August relate to the double-blind period only i.e. up to 29 February. There was no cross-over during the double-blind trial period.

A CSR was released earlier but the database was reopened following the identification of a small number of errors. The August CSR corrected the errors identified in the first CSR and was the one used in the submission.

b. If data after treatment switching is reported please provide an additional analysis of the trial data up to the August 2016 datalock which includes appropriate consideration of statistical adjustments for treatment switching.

The latest data-cut is 23 January 2017. After the original data-cut (29 February 2016) treatment was open-label and patients originally randomised to placebo could switch to regorafenib.

Of the 194 patients initially randomised to placebo only 4 (2.1%) switched to regorafenib during the open-label period. As this represents such a small proportion of patients we have not performed statistical adjustment for switching – rather, in our analysis we have assumed that these patients continue to receive placebo. The effect of this assumption is expected to be minimal, and if anything, slightly conservative as any benefit resulting from the switch to regorafenib is assumed to apply to placebo. The Kaplan-Meier data for OS and PFS are presented Figure 1 and Figure 2.

Figure 1. KM curves for January 23rd dataset (overall survival)

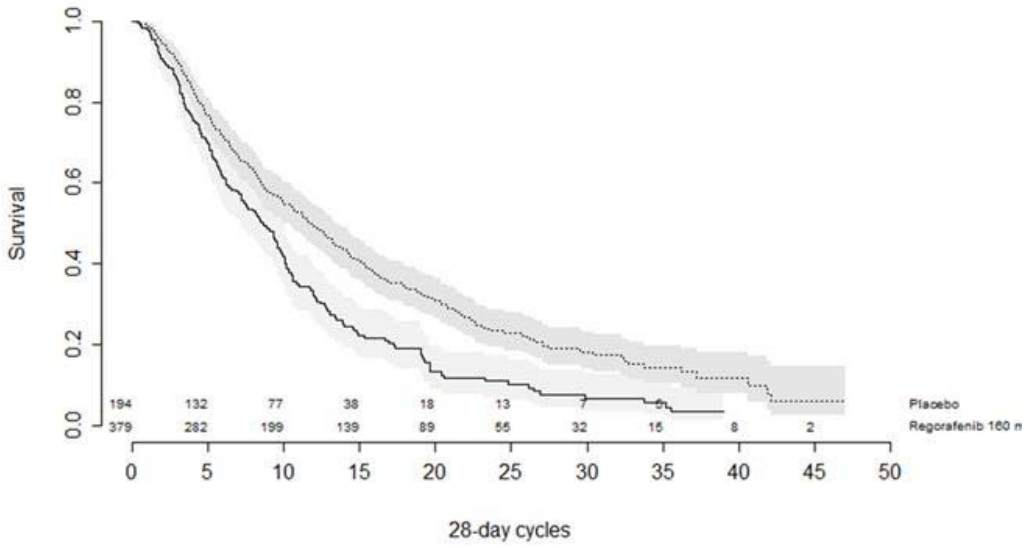
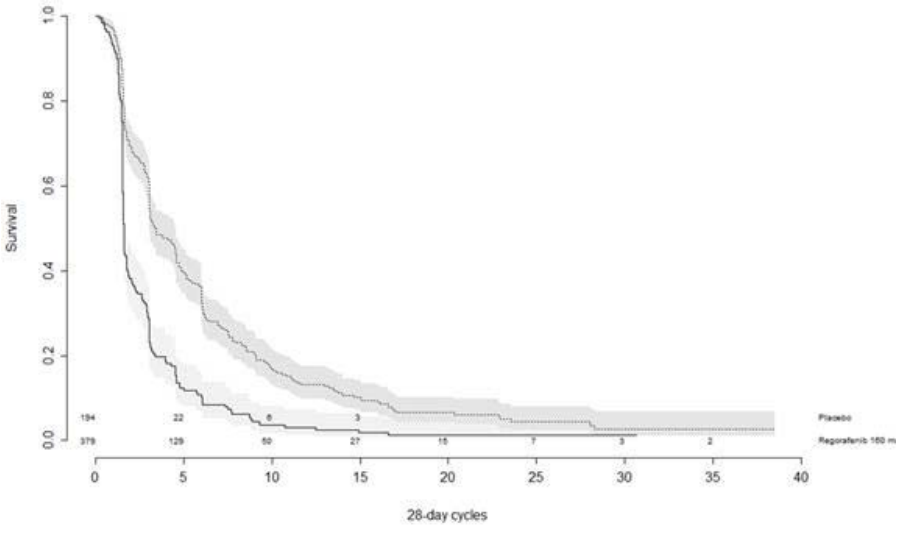


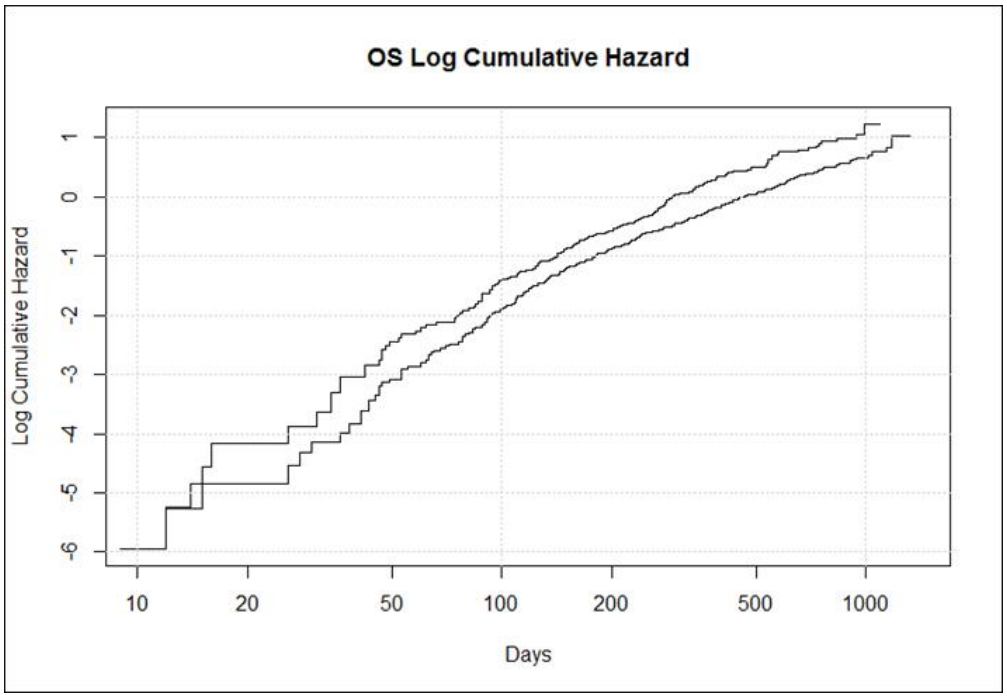
Figure 2. KM curves for 23rd January dataset (PFS)



Curve fitting

In keeping with our approach in the original submission parametric distributions were fitted to the OS KM data. Due to time constraints we have restricted our analyses to dependent curves as these are supported by the largely parallel log cumulative hazard plot presented in Figure 3 and the Grambsch and Therneau's correlation test between Schoenfeld residuals – the p value of greater than 0.05 shows that the proportional hazards assumption is not violated (p=0.608). In addition, our response to question B2b showed that the ICERs for independent curves were generally lower than their dependent equivalents - see Table 1.

Figure 3. Log cumulative hazard plot (23/01/17dataset)



Top curve represents the placebo arm and the bottom curve the regorafenib arm

Table 1. Cost-effectiveness results: original data-cut (29th February 2016)

	Original submission (dependent curves)	Question B2b (independent curves)
Lognormal (basecase curve)	**33,437**	**33,334**
Loglogistic	32,379	33,463
Weibull	25,726	25,248
Exponential	26,212	26,428
Gamma	39,466	33,028*
Gompertz	27,587	27,033

*generalised gamma

Statistical fit

The statistical fits for each parametric distribution are presented in Table 2. As was the case in the company submission the lognormal curve provides the best statistical fit to the data.

Table 2. Statistical fit of dependent OS parametric curves

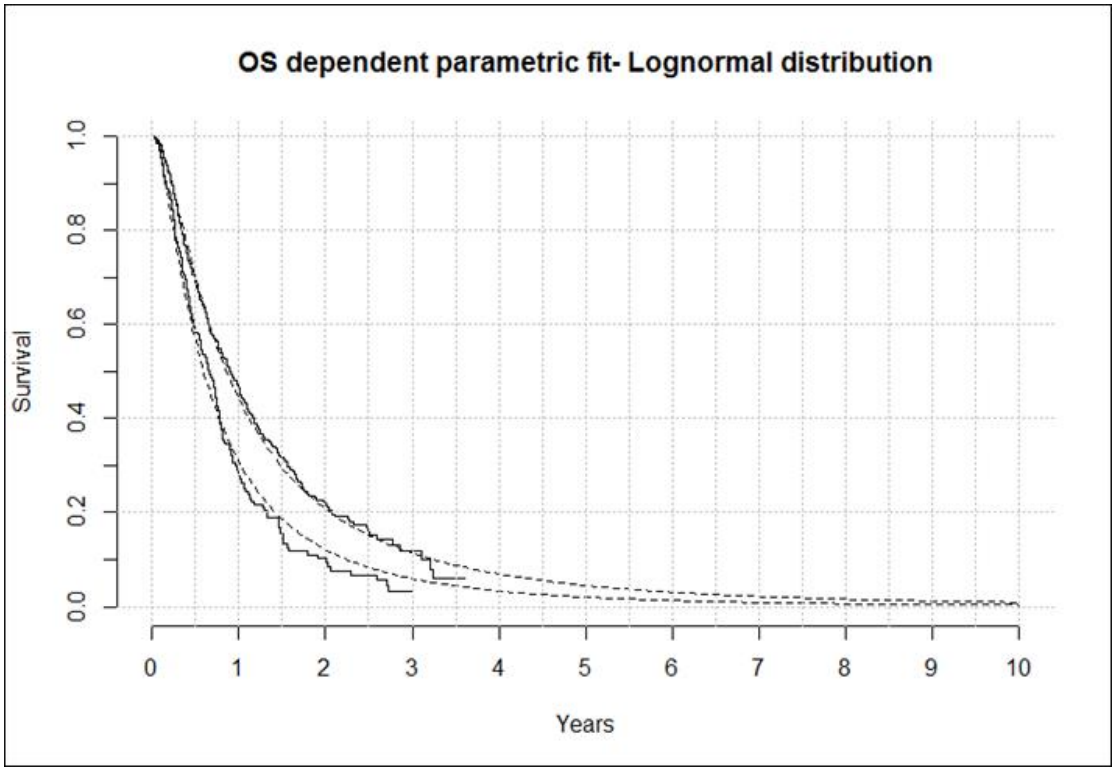
Distribution	AIC	BIC
Lognormal	6422.002	6435.054
Loglogistic	6425.492	6438.544
Generalised Gamma	6421.354	6438.757
Gamma	6437.777	6450.83
Weibull	6445.778	6458.831
Exponential	6460.862	6469.564
Gompertz	6461.486	6474.539

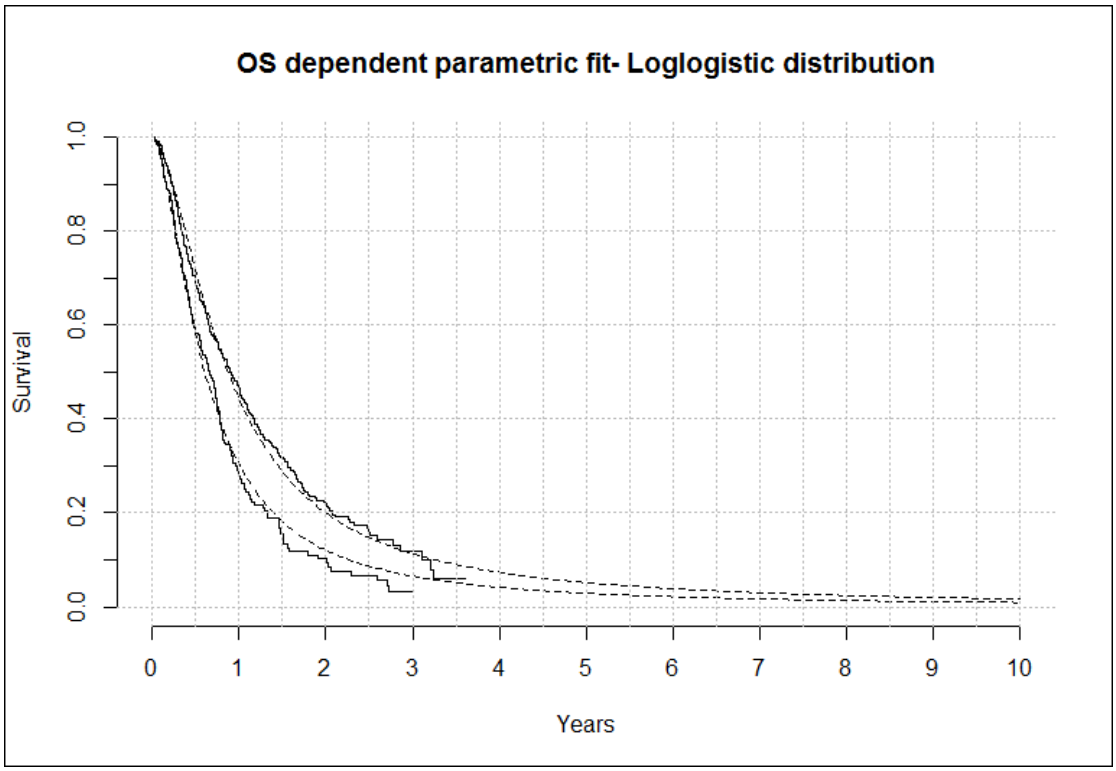
Visual fit

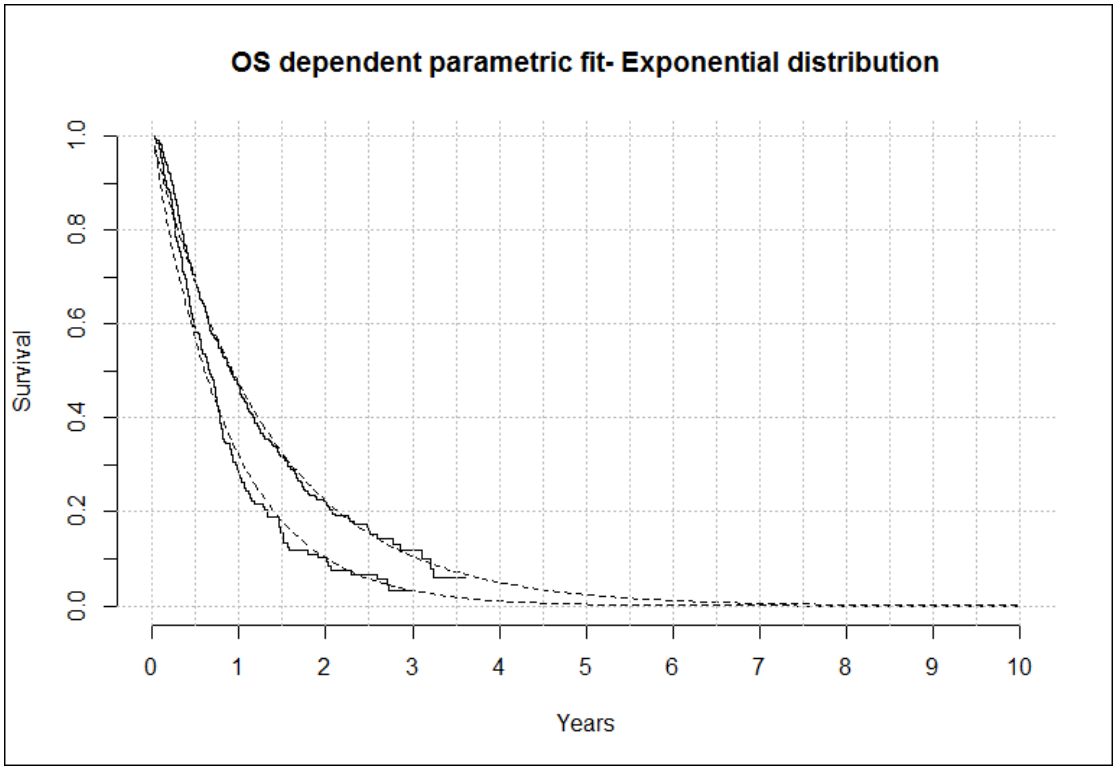
Visual inspection of the OS extrapolations (Figure 4) for the most recent data-cut suggests some differences in the fit of the different OS extrapolations.

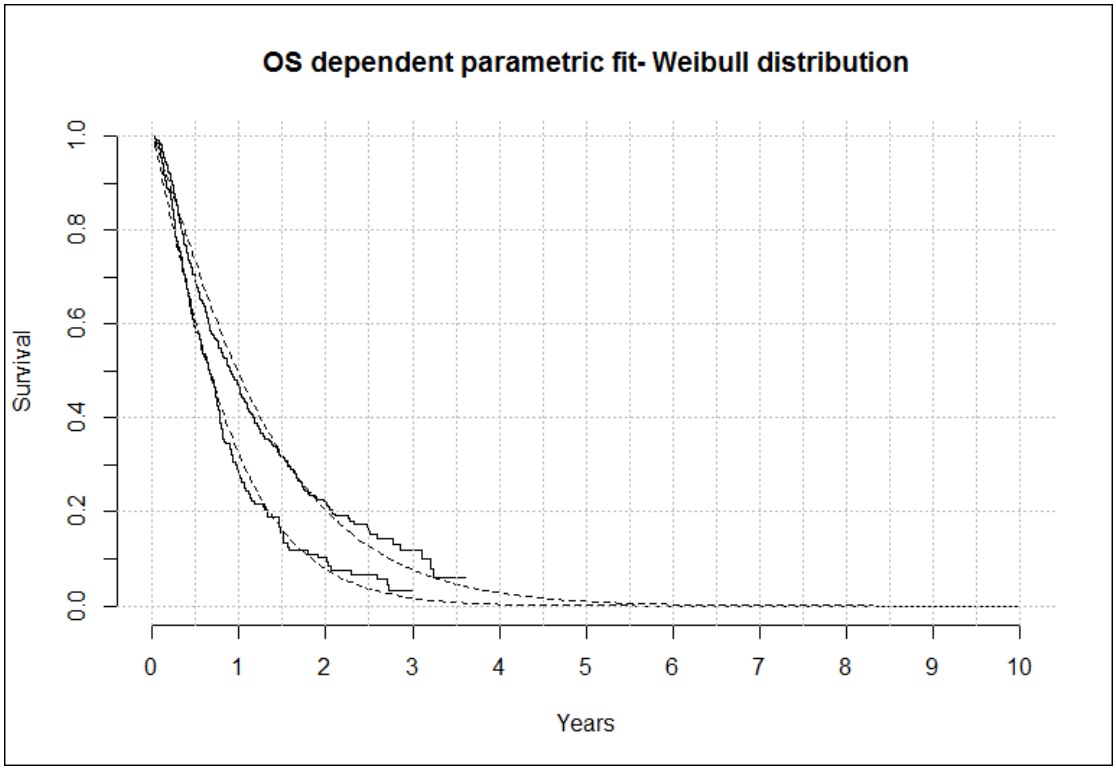
- Visually both the lognormal and loglogistic curves provide close fits to the regorafenib arm along the majority of the KM curve. The fit to the placebo arm is poorer with overestimation of survival for placebo in the later sections
- The exponential curve looks to provide a reasonable fit to both arms with some degree of overestimating survival in the mid-section of the KM curve for placebo.
- The Weibull curve appears to underestimate survival for both arms in the later portion of the KM curve, but to a greater extent for regorafenib.
- The generalised gamma distribution appears to slightly underestimate survival for regofarenib in the later portion of the KM curve and overestimate placebo survival.
- The Gompertz distribution appears to fit both arms relatively well with over/underestimation for one arm tending to be matched by the same direction of over/underestimation in the other arm.

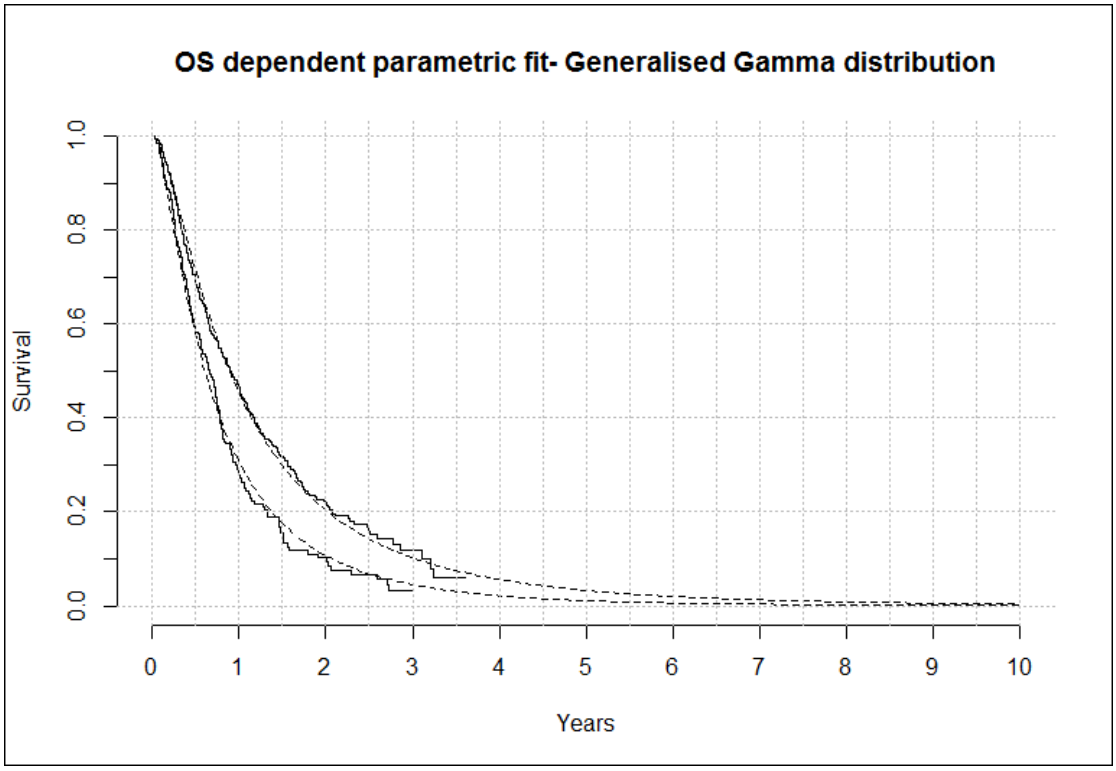
Figure 4. Dependent Parametric fits (overall survival)

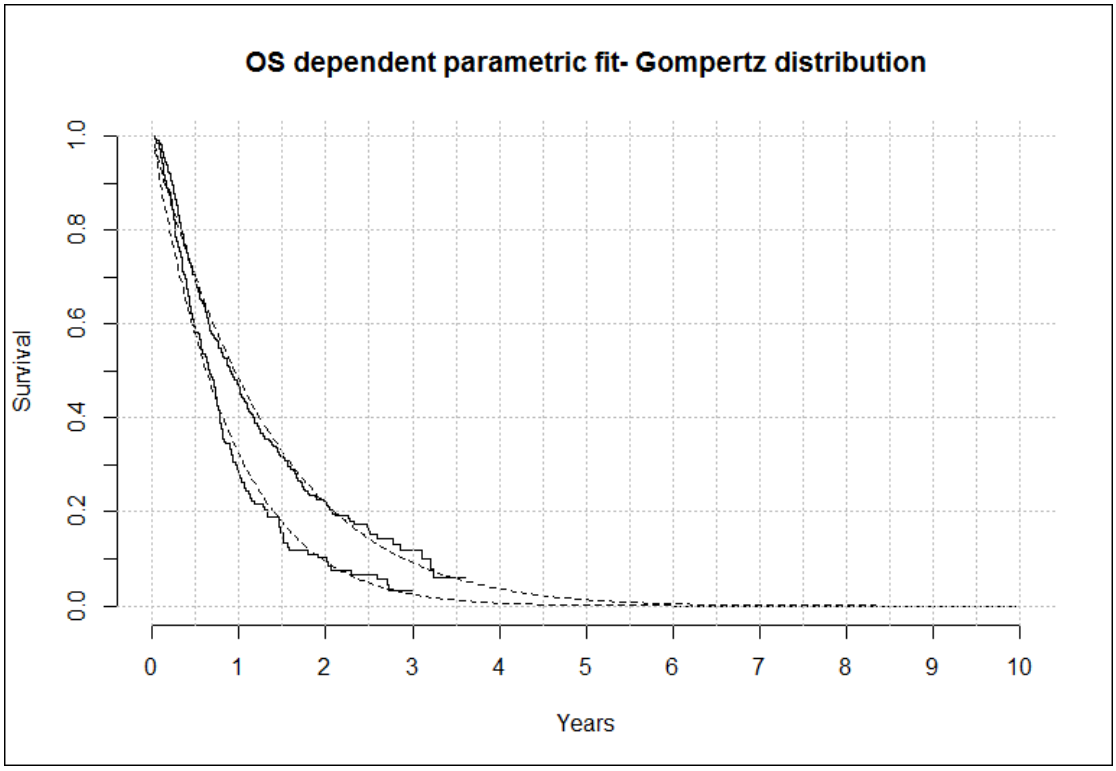





OS dependent parametric fit- Exponential distribution
Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
9
10
Years


OS dependent parametric fit- Weibull distribution
Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
9
10
Years


OS dependent parametric fit- Generalised Gamma distribution
Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
9
10
Years


OS dependent parametric fit- Gompertz distribution
Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
9
10
Years

Clinical Validity

To assess clinical plausibility the survival at different points in time was compared with the KM observed data from the RESORCE study. As acknowledged in our response to B2d the selection of a base case curve is not straightforward. As can be seen from Table 3 the curves differ in how closely they align to the observed KM data at different points in time i.e. some fitting better at some points and not others.

For regorafenib, at 2 years each curve aligns to the KM data relatively closely. In broad terms, considering the 35 cycle and 47 cycle timepoints together, the Weibull distribution tends to align least well to the observed data – underestimating survival. Considering later timepoints each curve predicts a low chance of survival with the Weibull and Gompertz curves being the most pessimistic. Estimated survival at the 10 year point ranges from 0-2%.

For placebo, considering the 2-year and 35-cycle timepoints together, the Gompertz, Exponential and generalised gamma appear to align most closely to the data but by quite narrow margins. As it did for regorafenib, the Weibull curve underestimates survival in comparison to the observed data. Considering the later timepoints survival ranges from 0-3% at 5 years and 0-1% at 10 years.

Table 3. Overall survival probabilities (dependent curves)

	Kaplan-Meier	Loglogistic	Weibull	Lognormal	Gompertz	Exponential	Generalised Gamma
Regorafenib							
2 years	0.21	0.2	0.2	0.21	0.22	0.22	0.20
35 cycles	0.15	0.13	0.11	0.14	0.12	0.13	0.13
47 cycles	0.06	0.07	0.04	0.08	0.05	0.07	0.07
5 years		0.05	0.01	0.04	0.01	0.02	0.03
10 years		0.02	0	0.01	0	0	0.00
BSC							
2 years	0.10	0.12	0.08	0.12	0.09	0.1	0.11
35 cycles	0.06	0.08	0.03	0.07	0.04	0.05	0.06
47 cycles		0.05	0.01	0.04	0.01	0.02	0.03
5 years		0.03	0	0.02	0	0	0.01
10 years		0.01	0	0	0	0	0.00
Difference: regorafenib minus BSC							
2 years	0.11	0.08	0.12	0.09	0.13	0.12	0.10
35 cycles	0.09	0.05	0.08	0.07	0.08	0.08	0.07
47 cycles		0.02	0.03	0.04	0.04	0.05	0.04
5 years		0.02	0.01	0.02	0.01	0.02	0.02
10 years		0.01	0	0.01	0	0	0.00

Selection of the best fitting curve

It is not possible to categorically state that one curve is the most clinically plausible. For transparency we suggest the lognormal as the best curve on the basis that it provides the best statistical fit to the data. Visually the lognormal curve fits the KM data very well for regorafenib. There is some overestimation of survival for placebo which will be conservative in relation to regorafenib. This choice of curve also maintains consistency with the best fitting curve for sorafenib as it applies in the same disease area.

Time on treatment

A time on treatment KM curve has been produced using the 23 January 2017 data-cut (Figure 5). Patients still on treatment at cut-off were censored. Table 4 shows the statistical fit of each parametric distribution. The loglogistic curve was the best fitting statistically. Figure 6 shows each curve fitted to the data.

Figure 5. KM plot – time on treatment

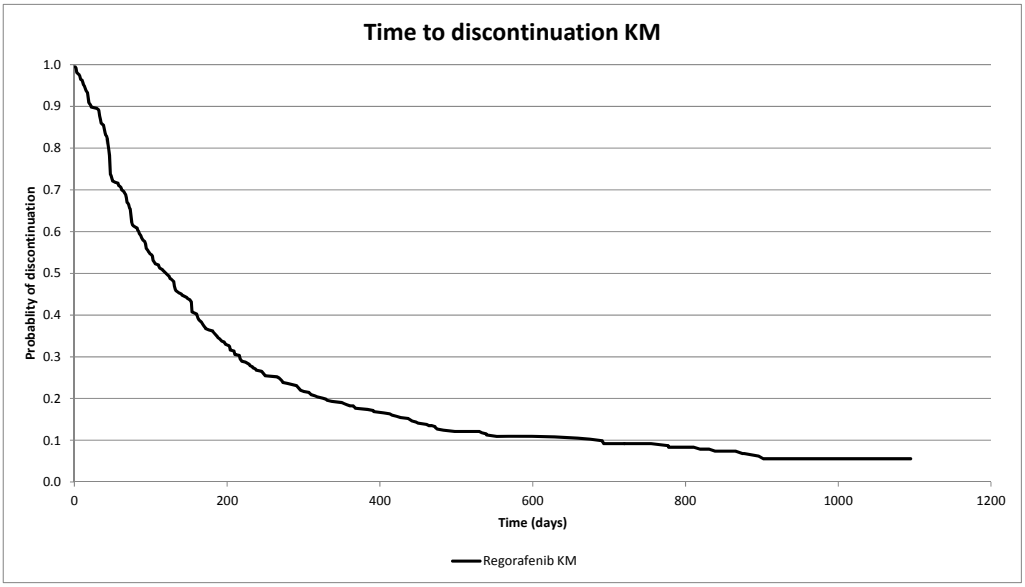
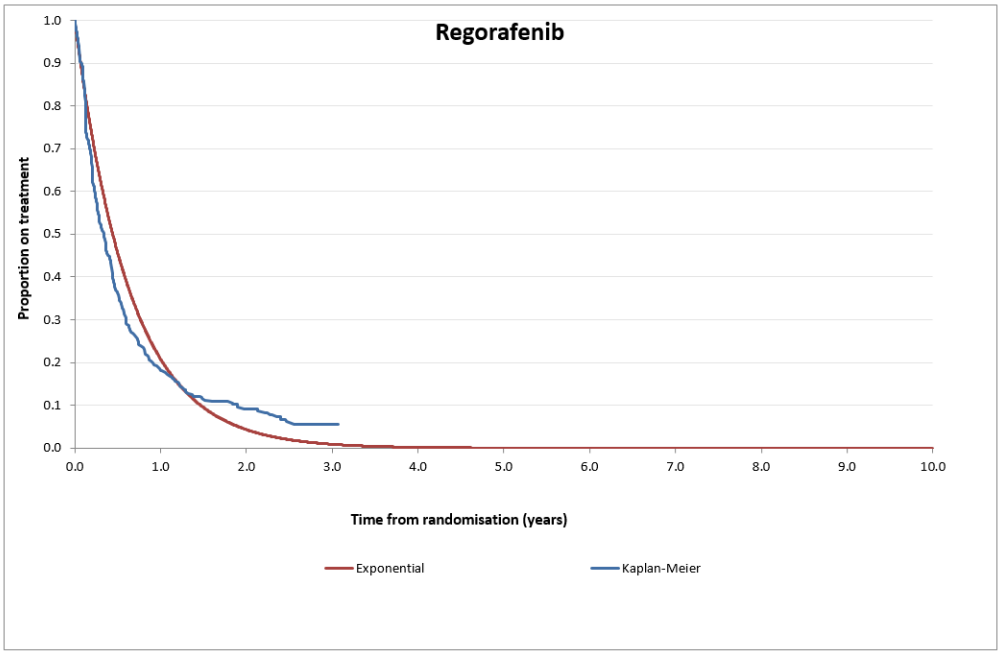
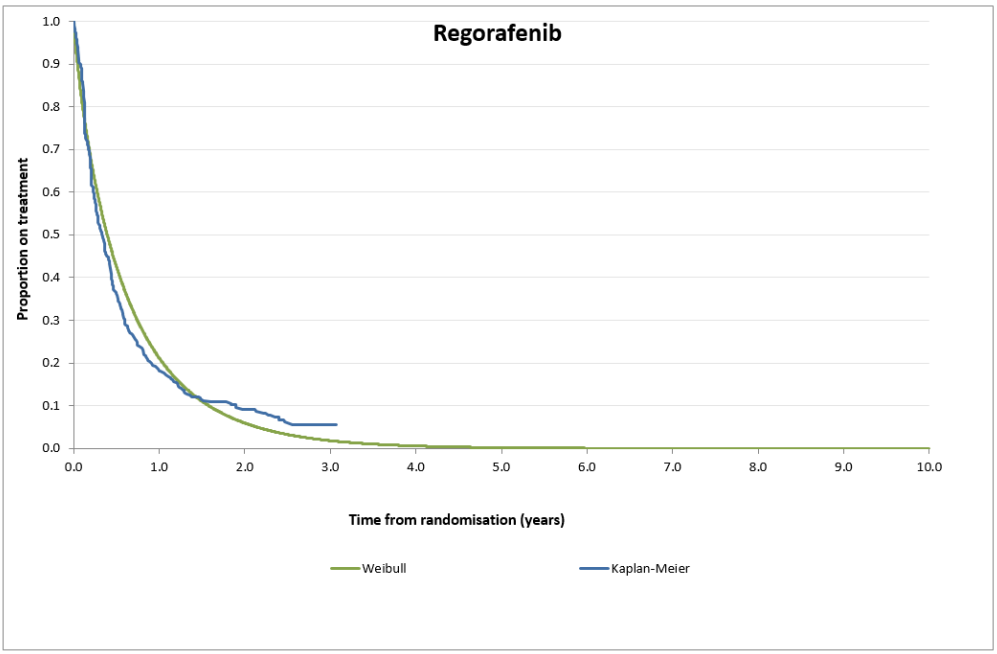


Figure 6. Parametric fits (time on treatment)

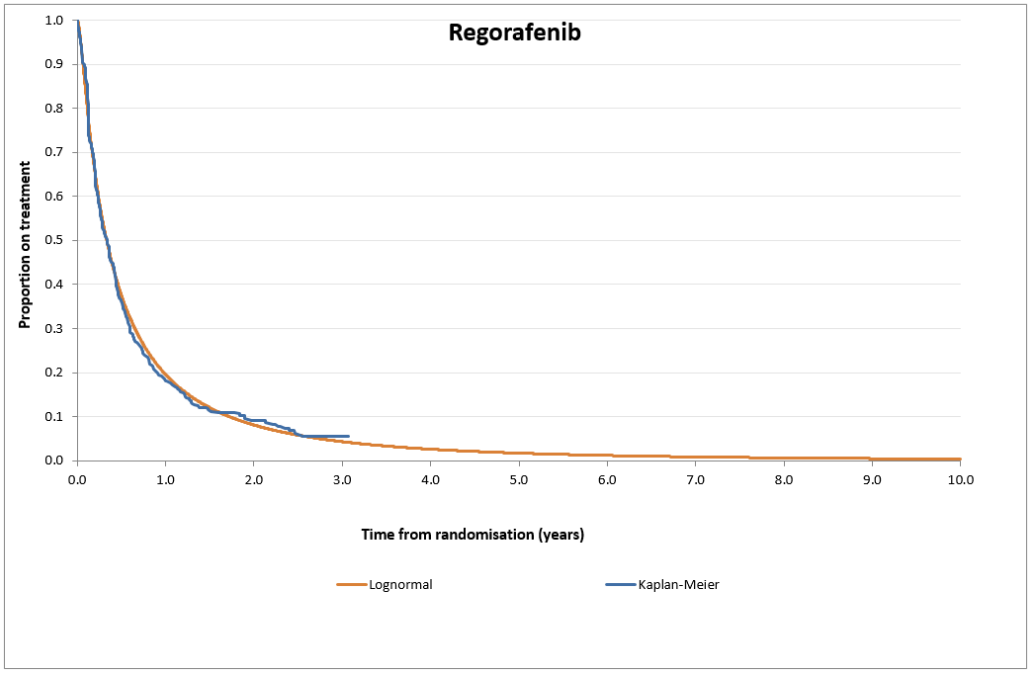
Exponential



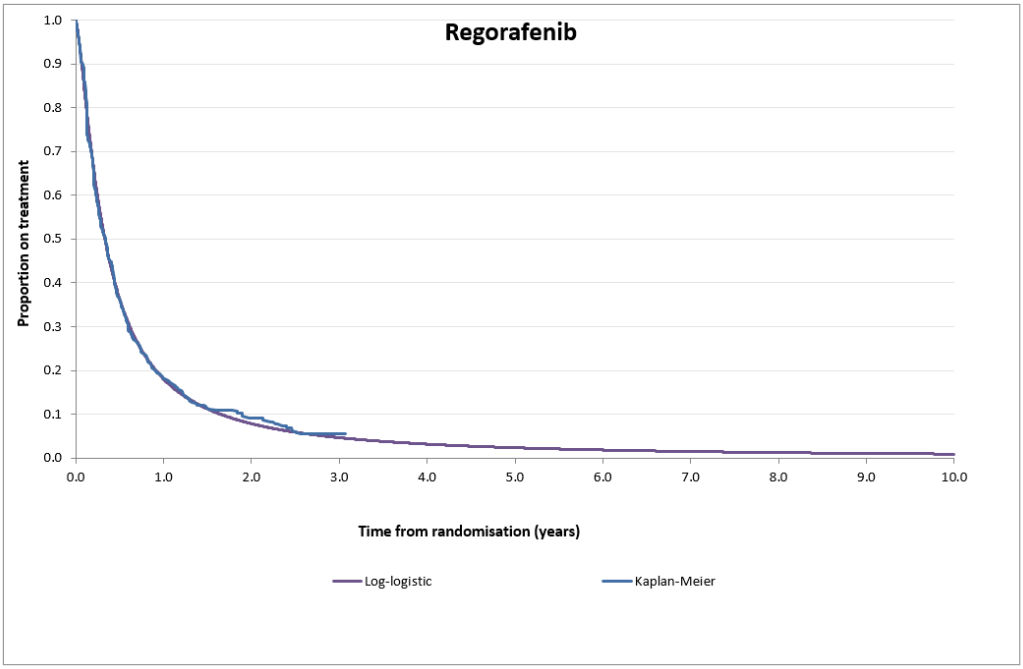
Weibull



Lognormal



Loglogistic



Gompertz

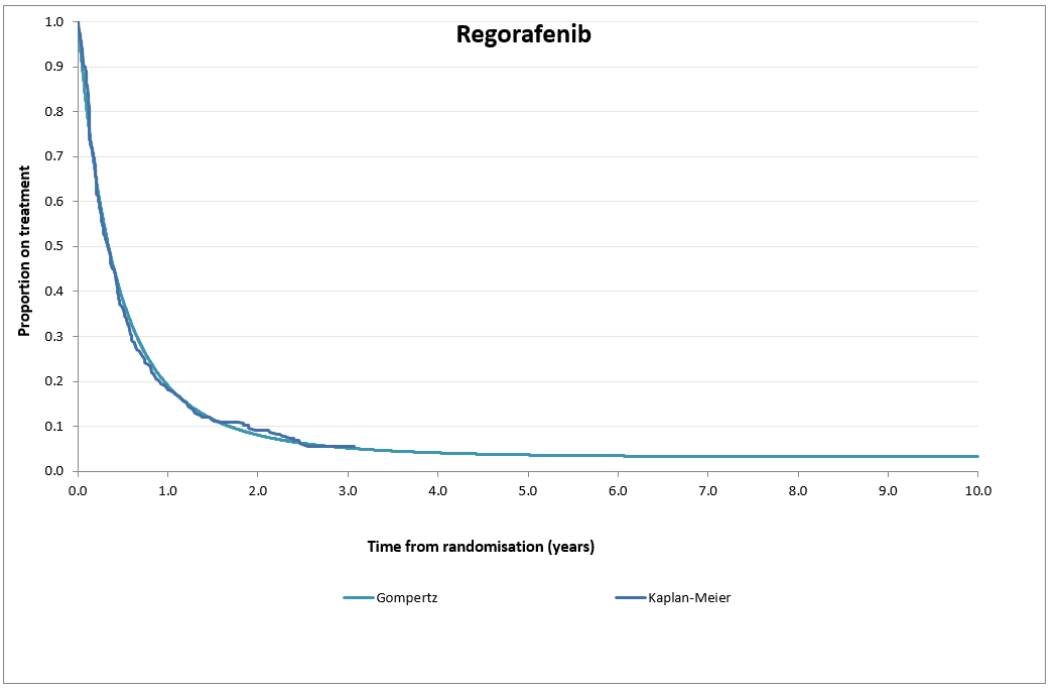


Table 4. Statistical fit (time on treatment)

Distribution	AIC	BIC
Loglogistic	1218.35	1226.19
Lognormal	1222.53	1230.38
Weibull	1263.10	1270.94
Exponential	1274.81	1278.73
Gompertz	1234.08	1241.92

Cost-effectiveness Results

The cost-effectiveness results for the revised base case are shown in Table 5. This analysis is based on the most recent data-cut from the RESORCE study (23 January 2017). The revised base case inputs are:

- PFS – raw trial data
- OS – lognormal extrapolation (dependent curves)
- Time on treatment – loglogistic parametric distribution
- Utilities – from the RESORCE study (as per original submission)
- Corrections identified in questions B16, B22 and B24 implemented
- Resource use – 2015 estimates (please see response to B14)

In Table 6 two scenario analyses are presented. The first scenario considers a mean treatment of [redacted] packs of regorafenib. This was the mean treatment received in the RESORCE study at the primary cutoff date of 29 February 2016. We believe that in the UK treatment is unlikely to exceed this amount. The second scenario considers a 75/25% weighting between the lognormal and Weibull extrapolations respectively. This scenario is of relevance because in the CDF re-appraisal for sorafenib, where there was also uncertainty regarding the most appropriate extrapolation, the committee preferred this scenario. In this scenario the loglogistic time on treatment curve is used as this provided the best statistical fit to the data.

Table 7 presents the results of a wide range of other scenario analyses whereby, for each time on treatment curve the results for the different OS extrapolations are presented.

Table 5. Base case cost-effectiveness results

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Original base case	12,262	0.367	33,437
New base case: - 23 Jan 17 datacut: - lognormal OS - loglogistic mean treatment	14,743	0.405	36,434

Table 6. Scenario analyses: cost-effectiveness results

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Mean treatment received – [redacted] packs			
Lognormal	12,936	0.405	31,968
Loglogistic	13,726	0.439	31,291
Weibull	12,302	0.275	44,659
Exponential	14,253	0.337	42,327
Gompertz	13,651	0.307	44,398
Generalised gamma	12,098	0.361	33,518
Time on treatment: loglogistic curve			
75% lognormal; 25% Weibull	14,585	0.372	39,168

Table 7. Other scenario analyses: cost-effectiveness results

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Time on treatment curve: raw KM data			
Lognormal	14,685	0.405	36,290
Loglogistic	15,475	0.439	35,278
Weibull	14,051	0.275	51,008
Exponential	16,002	0.337	47,521
Gompertz	15,400	0.307	50,086
Generalised gamma	13,847	0.361	38,364
Time on treatment curve: lognormal			
Lognormal	15,012	0.405	37,097
Loglogistic	15,801	0.439	36,023
Weibull	14,378	0.275	52,194
Exponential	16,329	0.337	48,491
Gompertz	15,727	0.307	51,148
Generalised gamma	14,174	0.361	39,269
Time on treatment curve: Exponential			
Lognormal	14,846	0.405	36,688
Loglogistic	15,636	0.439	35,645
Weibull	14,212	0.275	51,593
Exponential	16,163	0.337	48,000
Gompertz	15,562	0.307	50,610
Generalised gamma	14,008	0.361	38,810
Time on treatment curve: Weibull			
Lognormal	15,373	0.405	37,990
Loglogistic	16,163	0.439	36,847
Weibull	14,739	0.275	53,506
Exponential	16,691	0.337	49,565
Gompertz	16,089	0.307	52,324
Generalised gamma	14,535	0.361	40,270

Time on treatment curve: loglogistic			
Lognormal	14,743	0.405	36,434
Loglogistic	15,533	0.439	35,411
Weibull	14,109	0.275	51,220
Exponential	16,061	0.337	47,694
Gompertz	15,459	0.307	50,275
Generalised gamma	13,905	0.361	38,525
Time on treatment curve: Gompertz			
Lognormal	14,925	0.405	36,883
Loglogistic	15,714	0.439	35,825
Weibull	14,291	0.275	51,879
Exponential	16,242	0.337	48,234
Gompertz	15,640	0.307	50,866
Generalised gamma	14,087	0.361	39,029

Updated Model

A revised model incorporating the data from the 23 January 2017 cut-off has been uploaded as a separated file. Please note that the corrections (B16, B22, B24) can be switched on/off on the 'Model Summary' tab (N22:O25) and the source of Resource use can be selected also. Different extrapolations for time on treatment are accessible via the 'KM discontinuation' tab.

Clarification Question received 17 August 2017

As the ERG will need to report your base case ICER in the ERG report they provide, could you explicitly detail your base-case and the analyses that inform it. Additionally, please provide a model incorporating this base-case.

In our response to B1 (sent 18th August 2017) we have detailed a revised base case. An economic model incorporating the revised base case has been uploaded also.

Clarification Question Received 17 August 17

In Table 121 of Appendix 0 in the top right hand cell of the table, clinicians were asked to provide the 'number of admissions per month'. However, the ERG have identified that in all uses of this parameter the number is less than 1. The number of admissions per month must logically be 1 or above.

The questionnaire asks for the number of admissions per month. Throughout the questionnaire physicians were instructed to enter a decimal if the unit of interest occurred less frequently than once per month. For example, if the frequency was once every three months they were instructed to enter 0.33 (1 divided by 3). On this basis parameter values less than one are logical and in this case indicate that patients on average are hospitalised less than once per month.

Regorafenib in HCC – Clarification questions

Please find below (starting page 4) our response to the clarification question received on 25th August. Presented before this are results following the identification of an error in the model used to answer question B1.

Error found in model used to answer question B1

Since submitting the response to clarification question B1 we have found a small error in the way the data from 23 January 2017 was implemented in the model – we apologise for this error. The new data cut contained additional treatment cycles, however, these were not linked correctly in the model in the case where the user selected KM data to be used i.e. the 'raw data' option. In respect of the base case OS is not affected as the model uses the lognormal distribution – not KM data. However, the error does impact PFS, since the KM data is used in the base case. Incorporating the PFS data correctly slightly improves the cost-effectiveness of regorafenib (the base case ICER decreases from £36,434 to £36,050). The cost-effectiveness results pertaining to question B1, following the correction are provided below.

Please note that the corrected results presented in table 1 constitute our base case.

Table 1. Base case cost-effectiveness results

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Original submission base case	12,262	0.367	33,437
New base case: - 23 Jan 17 data cut: - lognormal OS - loglogistic mean treatment - PFS: raw trial data - utilities: from RESORCE - corrections as per B16, B22, B24 - Resource use: 2015 estimates	14,625	0.406	36,050

Table 2. Updated table 6 from answer to question B1 (Scenario analyses: cost-effectiveness results)

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Mean treatment received – [redacted] packs			
Lognormal	12,817	0.406	31,595
Loglogistic	13,607	0.440	30,949
Weibull	12,302	0.275	44,659
Exponential	14,253	0.337	42,327
Gompertz	13,651	0.307	44,398
Generalised gamma	11,979	0.362	33,096
Time on treatment: loglogistic curve			
75% lognormal; 25% Weibull	14,496	0.373	38,850

Table 3. Updated table 7 from answer to question B1 (Other scenario analyses: cost-effectiveness results)

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Time on treatment curve: raw KM data			
Lognormal	14,566	0.406	36,906
Loglogistic	15,356	0.440	34,927
Weibull	14,051	0.275	51,008
Exponential	16,002	0.337	47,521
Gompertz	15,400	0.307	50,086
Generalised gamma	13,728	0.362	37,928
Time on treatment curve: lognormal			
Lognormal	14,893	0.406	36,712
Loglogistic	15,683	0.440	35,670
Weibull	14,378	0.275	52,194
Exponential	16,329	0.337	48,491
Gompertz	15,727	0.307	51,148
Generalised gamma	14,055	0.362	38,831
Time on treatment curve: Exponential			
Lognormal	14,674	0.406	36,172
Loglogistic	15,464	0.440	35,171
Weibull	14,159	0.275	51,399
Exponential	16,110	0.337	47,841
Gompertz	15,508	0.307	50,436
Generalised gamma	13,836	0.362	38,226
Time on treatment curve: Weibull			
Lognormal	15,254	0.406	37,603
Loglogistic	16,044	0.440	36,492
Weibull	14,739	0.275	53,506
Exponential	16,691	0.337	49,565
Gompertz	16,089	0.307	52,324
Generalised gamma	14,417	0.362	39,829
Time on treatment curve: loglogistic			
Lognormal	14,625	0.406	36,050
Loglogistic	15,414	0.440	35,059
Weibull	14,109	0.275	51,220
Exponential	16,061	0.337	47,694
Gompertz	15,459	0.307	50,275
Generalised gamma	13,787	0.362	38,089
Time on treatment curve: Gompertz			
Lognormal	14,806	0.406	36,498
Loglogistic	15,596	0.440	35,472
Weibull	14,291	0.275	51,879
Exponential	16,242	0.337	48,234
Gompertz	15,640	0.307	50,866
Generalised gamma	13,968	0.362	38,591

On comparison of the above results with those sent originally for question B1 we noticed that there had been no change for the Weibull, Exponential and Gompertz distributions. On investigation the reason was found to be related to the use of KM data for PFS and parametric distributions for OS. For these 3 OS distributions there was a single cycle where PFS exceeded OS i.e. cycle 2. This is not logical and the model formula had been set to move patients to the progressed health state in this eventuality. The net effect was that from cycle 2 onwards the KM data for PFS had been overwritten.

To overcome this anomaly for the 3 affected non-base case curves we implemented a scenario whereby PFS used the same parametric distribution as for overall survival. The results are presented in table 4.

Table 4. Results using the same distribution for PFS and OS

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Mean treatment received – [redacted] packs			
Weibull	11,206	0.295	38,040
Exponential	12,318	0.348	35,439
Gompertz	11,662	0.319	36,557
Time on treatment curve: raw KM data			
Weibull	12,955	0.295	43,977
Exponential	14,067	0.348	40,471
Gompertz	13,411	0.319	42,040
Time on treatment curve: lognormal			
Weibull	13,282	0.295	45,086
Exponential	14,393	0.348	41,410
Gompertz	13,738	0.319	43,064
Time on treatment curve: Exponential			
Weibull	13,063	0.295	44,342
Exponential	14,174	0.348	40,780
Gompertz	13,519	0.319	42,377
Time on treatment curve: Weibull			
Weibull	13,643	0.295	46,313
Exponential	14,755	0.348	42,450
Gompertz	14,100	0.319	44,197
Time on treatment curve: Loglogistic			
Weibull	13,013	0.295	44,175
Exponential	14,125	0.348	40,638
Gompertz	13,470	0.319	42,223
Time on treatment curve: Gompertz			
Weibull	13,195	0.295	44,791
Exponential	14,307	0.348	41,161
Gompertz	13,651	0.319	42,792

Clarification Question – Received 25 August 2017

The ERG believes that the implementation of the survey resources is unlikely to be consistent with the way in which it was intended. They demonstrate this using the costs of hospitalisation, assuming that the 2015 survey is appropriate. For pre-progression patients having sorafenib the cost of a general ward stay is calculated using four elements:

- ***P – the proportion of patients requiring hospitalisation (6.7%)***
- ***D – the duration of an average ward stay (5.83 days)***
- ***H – the number of hospitalisations (0.40)***
- ***C – cost per bed day (£801)***

The model calculates the cost per cycle as P * D * H * C

This formula is only conceptually correct if P is dividing the population into those who are susceptible to hospitalisation and those who are immune. In this instance, H would be therefore only be applied to P.

If, however, P is the proportion of the total population who are hospitalised then H is not needed, unless the model is taking multiple hospitalisations into account.

If multiple hospitalisations are not included the formula should be P*D*C

If multiple hospitalisations are included, then P*D*H*C is correct but H would need to be ≥ 1. (In the submitted model H<1 in all cases)

A similar problem applies for other costs. For example, in cell N84 of the costs sheet it is assumed that for best supportive care, 50% of patients do not have INR tests, and that the remaining 50% of patients average 0.67 tests.

The instructions to the questionnaire states that the expert should assess the 'average or typical' patient. As such, it is unlikely that they would be answering assuming a proportion of susceptible patients. Can you clarify what the clinicians were intended to be asked? Can you also provide plausible reasons for why P * D * H * C, with H < 1 is correct?

The survey question to which this query relates is in the box below. 'A' and 'B' have been added to the table in order to try to make our response clearer.

Acute Care

Q6a Still thinking about a typical 'pre-progression' advanced HCC patients, what proportions of patients receiving treatment or taking no other active treatment (BSC) require each of the following resources as part of acute care?

Table 121. Acute care for 'pre-progression' patients with advanced HCC for patients treated with sorafenib

Acute Care	Average proportions for 'pre-progression' patients	Number of admissions per month
Proportion requiring a hospitalisation (per month)	A	B

The intention of this question was to isolate what has been described above as 'susceptible' patients i.e. the subset of patients who are hospitalised. Looking at this group of patients the questionnaire was structured to allow for multiple hospitalisations as our *a priori* assumption was that for population 'A' the number of admissions 'B' would have a lower bound of 1 (as put forward by the ERG). According to the intention of the questionnaire the appropriate inclusion in the model is P*H*D*C.

The ERG queries whether the questionnaire has been answered as intended given the response to the number of hospitalisations is less than 1.

We believe the response indicates that 6.7% of patients are hospitalised in the pre-progressed health state and that the number of admissions per month relates to this group, as was the intention. We appreciate that for this to be the case the respondents would need to have not seen the time period of 'one month' as indicated in the first column of the table – however, we suspect this is what has happened. We have sought expert clinical opinion regarding this which supports our interpretation (see 'Expert Opinion' overleaf). The responses therefore indicate that 6.7% of patients are 'susceptible' in the pre-progressed health state and that admissions occur less frequently than monthly for this specific population.

We believe it is possible that the survey question immediately preceding question 6a (see box below) may have had an influence. In question 5 respondents were guided to enter decimals when frequencies were less than once per month (i.e. once every three months).

Medical Staff Visits

Q5 Furthermore, when thinking about a typical 'pre-progression' advanced hepatocelluar carcinoma patients, on average how many and which type of physician, nurse and GP visits do they receive per month. If the test is likely to be performed less than once a month enter a decimal e.g. if performed once every 3 months enter 0.333 (1 divided by 3). Please keep in mind that this section is referring to any visits that would be planned (elective).

Table 120. Medical staff visits for 'pre-progression' patients with advanced HCC

Physician visits	Average number of visits (per month) and specialty if required
Pre-progression patients treated with sorafenib	
Specialist visit (e.g. oncologist, gastroenterologist etc.)	
Nurse visit (e.g. clinical nurse specialist, palliative care nurse etc.)	
GP visit	
Other physician visit (please specify)	
Pre-progression patients on BSC	
Specialist visit (e.g. oncologist, gastroenterologist etc.)	
Nurse visit (e.g. clinical nurse specialist, palliative care nurse etc.)	
GP visit	
Other physician visit (please specify)	

Expert opinion

Ideally it would have been possible to contact the original respondents to seek clarification on their answers. However, according to the market research code of practice re-contacting respondents is only allowed if permission is formally provided – such permission was not obtained by the medical research agency. We therefore sought advice from a clinical expert experienced in the management of advanced HCC. Based on their clinical experience they consider that the questionnaire is likely to have been answered as we thought since this is the level of hospitalisation they would expect i.e. 6.7% of patients have 0.4 admissions per month.

Sensitivity analysis

We have presented a sensitivity analysis assuming that 6.7% of patients are hospitalised with an admission frequency of once per month i.e. P*D*C. No changes have been made to the laboratory/radiological tests as the 2015 resource survey asks for the proportion of patients requiring each resource and the frequency 'of these' patients receiving each resource – the implementation in the model is correct.

Table 5. Sensitivity analysis – 6.7% of patients are hospitalised once/month

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case	14,625	0.406	36,050
Sensitivity analysis	15,538	0.406	38,303

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Email: info@britishlivertrust.org.uk
Website: www.britishlivertrust.org.uk

BRITISH LIVER TRUST

Pioneering liver health

British Liver Trust submission to NICE: ID991 regorafenib

The British Liver Trust would be very disappointed and concerned if NICE were not to approve the use of Regorafenib for advanced Hepatocellular Carcinoma.

This treatment is for patients with advanced stage hepatocellular carcinoma who have failed or are unsuitable for surgical or loco-regional treatment. There are very few treatment options for these patients apart from palliative care and Regorafenib can help improve the quality of their life and improve symptoms. . Evidence shows that outcomes for people with advanced liver cancer are particularly poor, so any increase in length of life is very important.

It is crucial NICE recognises that

- Hepatocellular Carcinoma (HCC) is the 18th most common cancer in the UK and accounts for approximately 85% of liver cancers. If HCC is detected early, potentially curative treatment options are available such as transplant or surgical removal but for advanced HCC there are no specific symptoms, and so less than 30% of patients are diagnosed in the early stages of the disease where potentially curative treatment is available.
- Patients with advanced HCC have a very poor prognosis and there are very few treatment options. Regorafenib, fulfils a key clinical need for patients with advanced inoperable HCC; Apart from palliative care, there is only one other drug treatment currently available for these patients (Sorafenib, Nexavar®) and it is vital that there are alternatives as for some patients this will not be suitable.
- Regorafenib is a treatment proven to increase survival in HCC, as well as providing quality of life benefits
- Regorafenib does have side effects for some patients. However, for most patients these are manageable. As an oral treatment it is convenient to administer and patients do not have to attend hospital for intravenous therapy
- Regorafenib would only be needed for a relatively small patient population so the overall cost to the NHS will be small - there were approximately 3,867 cases of liver cancer in England in 2012, of these 85% will be HCC resulting in approximately 3,287 cases. Of those with HCC, a smaller sub-population (25-30%) will be eligible for Regorafenib.

In summary:

- On behalf of patients with HCC, the British Liver Trust believes that there has not been enough significance placed on the benefits for patients of this life lengthening and life improving treatment.

- The clinical evidence needs to be read with the evidence from patient organisations so that a full holistic view can be taken of the need and benefits of the use of Regorafenib

3rd October 2017

NHS England submission to the NICE appraisal of regorafenib in the second line systemic therapy of hepatocellular carcinoma

1. NHS England notes the wording of the marketing authorisation of regorafenib in hepatocellular carcinoma: for those patients who have been previously treated with sorafenib. The wording excludes patients who are intolerant of sorafenib and the RESORCE trial excluded patients intolerant of sorafenib. NHS England notes that the side effects of regorafenib are similar to those of sorafenib and this may have been one of the reasons for the trial excluding sorafenib-intolerant patients. However, there is no biological reason why regorafenib would not be at least as efficacious in patients intolerant of sorafenib as those tolerant of sorafenib provided that patients can tolerate the regorafenib and both performance status remains good (ECOG 0 or 1) and liver function remains satisfactory (Child Pugh A). Patients often do tolerate TKIs differently. If NICE recommends regorafenib according to its marketing authorisation, then NHS England would wish to extend access to patients intolerant of sorafenib provided that all other relevant treatment criteria were met (see last paragraph).
2. NHS England notes that time to treatment discontinuation was greater than progression-free survival (PFS), it therefore being important that the economic model uses the actual treatment times and not the PFS times
3. NHS notes the relative immaturity of the overall survival data as 40% of the regorafenib arm and 30% of the placebo arm were still alive at the end of the trial follow-up. The modelling is thus important but the most mature follow up of patients treated with sorafenib (plus other treatments) in specialist centres (within the limits imposed of small numbers of patients) show 5 year survival figures of 5-8% (eg as published in Liver Cancer 2017; 6: 313-324). This does not mean that the 5 year survival of patients without further therapies after sorafenib is zero: some patients are lucky enough to have indolent disease and thus a few do survive 5 years.
4. NHS England notes that the average dose of regorafenib pre-progression was 124mg/day and post progression was 117mg/day. Regorafenib comes in 40mg tablets and so it is important to model the doses of medication that the patient can be given in practice rather than an average dose in an economic model. For example, a modelled 124mg dose would need 4 tablets daily per month. Patients are also given whole month supplies of regorafenib supply and any unused drug cannot be re-used by other patients. So only whole months of drug supply should be modelled: for example the mean treatment duration was 5.4 packs of regorafenib but 6 packs have to be modelled.
5. NHS England notes that the utility values seem high for a population of patients who enter the model with progressed disease and who have recently been on sorafenib (utility 0.81) even if patients have a performance status of 0 or 1 at entry into the study. The utility of 0.76 also seems high for progression after 2nd line therapy.

6. The generalisability issues as always apply and have been particularly noted by the ERG. These to a certain extent will be mitigated by NHS England only commissioning regorafenib (subject to a NICE recommendation of course) to reflect the population of patients assessed by NICE in this appraisal (see next paragraph).
7. Should NICE recommend regorafenib for the second line systemic therapy of hepatocellular carcinoma and in the absence of knowing any qualifications recommended by the TAC and contained in any ACD/FAD, NHS England would wish to commission regorafenib in patients and satisfying the following criteria:

- histologically or cytologically confirmed diagnosis of hepatocellular carcinoma
- metastatic disease or advanced local disease that is ineligible for or failed surgical or locoregional therapies
- previous systemic therapy for hepatocellular carcinoma with sorafenib, either treated to disease progression with sorafenib or intolerant of sorafenib despite appropriate dose reductions
- Child-Pugh liver function class A
- ECOG performance status of 0 or 1
- regorafenib to be otherwise used in its SPC.
  (Sorafenib is also only commissioned for patients with Child-Pugh A liver function and ECOG performance status of 0 or 1)

[redacted]

NHS England National Chemotherapy Lead and National Clinical Lead for the CDF

October 2017

NICE National Institute for Health and Care Excellence

Clinical expert statement

Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Daniel Palmer**
2. Name of organisation	**University of Liverpool**

3. Job title or position	**Professor of Medical Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? **x** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prolong survival time of patients with advanced hepatocellular carcinoma (HCC) who have progressed on the current standard first line systemic therapy, sorafenib.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A relative improvement in overall survival by approx. 30% (hazard ratio ~ 0.7)
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are no current standard therapies in this setting, indicating a clear unmet need.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	For patients with advanced HCC, currently the only standard first line systemic therapy remains sorafenib, which has been demonstrated in large randomised trials to confer significant survival benefit compared with placebo. However, disease progression is inevitable and there are currently no standard systemic therapies in this setting. Regorafenib is the first drug to demonstrate survival benefit compared with placebo for patients with advanced HCC progressing on sorafenib.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes: EASL; AASLD
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care for patients with HCC is well defined and generally homogenous across the UK, although there may be some variation in access to/referral for some therapies (notably systemic therapy). Patients with early stage disease may be offered curative treatments including liver resection, transplantation or local ablation. Patients with intermediate stage disease may be offered loco-regional therapies, typically transarterial (chemo-)embolization. Patients with advanced disease may be offered systemic therapy in the form of sorafenib or may be offered clinical trials where available.
• What impact would the technology have on the current pathway of care?	The technology would not alter this pathway. Rather, it would be included as an addition for those patients with advanced HCC who progress on sorafenib but remain sufficiently fit for further systemic therapy.
11. Will the technology be used (or is it already used) in the same way as current care	

in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	Since there are no other proven systemic therapies for patients with advanced HCC progressing on sorafenib, current standard of care comprises symptom control/supportive care or enrolment into clinical trials. The technology would therefore be used in addition to this current standard.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics by oncologists experienced in the management of patients with advanced HCC and the use of sorafenib for this indication.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Use of the technology should be incorporated into existing specialist clinics as described above.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than	Yes. This has been clearly and robustly demonstrated in a large, well designed placebo controlled randomised phase III trial.

current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	This is likely to be balance between delaying symptoms by delaying disease progression versus technology-related adverse events. Overall, I would anticipate HR-QoL to be maintained rather than increased.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	None known.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	The technology would be used in addition to current practice (supportive care). However, its use should be in the context of clinics experienced in the management of systemic therapy for advanced HCC and the use of sorafenib in the first line setting such that the clinical expertise and infrastructure should already be in place.

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting treatment with the technology will be based on existing routine assessments for the use of first line sorafenib. If these indicate disease progression on sorafenib then use of the technology may then be considered. Since there is no current standard of care for these patients, monitoring the effects of the technology would require additional tests (blood test; cross-sectional imaging).
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The main potential benefit of the technology is prolongation of survival, which should be captured in the QALY.
17. Do you consider the technology to be innovative in its potential to make a	Since there are no existing standards of care in this setting, the technology is considered to be innovative and has the potential to improve outcomes in a setting with great unmet needs.

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. This is the first systemic agent to demonstrate a survival benefit in this setting.
• Does the use of the technology address any particular unmet need of the patient population?	Yes. As above.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Although there are potential side effects from the technology, its use should be by clinicians experienced in the management of HCC and of drug-related adverse events such that the dose and schedule of treatment may be modified accordingly to reduce toxicities and maintain quality of life.
Sources of evidence	
19. Do the clinical trials on the	Yes. The choice of placebo as the control arm reflects the current unmet need and absence of any proven

technology reflect current UK clinical practice?	therapies in this setting.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival. Yes, this was the primary outcome measure of the trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None known.
20. Are you aware of any relevant evidence that might not be found by a systematic	No

review of the trial evidence?	
23. How do data on real-world experience compare with the trial data?	None known yet in terms of efficacy. However, the drug is used in other cancer types, confirming a predictable and manageable safety profile.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	Risk factors for HCC are those of chronic liver disease and include alcohol, chronic viral hepatitis (B or C) and thus HCC occurs in diverse socio-economic and ethnic backgrounds, who may not always find easy access to healthcare services
25b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
25. Would you agree that regorafenib would only ever be used after treatment with sorafenib in UK clinical	Yes.

practice?	

Key messages

26. In up to 5 bullet points, please summarise the key messages of your statement.

- No current standard treatment upon progression on sorafenib
- Great unmet need
- Clear improvement in overall survival for regorafenib
- Manageable side effects when used by clinicians experienced in systemic therapy for HCC
- Regorafenib is a new standard of care internationally in this setting

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Tim Meyer**
2. Name of organisation	**UCL and Royal Free Hospital London**

3. Job title or position	**Professor of Experimental Cancer Medicine and Consultant in Medical Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Regorafenib therapy aims to improve survival in patients with advanced hepatocellular carcinoma (HCC) who have progressed on first line sorafenib therapy.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An improvement in median survival of around three months or more, or to achieve a HR of 0.7 in terms of reduction of risk of death compared to control.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Sorafenib has been the only approved therapy for advanced HCC for 10 years and is associated with a modest benefit resulting in a median overall survival of 10.7 months (Llovet et al NEJM 2008). There has been an unmet need for patients who progress or are intolerant to sorafenib.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Advanced HCC occurring in patients with good performance status and well preserved liver function is treated with sorafenib which has been shown to increase median survival from 7.9 to 10.7 months.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. J Hepatol. 2012 Apr;56(4):908-43. doi: 10.1016/j.jhep.2011.12.001. These guidelines are currently being updated
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is broad consensus across the UK and Europe
• What impact would the technology have on the current pathway of care?	For a highly selected population of patients with HCC, there would be a second line treatment option which has level one evidence demonstrating an improvement in survival.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The use of regorafenib for HCC is a new indication and it is not currently used for this disease.

• How does healthcare resource use differ between the technology and current care?	Currently there is no approved second line therapy and patients receive best supportive care, a clinical trial and occasionally cytotoxic chemotherapy.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Regorafenib should be prescribed by oncologists with a specialist interest in managing HCC.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Regorafenib is an oral multikinase inhibitor which has a well-defined toxicity profile. It is similar to other drugs in this class such as sorafenib which is routinely used in HCC. The availability of a second line therapy may increase demand on outpatient services.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. In selected patients, the RESORSE trial demonstrated that regorafenib improved median survival from 7.8 months (95% CI 6.3-8.) to 10.6 months (9.1-12.1) months compared to placebo with a hazard ratio of 0.63 (95% CI 0.5-o.750・63 (95% CI 0・50–0・79; one-sided p<0・0001) .
• Do you expect the technology to increase length of life more than current care?	Yes – see above

• Do you expect the technology to increase health-related quality of life more than current care?	No
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The evidence for regorafenib is in a specific subpopulation of patients as defined by the eligibility criteria for the RESORSE trial namely; adults with HCC who progressed on sorafenib but had tolerated sorafenib (≥400 mg/day for ≥20 of last 28 days of treatment), Child-Pugh A liver function and performance status 0 or 1.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	The toxicity of regorafenib is similar to other multikinase inhibitors and will require regular clinical review in order to make dose adjustments and manage emergent side effects such as hypertension, hand foot skin reaction, diarrhoea and anorexia. Patients will require counselling in the management and reporting of side effect which may require the use of adjunctive medication. Regular blood tests will be required to measure full blood count, liver function and phosphate and follow-up imaging to assess response to treatment will be needed at 2-3 month intervals.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Most clinicians will discontinue therapy on radiological progression which implies the need for regular CT or MRI on 2-3 monthly basis.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes. It will prolong survival in selected patient.

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. After 10 years of negative randomised trials in the second line setting, regorafenib is the first to show a survival benefit.
• Does the use of the technology address any particular unmet need of the patient population?	Yes – there is currently no approved second line therapy after sorafenib.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Patient's quality of life is effected by the presence of underlying malignancy and chronic liver disease that is present in the majority of patients. Despite the toxicity of regorafenib, there did not appear to be any clinically meaningful reduction in quality of life in patients taking regorafenib as compared with placebo.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the clinical trial was conducted globally and included UK sites
• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival is the most important outcome and was the primary endpoint in the trial. Secondary endpoints included time to progression, progression free survival, response rate and health related quality of life.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
23. How do data on real-world experience compare with the trial data?	There is no real-world data on the sequence of sorafenib followed by regorafenib.
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
25b. Consider whether these issues are different from issues with current care and why.	NA
Topic-specific questions	
25. Would you agree that regorafenib would only ever be used after treatment with	The benefits of regorafenib have only been demonstrated in patients who have been tolerant to sorafenib and should only be used in this setting.

sorafenib in UK clinical practice?	

Key messages

26. In up to 5 bullet points, please summarise the key messages of your statement.

- Regorafenib is the first drug to show a survival benefit as second line therapy following sorafenib.
- The survival benefit is approximately three months
- Patients that benefit from regorafenib are highly selected based on tolerance to sorafenib, preserved liver function and good performance status
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Declared competing interests of the authors

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.

Standard copyright statement on the front page of the ERG/AG report:

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ABBREVIATIONS

A&E	Accident and emergency
AACR	American Association for Cancer Research
AASLD	American Association for the Study of Liver Diseases
AE	Adverse events
AFP	Alpha-fetoprotein
AFT	Accelerated Failure Time
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BIC	Bayesian Information Criterion
BP	Blood pressure
BSC	Best Supportive Care
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRF	Case report form
CS	Company's submission
CSCO	Chinese Society of Clinical Oncology
CSR	Clinical Study Report
CT	Computerised tomography
DCO	Data cut-off
DCR	Disease control rate
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EASL-EORTC	European Association for Study of the Liver / European Organisation for the Research and Treatment of Cancer
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EMBASE	Excerpta Medica dataBASE
EQ-5D	EuroQol – 5 Dimensions
ERG	Evidence Review Group
ESDO	European Society of Digestive Oncology
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-Hep	Functional Assessment of Cancer Therapy – Hepatobiliary
FAD	Final Appraisal Determination
FCE	Finished consultant episode
HCC	Hepatocellular carcinoma
HR	Hazard ratio
HRG	Healthcare resource group
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio

ILCA	International Liver Cancer Association
IPD	Individual patient-level data
IQR	Interquartile range
ITT	Intention-to-treat
IVRS	Interactive voice response system
JSMO	Japanese Society of Medical Oncology
LSM	Least-Squares Mean
LYG	Life year gained
MedDRA	Medical Dictionary for Regulatory Activities
MEDLINE	Medical Literature Analysis and Retrieval System Online
MID	Minimally important difference
mRECIST	Modified Response Evaluation Criteria In Solid Tumors
MRI	Magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLM	National Library of Medicine
NYHA	New York Heart Association
OLS	Ordinary least squares
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressed disease
PFS	Progression-free survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RESORCE	Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TACE	Transarterial chemoembolisation
TESAE	Treatment-emergent severe AEs
TKI	Tyrosine kinase inhibitor
TOI	Trial Outcome Index
TTP	Time to progression
ULN	Upper limit of normal
VAS	Visual analogue scale
WTP	Willingness-to-pay

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 – Hepatobiliary (FACT-Hep)

total and the Trial Outcome Index (TOI), but did not reach clinical significance according to pre-specified thresholds.

Adverse events (AEs) were frequent: 100% of regorafenib patients receiving the study drug experienced at least one AE (compared with 93% on placebo), and 93% of regorafenib patients experienced treatment-emergent drug-related AEs compared with 52% of placebo patients. The principal AEs were: hand foot skin reaction (53% in the regorafenib arm compared with 8% in the placebo arm); diarrhoea (41% vs 15%); fatigue (40% vs 32%); hypertension (41% vs 6%); and anorexia (31% vs 15%). AEs of Grade 3 or higher were reported for 80% of patients in the regorafenib group compared with 59% in the placebo group. More regorafenib patients than placebo patients also experienced Grade 3 (46% compared with 16%) and Grade 4 (4% compared with 1%) drug-related AEs. The incidence of haemorrhage events of ≥ Grade 3 was higher in the placebo group (8%) than the regorafenib group (6%), but the incidence of drug-related haemorrhage events of ≥ Grade 3 was higher in the regorafenib group (1.6%) than the placebo group (0%). According to the CS, the incidence of drug-related severe adverse events (SAEs) was relatively low in both groups, but was 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 patients in the placebo group. The AE profile of regorafenib in the RESORCE trial is generally similar to trials of regorafenib undertaken in patients with colorectal cancer. 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.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company's systematic review was generally well conducted. However, some processes could have been reported better and some relevant abstracts and additional analyses relating to the pivotal RESORCE trial should have been identified and included in the CS. This additional literature is cited, where appropriate, throughout this ERG report. The included relevant study, the RESORCE trial, is a high quality randomised controlled trial (RCT), with a low risk of selection, performance, detection, attrition and reporting bias.

The principal issue with the evidence relates to the generalisability of the trial population to the population of patients seen in clinical practice in the UK. The RESORCE trial only included meaningful data on patients who were not found to be intolerant to sorafenib, who had an Eastern Cooperation

Oncology Group (ECOG) Performance Status (PS) of 0 or 1, and who were categorised as Child-Pugh class A, whilst the marketing authorisation for regorafenib covers all adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (even if they are found to be intolerant to sorafenib, or are ECOG PS 2 or Child-Pugh class B). A recent audit of sorafenib use in the UK found that sorafenib is 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 than patients enrolled in the RESORCE trial. There is therefore a lack of clinical data on the efficacy and safety of regorafenib in these groups - this issue is acknowledged in the CS. This is important because the sorafenib audit found that ECOG PS $\geq$2 was an independent predictor of mortality and OS was substantially worse in patients who were Child-Pugh class B (4.6 months) compared with those who were Child-Pugh class A (9.5 months). Pre-specified subgroup analyses conducted using data from RESORCE also found that patients who were PS 0 and Child-Pugh A5 experienced better efficacy than those who were PS 1 and Child-Pugh A6. 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 PS (47% vs 32%). It is therefore possible that patients treated in UK clinical practice may experience less efficacy and more AEs than patients enrolled in RESORCE. The lack of relevant data and its implications are acknowledged in the Summary of Product Characteristics (SmPC) for regorafenib, which recognises the potential adverse impact of regorafenib on hepatic function in patients who are Child-Pugh class B and the need to monitor all AEs carefully in this group. There is therefore substantial uncertainty concerning the benefits of regorafenib in patients who do not satisfy the inclusion criteria of the RESORCE trial.

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted a health model constructed in Microsoft Excel®. The model adopts a partitioned survival approach based on three health states: (1) progression-free; (2) progressed disease, and (3) dead. The time horizon was approximately 15 years with 28-day cycles. The clinical parameters of the model were informed by analyses of time-to-event data (PFS, OS and time on treatment) collected within the RESORCE trial. Resource use and unit costs were drawn from the RESORCE trial and other sources, including a survey of three leading clinical experts. Based on the deterministic version of the company's original submitted model, the incremental cost effectiveness ratio (ICER) for regorafenib versus BSC was estimated to be £33,437 per quality-adjusted life year (QALY) gained. Following the clarification process, two further versions of the model were submitted by the company. The company's revised base case analysis, which includes longer-term data corresponding to the 23rd January 2017 data cut-off (DCO), dependent log normal OS curves and a truncated log logistic time to treatment discontinuation function, produces a deterministic ICER for regorafenib versus BSC of £36,050 per QALY gained.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG critically appraised the company's economic analysis and double-programmed the deterministic version of the company's original submitted model. The ERG's critical appraisal identified several issues relating to the company's economic analysis and the evidence used to inform it. The most pertinent of these include: (i) the inappropriate use of a hazard ratio (HR) to model relative treatment effects on OS; (ii) limited consideration of the clinical plausibility of the extrapolated OS curves; (iii) concerns regarding the modelling of time to treatment discontinuation; (iii) the inclusion of potentially unrealistic cost savings due to dose reductions and treatment interruptions; (iv) the use of the 2015 survey of three experts to inform health state resource use (and the exclusion of the earlier survey used to inform the recent sorafenib appraisal); (v) concerns regarding the appropriateness of several unit cost estimates; (vi) the questionable reliability of the post-progression utility estimate and (vii) the inadequate representation of parameter uncertainty.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The systematic review presented within the CS has been undertaken to a good standard. The ERG considers the RESORCE study to be a high quality RCT.

With the exception of the approach adopted to model time spent receiving regorafenib, the ERG considers the general model structure adopted by the company to be appropriate.

1.6.2 Weaknesses and areas of uncertainty

There is an absence of trial evidence on some patient groups who would be eligible to receive regorafenib: adults with HCC who are sorafenib intolerant or who are Child-Pugh class B or who have ECOG PS 2.

The rationale for some of the assumptions used within the company's model were unclear or contentious. Many of these assumptions were favourable to regorafenib; when alternative more appropriate parameter values are used, the ICER for regorafenib increases substantially.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG performed seven sets of exploratory analyses to explore the impact of alternative assumptions on the ICER. These analyses involve: (1) the correction of unequivocal model errors and use of alternative unit costs; (2) the inclusion of a more appropriate general ward day bed cost; (3) the use of full pack dosing which does not include cost savings due to reduced dosing; (4) the removal of half-cycle correction for drug acquisition costs; (5) the use of combined 2007 and 2015 survey costs (as preferred by the Cancer Drugs Fund [CDF] Appraisal Committee within the recent appraisal of

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]	-	-	-

2 BACKGROUND

2.1 Critique of company's description of the underlying health problem

The company's submission[1] (CS) provides an adequate description of hepatocellular carcinoma (HCC) which includes stating that: it the 17th most common cancer in the UK; that it affects more men than women, and that incidence of the disease increases with age.[2] HCC is stated to be "*often diagnosed at a late stage of the disease when patients present with symptoms including fatigue, jaundice, pruritus, encephalopathy, weight loss, ascites, abdominal pain / distension and the presence of a mass.*" (CS,[1] page 19).

Figure 1 of the CS provides the classification of HCC using the joint European Association for Study of the Liver / European Organisation for the Research and Treatment of Cancer (EASL-EORTC) guidelines.[3] The company also present a table representing the staging of HCC using the Barcelona Clinic Liver Cancer (BCLC) classification and how this relates to Eastern Cooperative Oncology Group (ECOG) performance status (PS) and Child-Pugh class. These data are reproduced in Figure 1 and Table 2, respectively.

Figure 1: Classification of HCC (from EASL-EORTC Clinical Practice Guidelines)

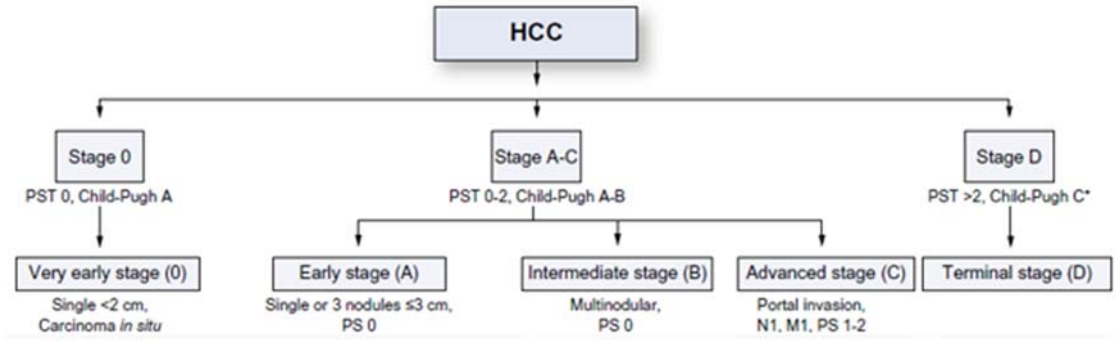


Table 2: Staging of HCC (using the BCLC classification)

BCLC Stage	Tumour status	ECOG performance status	Liver Function (Child-Pugh)
0 (Very early HCC)	Single tumour < 2cm in diameter without vascular invasion / satellites	0	Well preserved liver function Child-Pugh A
A (Early HCC)	Single tumours >2 cm or 3 nodules <3 cm of diameter	0	Child–Pugh A or B
B (Intermediate HCC)	Multinodular asymptomatic tumours without an invasive pattern	0	Child-Pugh A-C
C (Advanced HCC)	Symptomatic tumours; macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases)	1–2	Child-Pugh A-C
D (End stage HCC)	Tumours leading to a very poor performance Status which reflects a severe tumour-related disability	3-4	Child-Pugh C

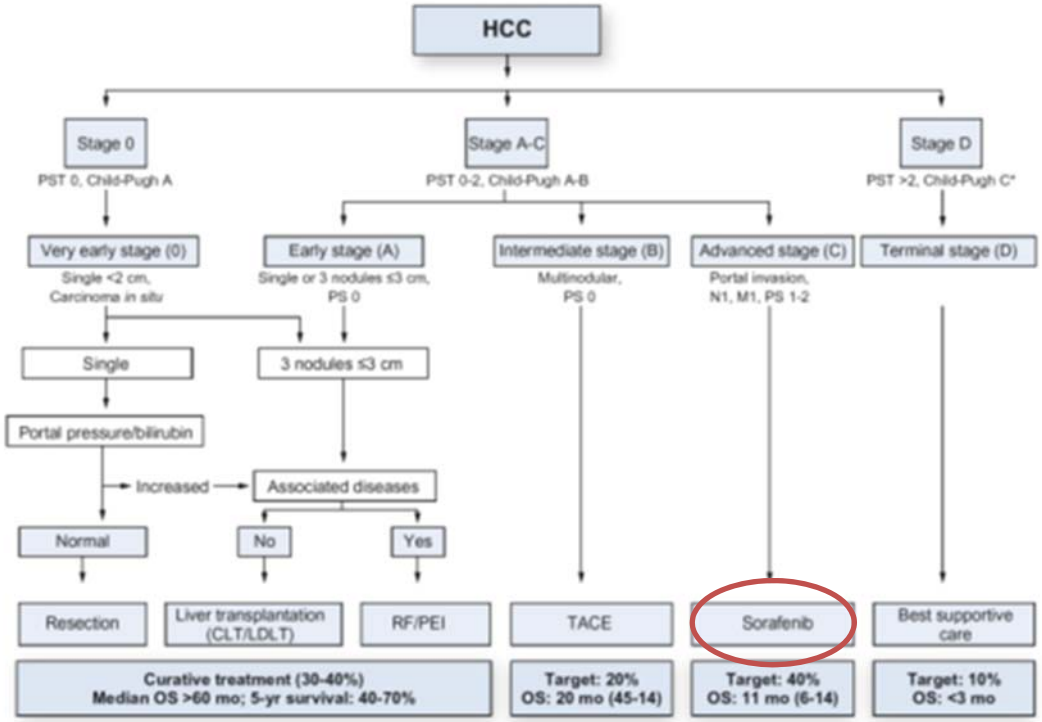
Whilst the CS summarises expected Child-Pugh grade in terms of the BCLC stage, it does not detail how the Child-Pugh classification was estimated. A full description may be of value to the Appraisal Committee as clinical advice received by the Evidence Review Group (ERG) suggests that there is little difference between a person with a Child-Pugh score of 6 (which is classified as an A) and a person with a Child-Pugh of 7 (which is classified as a B). The Child-Pugh score is generated from five clinical measures of liver disease: (i) total bilirubin; (ii) serum albumin; (iii) prothrombin time; (iv) ascites, and (v) hepatic encephalopathy. Each measure is scored between one and three (with a score of three indicating greater severity), thereby resulting in an overall score between five and fifteen. Scores of 5 or 6 are classified as Child-Pugh A, scores of 7, 8 or 9 are classified as Child-Pugh B and scores of ten and over are classified as Child-Pugh C.[4] Further details are provided in Section 4.2.1.

2.2 Critique of company's overview of current service provision

The CS[1] provides a satisfactory overview of current service provision. The CS states that as UK-specific guidelines are dated, these have been largely superseded by the EASL-EORTC guidelines for the treatment of advanced HCC. Within these guidelines, choice of therapy is determined by disease stage and the severity of the underlying cirrhosis. The potential positioning of regorafenib by the company in its submission is in those patients who have previously been treated with sorafenib. The company's diagram of current guidelines is reproduced in Figure 2: the ERG has added a red oval showing where

sorafenib is recommended under EASL-EORTC guidelines. In England, sorafenib has recently been reviewed as part of a Cancer Drugs Fund (CDF) reappraisal. The Final Appraisal Determination (FAD) states that: "*sorafenib is recommended as an option for treating advanced hepatocellular carcinoma only for people with Child-Pugh grade A liver impairment, only if the company provides sorafenib within the agreed commercial access arrangement.*"[5] Clinical advice received by the ERG also suggests that sorafenib could also be appropriately used in intermediate stage (B) disease if that disease was not amenable to transarterial chemoembolisation (TACE).

Figure 2: The EASL-EORTC guidelines as represented by the company



CLT=cadaveric liver transplant; DLT=domino liver transplant; HCC=Hepatocellular cancer; mo=months; OS=overall survival; PEI=percutaneous ethanol injection; PST=performance status; RF=radio-frequency ablation; TACE=trans-arterial chemoembolisation

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

3.1 Population

The remit detailed in the final scope issue by the National Institute for Health and Care Excellence (NICE) is to appraise the clinical and cost-effectiveness of regorafenib within its licensed indication for previously treated unresectable HCC. The Summary of Product Characteristics (SmPC) for regorafenib indicates that the therapeutic indication within HCC is for patients "*who have been previously treated with sorafenib.*" A more detailed discussion of the patients in the RESORCE study[6] and those included within the anticipated licence is provided in Section 4.2.1. However, potential key differences are highlighted here. There is uncertainty regarding the generalisability of the results presented to the following groups which were excluded from the RESORCE study:

- adult patients with HCC who were sorafenib intolerant (i.e. having been unable to receive sorafenib at ≥400mg/day for ≥20 of the last 28 days of treatment);
- adult patients with HCC who were Child-Pugh class B;
- adult patients with HCC who had an ECOG PS of 2 or more.

The CS[1] states that regorafenib is "*not recommended for use in patients with severe hepatic impairment (Child-Pugh C) as it has not been studied in this population*".

3.2 Intervention

The intervention evaluated by the company is regorafenib (Stivarga®). Regorafenib is an oral bi-aryl urea that inhibits multiple protein kinases. The standard dose of regorafenib is 160mg daily taken in the form of four 40mg tablets. Within the RESORCE study, two levels of dose reduction due to toxicity were allowed, with reduced doses of either 120mg daily or 80mg daily. The list price for regorafenib is £3,744 per treatment cycle, which consists of three weeks of treatment followed by one week off therapy. The company has agreed a patient access scheme (PAS) with the Department of Health that takes the form of a simple discount ([redacted]): this reduces the cost per treatment cycle to [redacted]. The CS states that the average number of packs received in the RESORCE study was [redacted], equating to an average course of treatment of [redacted] at the list price and [redacted] when the PAS is applied. Any treatment costs accruing beyond the study cut-off date are not included in these estimates. Further details on the intervention are provided in Table 2 of the CS.

3.3 Comparators

The final scope indicated that the sole comparator is best supportive care (BSC). The ERG believes that the RESORCE study, which compared regorafenib in addition to BSC versus placebo in addition to BSC, is an appropriate study to address the decision problem.

3.4 Outcomes

All outcomes listed in the final scope were addressed in the clinical section of the CS. The company's model includes outcomes relating to PFS, OS time to treatment discontinuation and HRQoL (including the impact of AEs).

3.5 Other relevant factors

The company comment that "*the prevalence of liver cancer deaths is higher in socially deprived areas.*" Beyond this statement, this potential equality issue is not considered further within the CS.

4 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the company's review of the efficacy and safety of regorafenib (Stivarga®, BAY73-4506) for the treatment of adult patients with HCC who have been previously treated with sorafenib (Nexavar®). The ERG's critique was performed following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist.[7]

4.1 Critique of the methods of review(s)

The CS[1] reports the methods and results of a systematic review of the efficacy and safety evidence for regorafenib in adult patients with HCC who have been previously treated with sorafenib (see CS,[1] Sections B2.1-B2.13). The systematic review of efficacy and safety evidence was generally well reported. Following a request for clarification from the ERG regarding certain process elements adopted by the company, the ERG considers the review to be generally sound (see company's clarification response,[8] questions A1). There was a single relevant trial: RESORCE. This was a Phase III trial which compared regorafenib with placebo in adult patients with HCC who had previously progressed on sorafenib.

4.1.1 Searches

The company performed one clinical effectiveness search to identify all RCTs investigating the efficacy and safety of regorafenib in previously treated unresectable HCC. For the original searches, several electronic bibliographic databases were searched including MEDLINE [via ProQuest], EMBASE [via ProQuest], the Cochrane Database of Systematic Reviews [via Wiley], the Database of Abstracts of Reviews of Effects [via Wiley], and the Cochrane Central Register of Controlled Trials [via Wiley]. The company searched one clinical trials register (Clinicaltrials.gov via NLM). Conference proceedings websites were searched covering the period from 2014 to January 2017 (American Association for Cancer Research [AACR], American Society of Clinical Oncology [ASCO], Gastrointestinal Cancers Symposium, European Society for Medical Oncology [ESMO], International Liver Cancer Association [ILCA], European Society of Digestive Oncology [ESDO], European Association for the Study of the Liver [EASL], ESMO World Congress on Gastrointestinal Cancer, Japanese Society of Medical Oncology [JSMO], and Chinese Society of Clinical Oncology, and American Association for the Study of Liver Diseases [AASLD].

The company's search strategies were fully reported in CS Appendix D.[9] Since the company searches were completed up until January 2017, the ERG conducted an update search in MEDLINE and EMBASE [via Ovid] on 25th July 2017. A total of 69 records were retrieved from the search. The ERG

found no new studies relevant for the review (see Section 4.2.1) and considers that the company's search strategies were sufficiently comprehensive to retrieve important citations relating to all eligible studies.

4.1.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria for the review of the efficacy and safety of regorafenib are described in CS Appendix D (Table 63, page 187) and are reproduced in Table 3. These criteria describe RCTs measuring the efficacy and safety of regorafenib compared with any intervention, including placebo, in adult patients with HCC who have been previously treated with sorafenib. One RCT satisfied these criteria: RESORCE. This Phase III trial compared regorafenib plus BSC, at a maximum dose of 160mg per day for 3 weeks, followed by a week without treatment, with placebo plus BSC in adult patients with HCC who have previously progressed on sorafenib.

Table 3: Inclusion and exclusion criteria for regorafenib RCTs (reproduced in part from CS, Appendix D, Table 63)

	Inclusion criteria	Exclusion criteria
Population	Adults (aged 18 or older) with advanced HCC	Other (oncology) indications not listed in the inclusion criteria
Intervention	Regorafenib (Stivarga®) (plus BSC)	All interventions not listed in the inclusion criteria
Comparators	Any comparator, including: • BSC* (placebo)	Not applicable
Outcomes	• Overall survival (OS) • Time to progression (TTP) • Progression-free survival (PFS) • Objective tumour Response Rate (ORR) • Disease control • Adverse events (AEs) • Overall AEs • Severe AEs • Quality of Life (QoL) • FACT-Hep • EuroQol – 5 Dimensions (EQ-5D) • Other QoL measurements • All other patient-relevant endpoints	Not applicable
Study design	• Phase II or III randomised controlled trials (RCTs) • Studies published as abstracts, conference presentations or press releases were eligible if adequate data were provided • Systematic reviews or meta-analyses of RCTs**	All other study designs not listed in the inclusion criteria
Language	No language limits	No language limits
*BSC is defined as included any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumour agents or antineoplastic chemo / hormonal / immunotherapy (CS,[1] p.33). **Systematic reviews were eligible for inclusion as a source of references to primary studies		

FACT-Hep - Functional Assessment of Cancer Therapy – Hepatobiliary

4.1.3 Critique of data extraction

The ERG was satisfied that standard systematic review good practice was followed in study selection: relevant papers were independently selected for inclusion at title, abstract and full text stage by two reviewers, with any discrepancies between reviewers resolved through discussion or the intervention of a third reviewer (see CS, Appendix D1.1).

No information was given regarding the data extraction process (for example, the number of reviewers involved, or the nature and extent of any actions taken to minimise error). This was addressed in

response to clarification requests from the ERG, in which the company detailed standard processes for data extraction in systematic reviews (see company's clarification response,[8] question A1). Data extraction was performed by one reviewer and independently checked for errors against the original trial report by a second reviewer. Any discrepancies were resolved through discussion or through the intervention of a third reviewer.

4.1.4 Quality assessment

Critical appraisal of included evidence, using relevant criteria, was performed and reported, although the critical appraisal tool was not identified in the CS (CS,[1] Section B.2.5, Table 18). As with data extraction, no details were provided regarding the critical appraisal process (e.g. number of reviewers undertaking the critical appraisal, processes followed in the event of discrepancies etc.). This was not addressed in response to clarification requests from the ERG: the response focused on data extraction only (see company's clarification response,[8] question A1), so the robustness of the process undertaken is uncertain. However, the identity of the critical appraisal tool used was clarified by the company: this was an adaptation of the Centre for Reviews and Dissemination (CRD) criteria specified in the NICE User Guide (see company's clarification response,[8] question A3).

The CS[1] (page 53) concludes that the RESORCE trial was at 'low risk of bias' across the domains assessed. The ERG also performed a critical appraisal of the relevant RCT to verify the findings reported in the CS. This was conducted by one reviewer (CC) using the Cochrane Risk of Bias tool.[10] The ERG accepts the company's assessments of bias for the domains of selection bias (randomisation, allocation concealment); performance and detection bias (blinding); attrition bias (drop-out, intention-to-treat [ITT] analysis and management of missing data) and reporting bias (this assessment was only confirmed when the company made available the original unpublished protocol: see company's clarification response,[8] question A8). The ERG disagrees with the assessment regarding other types of bias: for example, the extensive role of the funder was acknowledged in the publications, but industry influence is a known potential moderator of outcomes.[11, 12] Overall, however, the ERG assessed the potential risk of bias affecting outcomes in the RESORCE trial to be low. The details of the ERG and CS assessments are provided in Table 4.

Table 4: Risk of bias assessment for the RESORCE trial

Risk of bias	ERG		CS (Appendix D1.3, Table 67)		
Selection bias: Randomisation	"Patients were randomly assigned (2:1) to regorafenib or placebo using a computer-generated randomisation list prepared by the funder. Randomisation was stratified by geographical region (Asia *vs* rest of world), macrovascular invasion (yes *vs* no), extrahepatic disease (yes *vs* no), αfetoprotein concentration (<400 ng/mL *vs* ≥400 ng/mL), and ECOG PS (0 *vs* 1). The randomisation number for each patient was assigned based on information obtained from the interactive voice-response system."[6]	Low	Was randomisation carried out appropriately?	Randomisation was performed via an interactive voice response system (IVRS) using a computer-generated randomisation list. Randomisation was stratified by geographical region (Asia vs. rest of the world), ECOG performance status (0 vs. 1), AFP levels (<400ng/mL vs. ≥400ng/mL), extrahepatic disease (presence vs. absence), and macrovascular invasion (presence vs. absence).	Yes
Selection bias: Allocation concealment		Low	Was the concealment of treatment allocation adequate?	Patients, investigators, and the study sponsor were masked to treatment assignment using the unique randomisation code, assigned via IVRS, which linked them to a treatment arm and specified the treatment assigned. Placebo & active treatments were identical in appearance and given under identical conditions.	Yes
			Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Demographics and baseline disease characteristics were comparable between the regorafenib and the placebo groups.	Yes
Performance bias	"Investigators, patients, and the funder were masked to treatment assignment… Tablets with identical appearance were used for regorafenib and placebo."[6]	Low	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Investigators received a unique randomisation number for each participant through the IVRS and study drug supply was also managed via IVRS. All patients, investigators, and the study sponsor were masked to treatment assignment through this number. Also, regorafenib and placebo were identical in appearance to preserve blinding.	Yes
Detection bias	Masking of patients and investigators, as outlined above, minimises risk of detection bias for progression and quality of life outcomes. Overall survival (OS) is at very low risk of detection bias. "Investigators were blinded to study treatment for assessment of whether a death was considered related to study drug"[6]	Low			
Attrition bias	All drop-outs and withdrawals were fully reported. Imabalance in withdrawals was due principally to disease progression.	Low	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	A higher number of patients withdrew from double-blind treatment in the placebo arm of the study (94.3%) than in patients receiving regorafenib (81.5%). The main reason for dropout in both treatment groups was radiological progression.	No

Risk of bias	ERG		CS (Appendix D1.3, Table 67)		
	The primary endpoint (OS) and the secondary endpoints (PFS and TTP) were analysed by ITT. There was no imputatuon of missing data. All patients were analysed in the groups to which they had been randomised.		Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary analysis was performed (appropriately) in the FAS (ITT) population. Missing or unevaluable tumour assessments were not used in the calculation of derived efficacy variables unless a new lesion occurred, or the lesions that were evaluated already showed progressive disease (PD). No imputation was performed for missing lesion assessment and tumour response. For example, if a patient missed a scan visit and PD was documented at the next available scan visit, the actual visit date of the first documented PD was used to calculate PFS and TTP. If a date was incomplete, such as only the year and month were available, day 15 of the month was used for the calculation.	Yes / Yes / Yes
Reporting bias	The unpublished trial protocol, provided by the company (see company's clarification response,[8] question A8) permitted a confirmation that all pre-specified outcomes were reported.	Low	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Results of all pre-specified outcomes are reported in full.	No
Other bias	"The funder (Bayer) provided the study drug and worked with the principal investigator (JB) and the study steering committee to design the study. Data collection and interpretation, and preparation of this report, were done by the investigators and the funder. Statistical analyses were performed by the funder... The funder funded writing assistance".[6] "This study was funded by Bayer. Editorial assistance in the preparation of this manuscript was provided by Ann Contijoch (Bayer) and Jennifer Tobin (Choice Healthcare Solutions, with financial support from Bayer)." [6] Authors declare many conflicting interests.[6]	Moderate			

4.1.5 Evidence synthesis

The synthesis for the review of clinical efficacy was a basic descriptive summary of the evidence from the RESORCE trial for the following outcomes: overall survival (OS); progression-free survival (PFS); time to progression (TTP); health-related quality of life (HRQoL) and adverse events (AEs). The CS explains that a meta-analysis was not performed because there was only a single relevant trial (CS,[1] page 72, Section B.2.8) and that an indirect comparison was not performed because the included trial compared the intervention with the most relevant comparator, i.e. BSC/placebo (CS,[1] page 72, Section B.2.9). The ERG accepts these justifications.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

4.2.1 Review of clinical efficacy

The CS provides a detailed description of the RESORCE trial identified by the company satisfying the inclusion criteria, i.e. regorafenib compared with BSC (placebo) in adult patients with HCC who had previously progressed on sorafenib. The CS (Appendix D, page 189, Table 64) identified the following four papers for inclusion: the full trial publication,[6] the protocol (NCT01774344), and two abstracts:LBA-03[13] and LBA28.[13] CS Appendix D (Table 65, pages 190-91) also provided a second list of included studies, which, included the full trial publication, the protocol, the LBA-03 abstract and an earlier Phase II single-arm trial of regorafenib in the relevant population.[14] The CS, Appendix D, Table 65 also erroneously excluded the LBA28 abstract,[13] but reinstated it following a question from the ERG (see company's clarification response,[8] question A2). One full paper[15] and two additional relevant abstracts[6, 16] were identified by the ERG from its own searches. This represented all of the evidence for regorafenib in this population. The Phase II trial, which is included in the CS, was excluded from this report because it does not satisfy the inclusion criteria, which require studies to be comparative.

The trial and its population were slightly different from the NICE scope, which required assessment of regorafenib in all adult patients with HCC who have been previously treated with sorafenib. The RESORCE trial was largely consistent with this population, but did exclude those patients who had discontinued sorafenib treatment on account of toxicity. The inclusion and exclusion criteria for this trial are extensive and are presented in Table 5.

.

Table 5: RESORCE trial inclusion and exclusion criteria (reproduced from CS, Table 6)

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years old • Histologically or cytologically confirmed HCC or non-invasive diagnosis of HCC as per American Association for the Study of Liver Diseases (AASLD) criteria in patients with a confirmed diagnosis of cirrhosis. • Barcelona Clinic Liver Cancer (BCLC) stage Category B or C that could not benefit from treatments of established efficacy with higher priority such as resection, local ablation, chemoembolisation, or systemic sorafenib. • Failure to prior treatment with sorafenib (defined as documented radiological progression per the radiology charter). Randomisation had to be performed within 10 weeks after the last treatment with sorafenib. • Tolerability of prior treatment with sorafenib defined as not less than 20 days at a minimum daily dose of 400 mg QD (every day) within the last 28 days prior to withdrawal. • ECOG PS of 0 or 1 • Child-Pugh status A • Local or loco-regional therapy of intrahepatic tumour lesions (e.g. surgery, radiation therapy, hepatic arterial embolisation, chemoembolisation, radiofrequency ablation, percutaneous ethanol injection, or cryoablation) must have been completed ≥4 weeks before first dose of study medication. Note: patients who received sole intrahepatic intraarterial chemotherapy, without lipiodol or embolising agents were not eligible. • Life expectancy ≥ 3 months • Written consent • At least one uni-dimensional measurable lesion by computed tomography (CT) scan or magnetic resonance imaging (MRI) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, and mRECIST for HCC. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, may have been considered measurable if there had been demonstrated progression in the lesion.	• Prior liver transplantation or candidates for liver transplantation. • Prior treatment with regorafenib. • Prior and/or concomitant treatment within a clinical study other than with sorafenib during or within 4 weeks of randomisation. • Sorafenib treatment within 2 weeks of randomisation. • Patients with large oesophageal varices at risk of bleeding that were not being treated with conventional medical intervention: beta blockers or endoscopic treatment. • Prior systemic treatment for HCC, except sorafenib. • Permanent discontinuation of prior sorafenib therapy due to sorafenib-related toxicity. • Permanent discontinuation of prior sorafenib therapy due to any cause more than 10 weeks prior to randomisation. • Previous or concurrent cancer distinct from HCC *except* cervical carcinoma in situ, uteri, and/or non-melanoma skin cancer and treated basal cell carcinoma, superficial bladder tumours (Ta, Tis & T1) or any cancer curatively treated > 3 years prior to entry into the study. • Known history or symptomatic metastatic brain or meningeal tumours. • Major surgical procedure or significant traumatic injury within 28 days before randomisation. • Cardiac disease (congestive heart failure > New York Heart Association (NYHA) class 2, cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin). • Unstable angina (angina symptoms at rest, new-onset angina) or myocardial infarction (MI) within the past 6 months prior to randomisation. • Uncontrolled hypertension (systolic blood pressure [BP] >150 mmHg or diastolic pressure >90 mmHg despite optimal medical management). • Phaeochromocytoma. • Uncontrolled ascites (defined as not easily controlled with diuretic or paracentesis treatment). • Pleural effusion or ascites that caused respiratory compromise (National Cancer Institute [NCI]-common terminology criteria

• Adequate bone marrow, liver and renal function as defined by: haemoglobin >8.5 g/dL; Absolute neutrophil count (ANC) ≥ 1500/mm^3; platelet count ≥ 60,000/mm^3; total bilirubin ≤ 2 mg/dL. Mildly elevated total bilirubin (<6 mg/dL) was allowed if Gilbert's syndrome was documented; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 5 X upper limit of normal (ULN); prothrombin time-international normalised ratio (PT-INR) < 2.3 X ULN and partial prothrombin time (PTT) <1.5 X ULN; serum creatinine ≤ 1.5 X ULN; lipase ≤ 2 X ULN; glomerular filtration rate (GFR) ≥30 mL/min/1.73 m^2 per the Modified diet in renal disease (MDRD) study equation. • Women of childbearing potential and men must have agreed to use adequate contraception until at least 2 months for men and for women after the last study drug administration.	for adverse events [CTCAE] Grade ≥2 dyspnoea). • Persistent proteinuria of NCI-CTCAE Grade 3 or higher. Urine dipstick result of 3+ was allowed if protein excretion was < 3.5 g/24 hours. • Ongoing infection > Grade 2 per NCI-CTCAE grading. Hepatitis B was allowed if no active replication was present. Hepatitis C was allowed if no antiviral treatment was required; known history of human immunodeficiency virus (HIV) infection; • Clinically significant bleeding NCI-CTCAE Grade 3 or higher within 30 days before randomisation. • Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischaemic attacks), deep vein thrombosis or pulmonary embolism within 6 months before the start of study medication. • Unresolved toxicity higher than NCI-CTCAE Grade 1 (excluding alopecia or anaemia) attributed to any prior therapy/procedure. • Any illness or medical condition that was unstable or could have jeopardised the safety of the patient and his/her compliance in the study. • Seizure disorder requiring medication • History of organ allograft; substance abuse, medical, psychological or social conditions that may have interfered with the patient's participation or evaluation of study results; • Inability to swallow oral medications; • Pregnancy or breast-feeding • Non-healing wound, ulcer, or bone fracture. • Renal failure requiring haemo- or peritoneal dialysis. • Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation. • Interstitial lung disease with ongoing signs and symptoms at the time of screening. • Any malabsorption condition. • Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person of the investigational site that would have had access to study records and electronic case report form [eCRF] data).

HCC - heptaocellular carcinoma; ECOG - Eastern Cooperative Oncology Group; PS - p*erformance status; PT - prothrombin time; INR - International Normalized Ratio; PTT - partial thromboplastin time.*

It is important to note the following groups were excluded from the RESORCE trial:

- adult patients with HCC who were sorafenib intolerant (i.e. having been unable to receive sorafenib at ≥400mg/day for ≥20 of the last 28 days of treatment);
- adult patients with HCC who were Child-Pugh class B;
- adult patients with HCC who had an ECOG PS of 2 or more.

Each of these excluded groups is covered by the BCLC categories B and C (a diagnostic classification that was also included as eligibility criteria for the RESORCE trial) and by the NICE scope.

The Child-Pugh score is an accepted classification of liver function, with higher numbers indicating more impaired liver function and lower numbers (e.g. class A) indicating better preserved liver function.[17] The classification criteria are reproduced in Table 6.

Table 6: Child–Pugh classification[17]

	Score		
Measure	**1 point**	**2 points**	**3 points**
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged)	<4	4-6	>6
Encephalopathy grade	None	1–2	3–4 *

Child–Pugh A: 5 or 6 points; Child–Pugh B: 7–9 points; Child–Pugh C: >9 points

Methodologically, RESORCE is a high quality, international, multicentre placebo-controlled trial (which included five UK centres, four of which had a total of 20 included patients; CS,[1] page 29). Patients (n=573) were randomised 2:1 to receive either oral regorafenib 160mg (4 x 40mg tablets orally once daily) plus BSC (n=379), or 4 x matching placebo tablets plus BSC daily (n=194), for the first 3 weeks of each 4-week cycle. In the fourth week, no study drug/placebo was given. BSC included: antibiotics; analgesics; radiation therapy for pain control (limited to bone metastases); corticosteroids; transfusions; psychotherapy; growth factors; palliative surgery, or any other symptomatic therapy necessary to provide BSC (CS,[1] pages 39-40). A full list of the relative proportions of concomitant medications taken across arms is provided in the clinical study report[18] (CSR), Section 8.7, pages 97-98. The proportion of patients receiving at least one concomitant medication was similar between the two groups (regorafenib 98.2% versus BSC 96.4%[18]). The data cut-off (DCO) for the final analysis was 29th February 2016; the median follow-up was 7.0 months (interquartile range [IQR] 3.7 to 12.6 months[6]). Patients continued masked study treatment until disease progression, death, unacceptable toxicity, substantial non-compliance with the protocol or withdrawal of patient from the study (by physician or patient).

Dose reduction (to 120mg per day or 80mg per day) or interruption was undertaken as required, in response to toxicity or specific AEs (CS,[1] pages 34-38). Doses could be re-escalated once toxicities resolved. When the primary endpoint of the study was reached (i.e. significant survival benefit compared with placebo[6]), patients who were on placebo at that time were offered the opportunity to receive regorafenib through open-label treatment, as long as the risk/benefit profile of regorafenib was positive. Patients were evaluated every cycle for treatment compliance by counting tablets dispensed and returned.

Outcomes and their definitions are described in Table 7. The primary outcome was OS. All disease progression or response outcomes were evaluated by investigators masked to study treatment and based on the RECIST 1.1 criteria and the modified (mRECIST) criteria for HCC regarding the definition of Progressive Disease (PD) and response. The HCC-specific mRECIST[19] is different from RECIST 1.1[20]: it includes amendments developed for the pivotal, sorafenib SHARP trial,[21] requiring cytopathological confirmation of malignancy to classify pleural effusion or ascites as progression, and applies more stringent criteria to define progression due to lymph node involvement at the hepatic hilum or new intrahepatic sites. It also considers complete tumour necrosis on dynamic imaging studies.[6] HRQoL was assessed using two measures: one disease-specific instrument (Functional Assessment of Cancer Therapy – Hepatobiliary: FACT-Hep) and one generic instrument (EQ-5D).

Table 7: Relevant endpoints and measures in the RESORCE trial (adapted from CS, Table 14)

Endpoint	Definition & timing of assessment / measure
Primary endpoint	
Overall survival (OS)	Measured from the date of randomisation until the date of death due to any cause. After the last dose of study medication and the 'end of treatment' visit, all patients entered a follow-up period during which information on survival status was collected.
Secondary endpoints	
Progression-free survival (PFS)	Time (days) from date of randomisation to date of disease progression (radiological or clinical) or death due to any cause, if death occurs before progression is documented. Disease progression was based on RECIST 1.1 criteria and the mRECIST criteria for HCC regarding the definition of PD,15 i.e. greater than 20% increase in target lesions. This was performed at screening, every 6 weeks during treatment for the first 8 cycles, and every 12 weeks thereafter.
Time to progression (TTP)	Defined as the time (days) from randomisation to radiological or clinical disease progression.
Objective tumour Response Rate (ORR)	Defined as the proportion of patients with complete response (CR) or partial response (PR) compared with all randomised patients. CR is defined as the absence of all target lesions; PR is defined as a greater than 30% decrease in target lesions. Patients prematurely discontinuing the study without an assessment were considered to be non-responders for the analysis.
Disease Control Rate (DCR)	The rate of subjects, whose best response was not progressive disease compared with all treated subjects (i.e. complete response, partial response or stable disease). In order to be counted as a responder in DCR stable disease had to be maintained for at least 6 weeks. Stable disease is defined as neither PR nor PD.
Tertiary endpoints	
Duration of response	Measured from the date of first documented response (CR or PR) to date of disease progression or death (if death occurred before disease progression).
Duration of stable disease	The time (days) from randomisation to the date that disease progression or death (if death occurred before progression) was first documented. Only calculated for patients who failed to achieve a best response of CR or PR.
Exploratory endpoint	
Overall survival measured from the start of prior sorafenib therapy	Measured from the beginning of prior sorafenib treatment until the date of death due to any cause.
Health-related quality of life (HRQoL):	The FACT-Hep and EQ-5D were both self-administrated by the patient before seeing the physician at baseline, day 1 of each cycle, and at end-of-treatment visit.

Endpoint	Definition & timing of assessment / measure
Primary endpoint	
FACT-Hep (version 4)	FACT-Hep is a 45-item disease-specific module of the FACT questionnaire, used extensively in oncology clinical trials.[22, 23] FACT-Hep consists of five subscales: (1) physical well-being; (2) social/family well-being; (3) emotional well-being; (4) functional well-being; and (5) the hepatobiliary cancer subscale. (1) - (4) are summed to form the FACT-General (FACT-G) total score. (1) - (5) are summed to form the FACT-Hep total score (range 0 to 180).
EuroQol – 5 Dimension (EQ-5D)	The EQ-5D is a generic preference-based quality of life instrument which has been validated in cancer populations to measure both utility and health status.[24] The EQ-5D also contains a visual analogue scale (EQ-visual analogue scale [VAS]), which records the respondent's self-rated health status on a vertical graduated visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).
Other endpoints	
Safety	AE assessment took place at every visit until 30 days after last study treatment (excluding survival assessment). AEs were classified using NCI-CTCAE version 4.03 guidelines

NCI-CTCAE - National Cancer Institute - Common Terminology Criteria for Adverse Events

4.2.2 Results

Participants' baseline characteristics

The baseline demographic and clinical characteristics of patients in the RESORCE trial were comparable across treatment groups (see Table 8). This was the case across almost all characteristics: age; gender; ethnicity; number of target lesions assessed by mRECIST (similar percentages in both treatment groups had two target lesions at baseline, i.e. 46.2% for regorafenib compared with 45.4% for placebo, which was similar when patients were assessed by RECIST 1.1 criteria: [redacted]% for regorafenib compared with [redacted]% for placebo); aetiology (except for alcohol use); ECOG PS; BCLC stage; macroscopic vascular invasion and/or extrahepatic disease; Child-Pugh class; previous local anti-cancer therapy; median time since initial diagnosis of HCC to start of regorafenib treatment; median times since discontinuation of or progression on sorafenib until start of regorafenib treatment. The treatment groups were therefore well-balanced with respect to disease characteristics, prognostic factors[25] and progression on sorafenib. Alcohol use was reported as aetiology for 23.8% in the regorafenib group and 28.4% in the placebo group. There was a difference in median alpha-fetoprotein (AFP) between arms: 183.2ng/ml (range 1.0-477591.0ng/ml) in the regorafenib arm compared with 234ng/ml (range 1.0-310229.1ng/ml) in the placebo arm. However, this was less noticeable when categorised as < or ≥400ng/ml; clinical advice received by the ERG confirmed that this categorisation was appropriate.

It is important to note that patients in the RESORCE trial were exclusively diagnosed as ECOG PS 0 and 1 (100% in each arm) and were almost exclusively diagnosed as Child-Pugh class A (98% in the regorafenib arm compared with 97% in the placebo arm). Patients who were Child-Pugh class B were excluded from the trial, but the status of a very small number of patients changed between recruitment and first administration of the study drug. The RESORCE trial therefore does not provide any meaningful evidence on patients who are BCLC stage B or C who are also ECOG PS 2 or Child-Pugh class B (two populations which are covered by the marketing authorisation of regorafenib for this indication). This limitation is acknowledged by the company (CS[1] page 85 and clarification response,[8] question A6).

The CS[1] (Section B.2.13, pages 86-89) also presents the findings of a retrospective audit of medical records by King *et al* (2017) reporting details of 484 sorafenib-treated patients in 15 hospitals in the UK between 2007 and 2013.[26] Where data are available and a comparison is possible, the baseline demographics and clinical characteristics of these patients were generally similar to the RESORCE trial. However, the patients in the sorafenib audit are older (mean age 68 years compared to 61 or 62 years in the RESORCE trial); they are much less likely to have HCC caused by hepatitis B (12.3% in the sorafenib audit compared with 38% in the RESORCE trial) and are much less likely to have extrahepatic disease (40% in the sorafenib audit compared with between 70% and 76% in the RESORCE trial). The other principal differences are the considerably higher proportions of patients with Child-Pugh class B (21% in the sorafenib audit compared with 0% in the RESORCE trial) and ECOG PS 2 (16% in the sorafenib audit compared with between 1% and 3% in the RESORCE trial). These patients are currently covered by the license for regorafenib.

Table 8: Patient baseline characteristics in the RESORCE trial

	Regorafenib N=379 (%)	**Placebo N=194 (%)**	**Sorafenib audit N=484 (%)**
Age (yr) (mean ± SD)	61.8 ±12.4	61.1±11.6	68
Median age (range)	64 (54-71)	62 (55-68)	
< 65 years	199 (52.5)	116 (59.8)	
≥ 65 years	180 (47.5)	78 (40.2)	
Sex – no. (%)			
Male	333 (87.9)	171 (88.1)	325 (72.5)
Female	46 (12.1)	23 (11.9)	66 (14.7)
Not reported			57 (12.7)
Race			
White	138 (36.4)	68 (35.1)	
Black	6 (1.6)	2 (1.0)	
Asian	156 (41.2)	78 (40.2)	
White / Black	2 (0.5)	1 (0.5)	
Not reported	77 (20.3)	45 (23.2)	
Region – no. (%)			
Asia	143 (37.7)	73 (37.6)	
Rest of World	236 (62.3)	121 (62.4)	

	Regorafenib N=379 (%)	**Placebo N=194 (%)**	**Sorafenib audit N=484 (%)**
Number of target lesions (mRECIST) n=372			
1	67 (17.7)	31 (16.0)	
2	175 (46.2)	88 (45.4)	
3	68 (17.9)	37 (19.1)	
4	43 (11.4)	26 (13.4)	
5	19 (5.0)	12 (6.2)	
Cause of disease (Aetiology)* – no. (%)			
Hepatitis C	78 (20.6)	41 (21.1)	70 (15.6)
Alcohol use	90 (23.8)	55 (28.4)	110 (24.6)
Hepatitis B	143 (37.7)	73 (37.6)	55 (12.3)
Genetic / metabolic	16 (4.2)	6 (3.1)	
Non-Alcoholic steatohepatitis	25 (6.6)	13 (6.7)	
Unknown	66 (17.4)	32 (16.5)	
Other	12 (3.2)	4 (2.1)	
ECOG performance status – no. (%)			
0	247 (65)	130 (67)	117 (26.1)
1	132 (35)	64 (33)	218 (48.7)
2			94 (21.0)
3			6 (1.3)
No data			13 (2.9)
BCLC stage - no. (%)			
A (early)	1 (0.3)	0	3 (0.7)
B (intermediate)	53 (14.0)	22 (11.3)	104 (23.2)
C (advanced)	325 (85.8)	172 (88.7)	322 (71.9)
No data			19 (4.2)
Macroscopic vascular invasion – no. (%)			
Yes	110 (29.0)	54 (27.8)	91 (20.3)**
No	269 (71.0)	140 (72.2)	161 (35.9)**
No data			196 (43.8)
Extrahepatic disease – no. (%)			
Yes	265 (69.9)	147 (75.8)	172 (38.4)
No	114 (30.1)	47 (24.2)	269 (60.0)
No data			7 (1.6)
Macroscopic vascular invasion and/or extrahepatic disease – no. (%)	304 (80)	162 (84)	
Child-Pugh class – no (%)			
A	373 (98.4)	188 (96.9)	343 (76.6)
B†	5 (1.3)	6 (3.1)	72 (16.1)
C‡			2 (0.4)
No data			31 (6.9)
Child-Pugh score – no (%)			
5	244 (64.4)	118 (60.8)	
6	129 (34.0)	70 (36.1)	
7†	5 (1.3)	5(2.6)	
8	0	1 (0.5)	
AFP (ng/ml)			

	Regorafenib N=379 (%)	Placebo N=194 (%)	Sorafenib audit N=484 (%)
Mean (± S.D.)	13507.9 (±49056.8)	12621.7 (±38472.3)	
median (range)	183.2 (1.0-477591.0)	234 (1.0-310229.1)	
<400 ng/mL	217 (57.3)	107 (55.2)	227 (50.7)
≥400 ng/mL	162 (42.7)	87 (44.9)	141 (31.5)
Previous therapy – no. (%)			
Local anti-cancer therapy	256 (67.9)§	133 (68.6)	
Including use of drug given locally	224 (59.1)	115 (59.3)	
Radiotherapy	48 (12.7)	37 (19.1)	
Systemic anticancer therapy	379 (100)	194 (100)	
Time from initial HCC diagnosis to start of regorafenib treatment – (months)			
Median (IQR)	21 (11-38)	20 (12-32)	
Mean (SD)	29 (28)	27 (22)	
Duration of sorafenib treatment (months)			
Median (IQR)	7.8 (4.2-14.5)	7.8 (4.4-14.7)	
Time from progression on sorafenib to start on regorafenib			
Median (IQR)	1.4 (0.9-2.3)	1.4 (0.9-2.2)	
Time from discontinuation of sorafenib to start on regorafenib			
Median (IQR)	0.9 (0.7–1.3)	0.9 (0.7–1.3)	

Data reproduced from CS, Table 15, pages 49-50, Table 30, pages 87-88; CSR Table8-5, and Table 1[6]; and the sorafenib audit study[26].
SD - standard deviation; HCC - hepatocellular carcinoma; IQR - interquartile range:
** Patients may have had more than one aetiology of HCC ** reports vascular invasion*
‡Regorafenib is not licenced for Child-Pugh class C [redacted]
† The information in this table is based on the last observations on or before the first study drug intake. Changes may have occurred between the screening of patients and their first day of study drug intake. During the study, it was found that 3 patients were on anticoagulant medication which, per the study protocol, led to Child-Pugh classification of B.

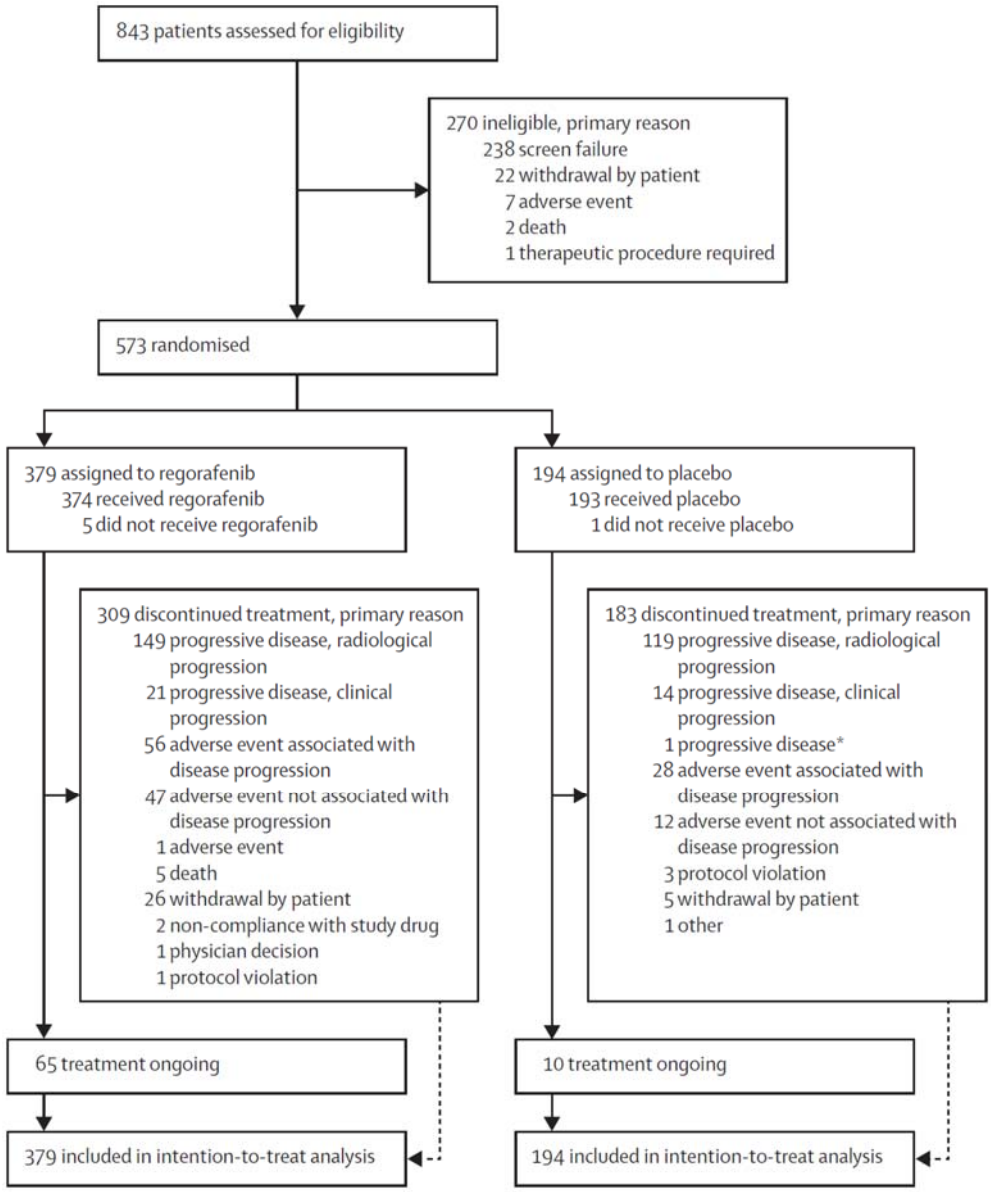
Participant flow and numbers

A total of 573 eligible patients were randomised 2:1 to regorafenib (n=379) and placebo (n=194), but 567 started treatment (five patients in the regorafenib group and one in the placebo group withdrew before first administration of the study drug). The reasons for these withdrawals were not provided in the CSR[18] (Section 8.2, page 82) but were provided by the company in response to a request from the ERG; they were principally due to the erroneous inclusion of patients who did not satisfy the eligibility criteria (see company's clarification response,[8] question A5). The patient in the placebo arm was excluded due to becoming Child-Pugh class B between randomisation and first study treatment (and therefore no longer satisfied the Child-Pugh class A inclusion criterion), but at least some of the 11 other patients who experienced a similar change in status before first study treatment were still included (see Table 8†). This anomaly is not explained. The ITT efficacy analysis included all randomised

patients (n=573), whilst the safety analysis only included patients who had started treatment (n=567). Details of the participant flow through the trial and reasons for discontinuation are provided in Figure 3. Three hundred and nine (83%) of the regorafenib patients who started treatment on regorafenib discontinued treatment, compared with 183 (95%) in the placebo arm of the trial. The numbers discontinuing due to disease progression were 226 (60%) in the regorafenib group and 162 (84%) in the placebo group. Discontinuations due to AEs not associated with disease progression were 15% (47/309) in the regorafenib arm, compared with 7% (12/183) in the placebo arm.

During the double-blind period (before reaching the primary endpoint), the median treatment duration for patients assigned to receive regorafenib was 3.6 months (IQR 1.6-7.6 months) compared with 1.9 months (IQR 1.4-3.9 months) for patients assigned to placebo (CS,[1] page 39). The median daily dose during the double-blind treatment period was reported to be 159.3mg for regorafenib-treated patients (CS,[1] page 39). The mean daily dose of regorafenib was 144.1mg (standard deviation [SD] 21.3mg) and 157.4mg of placebo (SD 10.3mg). Excluding treatment delays or interruptions, almost half of the regorafenib group (184 of 374 [49%]) received the full protocol dose (160mg/day) with no reductions (CS,[1] page 39). Full details of concomitant and disallowed concomitant medications, and required therapeutic and diagnostic and therapeutic procedures, were also provided in the CS (see CS,[1] pages 39-42).

Figure 3: 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

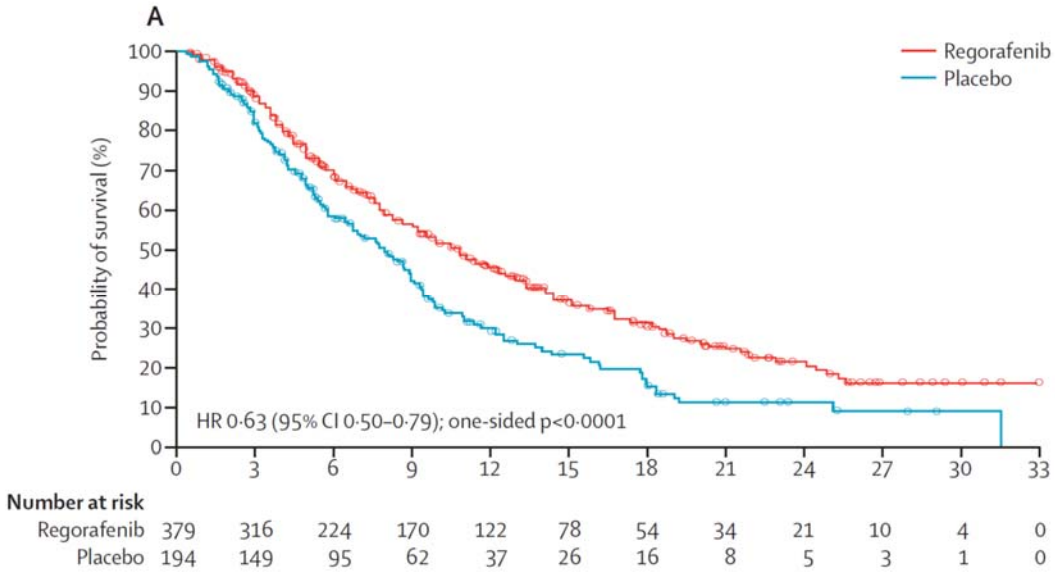
compared to placebo ([redacted]) (see CS,[1] Table 17, page 51). Details are presented in Table 9 and the Kaplan-Meier curve is reproduced in Figure 4**.**

Table 9: 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)	[redacted]	[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 4: Kaplan-Meier Curve for OS (FAS; mRECIST) (reproduced from Bruix *et al*, 2017, Figure 2A[6])



*Secondary outcome*s

4.2.2.2 Progression-free survival (PFS)

In the RESORCE trial, median PFS as measured by mRECIST was statistically 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. This represents a 54% reduced risk of progression for regorafenib group compared with placebo. Details are presented in

Table **10** and Figure 5.

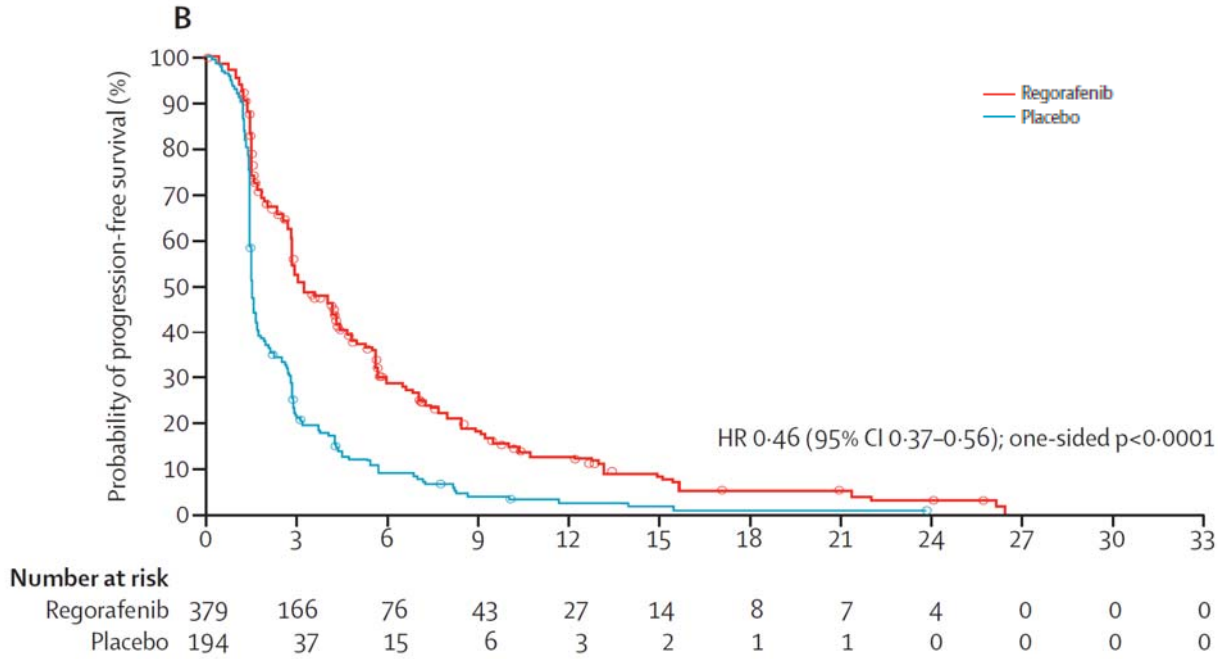
Table 10: Analyses of PFS in the RESORCE study (FAS; mRECIST) (reproduced from CS, Table 20)

	Regorafenib (N=379)	**Placebo (N=194)**
Number of patients (%) with event	[redacted]	[redacted]
Number of patients (%) censored	[redacted]	[redacted]
Median PFS, days (95% CI), Range (without censored values)	[redacted]	[redacted]
Median PFS, months (95% CI), Range (without censored values)	[redacted]	[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 were manually converted from days to months (1 month=30.44 days)

Figure 5: Kaplan-Meier curve for PFS in the RESORCE study (FAS; mRECIST) (reproduced from Bruix et al, 2017, Figure 2B[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 11 and Figure 6.

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

	Regorafenib	**Placebo**

	(N=379)	(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)	[redacted]	[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	

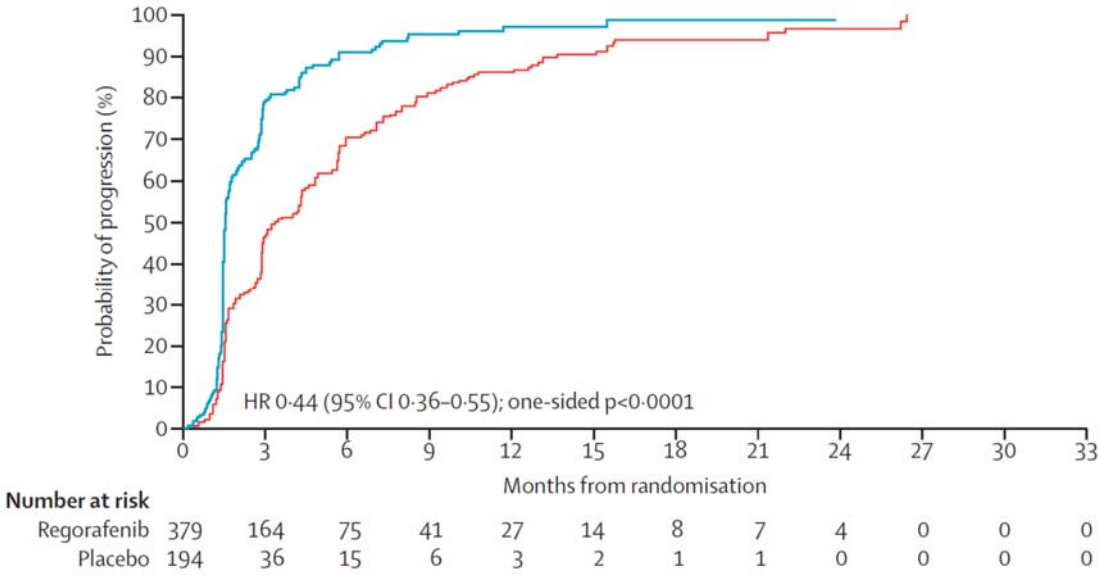
CI - confidence interval; FAS - full analysis set; IVRS - interactive voice response system

[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)

Figure 6: KM estimates of the TTP rate during RESORCE (FAS; mRECIST) (reproduced from Bruix *et al* 2017, Figure 2C[6])



4.2.2.4 Response

The objective response rate (ORR), the aggregation of CR and PR, according to mRECIST, was statistically significantly higher in the regorafenib group than in the placebo group (11% compared with 4%; *p*=0.0047, see Table 12**.**

Table 12: Response to therapy in the RESORCE study (FAS; mRECIST) (reproduced from CS, Table 22 and Bruix *et al*)

Best overall response	**Regorafenib N=379 (100%) [95% CI]**	**Placebo N=194 (100%) [95% CI]**
Complete response (CR)	2 (1%) [<1%; 2%]	0
Partial response (PR)	38 (10.0%) [7%; 14%]	8 (4%) [2%; 8%]
Stable disease (SD)	206 (54%) [49%; 59%]	62 (32%) [26%; 39%]
Non-CR / Non-PD	1 (0.3%) [0.0%; 1.5%]	0
Progressive disease (PD)	86 (23%) [19%; 27%]	108 (56%) [48%; 63%]
Not evaluable (NE)	19 (5%) [3%; 8%]	8 (4%) [2%; 8%]
Not assessed (NA)	27 (7%) [5%; 10%]	8 (4%) [2%; 8%]
Clinical progression	86 (23%) [19%; 27%]	40 (21%) [15%; 27%]
Response Rate	**40 (11%)**	**8 (4%)**
Disease Control Rate	**247 (65%)**	**70 (36%)**
Comparison of treatments – Inferential Statistics		

Regorafenib versus placebo	**Difference**	**[95% CI]**	***p*-value**
Response rate	-6.61	[-10.84, -2.39]	0.0047
Disease control rate	-29.31	[-37.52, -21.11]	<0.0001

CI - confidence interval; CR - complete response; FAS - full analysis set; HCC - hepatocellular carcinoma; mRECIST - modified RECIST for HCC; N - number of patients; NA - not assessed; NE - not evaluable; PD - progressive disease; PR - partial response; SD - stable disease

Based on mRECIST, the disease control rate (DCR), a combination of CR + PR +Stable Disease (SD), was also statistically significantly higher in the regorafenib group compared with the placebo group (65% compared with 36%; $p<0.0001$). Stable disease is defined as neither PR nor PD. Using the mRECIST criteria, two patients were reported as having had a complete response (CR) (0.5%) in the regorafenib arm (compared with no patients in the placebo arm, see Table 12**.**

It should be noted that according to RECIST 1.1 criteria, no patients achieved CR and the overall response rate was reduced: [redacted] vs [redacted] (regorafenib vs placebo), [redacted] (Online Table 6[6]), compared with 11% vs 4%, respectively, $p<0.0001$, according to mRECIST (see Table 12).

In terms of the tertiary endpoints, based on mRECIST criteria, the CS reported that the median duration of response and median duration of stable disease were longer in the regorafenib group than in the placebo group, however these differences were not statistically significant (no *p*-values were given, see Table 13).

Table 13: Duration of response and stable disease (FAS; mRECIST) (reproduced from CS, Tables 24 and 25)

Duration of response	**Regorafenib (N=40)**	**Placebo (N=8)**
Number of patients (%) with event	30 (75.0%)	5 (62.5%)
Number of patients (%) censored	10 (25.0%)	3 (37.5%)
Median [95% CI], months	3.5 (1.9-4.5)	2.7 (1.9, NE)
Duarion of stable disease	**Regorafenib (N=206)**	**Placebo (N=62)**
Number of patients (%) with event	151 (73.3%)	56 (90.3%)
Number of patients (%) censored	55 (26.7%)	6 (9.7%)
Median (95% CI) in months	5.5 (4.3 – 5.6)	3.1 (2.8, 4.2)

CI - confidence interval; CR - complete response; FAS - full analysis set

4.2.2.5 Health-related quality of life (HRQoL)

The CS[1] (page 67) reports that 'more than 80% of regorafenib and placebo patients completed questionnaires' and that, 'Of these, approximately 90% in either treatment group were valid for analyses'. The CSR[18] (Sections 9.3.3.3.1 and 9.3.3.3.2) refers to these figures, which are otherwise unpublished. The trial found that quality of life scores were generally similar across arms (see Table 14), but all of the different measures consistently favoured placebo compared with regorafenib (CS,[1] pages 67-70 and Bruix *et al* 2017[6, 13]). The Least-Squares Mean (LSM) time-adjusted Area Under the Curve (AUC) analysis found that only two measures produced a statistically significant difference between arms: the FACT-Hep total and Trial Outcome Index (TOI, a subscale of FACT-Hep) both favoured placebo compared with regorafenib ($p<0.0001$ and $p=0.0006$, respectively). The trial publications[6, 13] and the CS (page 67) stated that even though the differences were statistically

significant, they were not clinically meaningful because they did not exceed minimally important thresholds for the differences, as established in the literature (a change of 8-9 points for FACT-Hep[27] and 7-8 points, for the EQ-5D VAS[24]).

Table 14 : Summary of patient-reported outcomes; LSM time-adjusted AUC (FAS) (reproduced from CS, Table 27, page 68 and Bruix *et al,* 2017[6, 13])

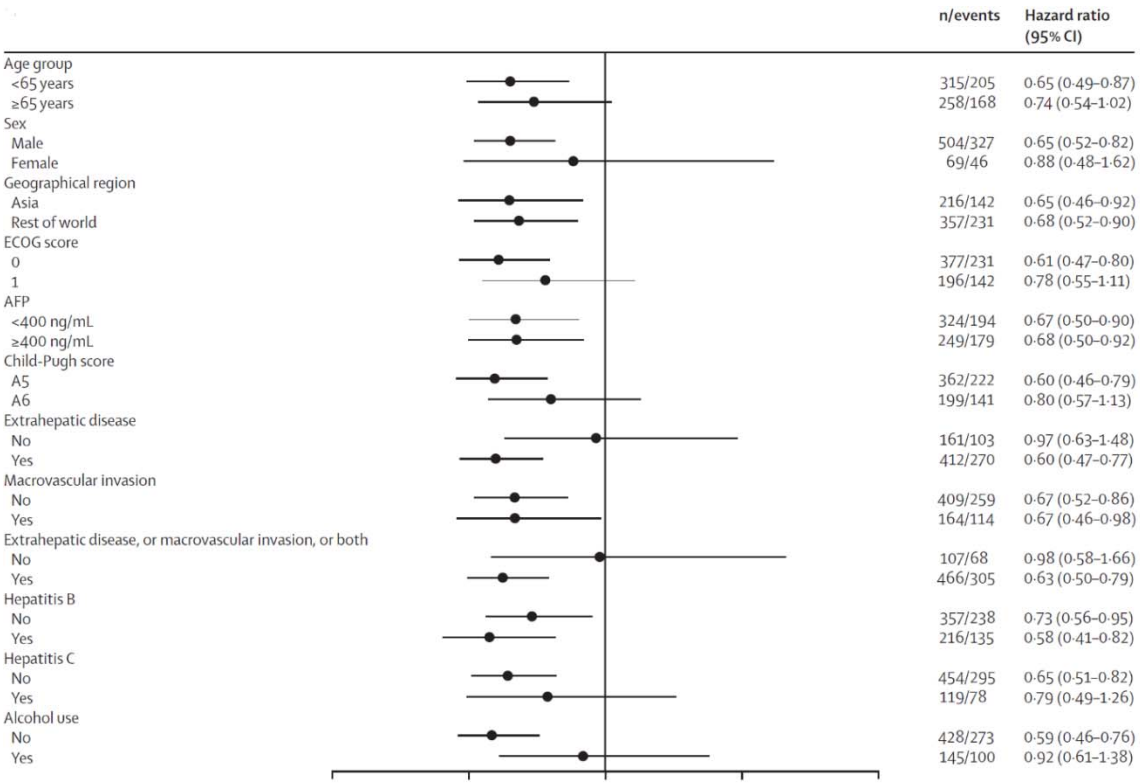
LSM time-adjusted AUC (95% CI)	Regorafenib	Placebo	Difference	*p*-value	MID
EQ-5D index	0.76 (0.75, 0.78)	0.77 (0.75, 0.79)	-0.01 (-0.03, 0.02)	0.4695	0.1
EQ-5D VAS	71.68 (70.46, 72.90)	73.45 (71.84, 75.06)	-1.77 (-3.58, 0.04)	0.0558	10
FACT-G	75.14 (74.12, 76.16)	76.55 (75.20, 77.90)	-1.41 (-2.93, 0.11)	0.0698	6-7
FACT-Hep total	129.31 (127.84, 130.79)	133.17 (131.21, 135.12)	-3.85 (-6.06, -1.65)	0.0006	8-9
Trial outcome index	91.47 (90.30, 92.64)	95.52 (93.98, 97.07)	-4.05 (-5.79, -2.31)	<0.0001	7-8

AUC - area under curve; FACT - Functional Assessment of Cancer Therapy; FACT-G - FACT-General; FACT-Hep - FACT-Hepatobiliary; LSM - Least squares mean; MID - minimally important difference; VAS - visual analogue scale

4.2.2.6 Subgroup and exploratory analyses

Subgroup analyses were conducted for OS, PFS and TTP. Full details of all of the subgroup analyses are provided in the CS, Appendix E, but the forest plot for the OS subgroup analyses is reproduced here. All of these analyses demonstrated consistent benefit for patients treated with regorafenib, regardless of geographical location, age, gender, AFP, aetiology or other covariates (see Figure 7**)**. A published abstract also reported that, while there was a consistent OS benefit regardless of pattern of progression under sorafenib, patients had a substantially worse prognosis if they developed new extrahepatic lesions under previous sorafenib treatment: on regorafenib, 9.7 months with new extrahepatic lesions compared with 14.7 months with no new such lesions; compared with 8.2 months and 10.5 months respectively on placebo.[6] A subgroup analysis of Chinese patients reported results similar to the overall trial, albeit being a younger population with slightly shorter survival times.[16] The CS correctly acknowledged (Appendix E) not only that the RESORCE trial was not powered for subgroup analyses, but also that the number of patients in some subgroups was small, with low event rates. This means that the results of these analyses should be interpreted with caution (see CS Appendix E[9]).

Figure 7: Forest plot of subgroup analyses – overall survival (FAS) (reproduced from Bruix *et al*, 2017, Figure 3A[6])



Note: the left-hand side of the line of no effect favours regorafenib

Sensitivity analyses

Sensitivity analyses were conducted for the outcomes of OS, PFS and TTP to take into account any differences between the primary analysis stratification data collected by the investigator at the time of randomisation (the IVRS analysis), and those collected later on each patient's Case Report Form (CRF) by a validated electronic system for data collection (the RAVE analysis), as well as an analysis that did not use the stratification factors (CS,[1] page 57). The findings across these sensitivity analyses were consistent with the primary analysis using the data according to the IVRS (see CS,[1] pages 56-61).

Exploratory analysis

An exploratory analysis evaluating OS from the beginning of previous sorafenib treatment was also undertaken for the RESORCE trial. This demonstrated that the median OS was statistically significantly improved by the sequence of sorafenib followed by regorafenib from [redacted] months on placebo (95% CI [redacted] months) to [redacted] months on regorafenib (95% CI [redacted] months) (a difference of [redacted] months, see

Table 15).

Table 15: OS from start of prior sorafenib treatment (adapted from CS, Table 26)

		Regorafenib (N=379)	Placebo (N=194)
	n N missing	[redacted]	[redacted]
Time (days) from start of sorafenib to progression while on sorafenib	Median (95% CI) (range)	[redacted]	[redacted]
Time (days) from start of sorafenib to progression on regorafenib	Median (95% CI) (range)	[redacted]	[redacted]
Time (days) from start of sorafenib to death	Median (95% CI) (range)	[redacted]	[redacted]

CI - confidence interval

4.2.3 Safety

AEs were assessed using the MedDRA preferred terms (https://www.meddra.org/) and NCI-CTCAE grading (https://evs.nci.nih.gov/ftp1/CTCAE/About.html) for the safety population (n=567). It should be noted that although many data were similar or the same, the data on AEs presented below (as published[6]) differ from some of the data presented (as academic-in-confidence) in the CS (pages 74-77 and Table 28) and in the CSR. The CS (Section B.2.10, pages 74-80) and the CSR (Section 10.3.2) AE rates from the 'safety analysis set', are almost always lower. However, in such cases, the differences in comparison with placebo are either similar or indicate a comparable difference between arms, e.g. anaemia of any grade [redacted] compared with 16% and 11% (published); for fever, [redacted] compared with 19% vs 11% (published); and for fatigue, [redacted] compared with 40% vs 32% (published, see Table 16). Given these disparities, the ERG has decided to present only the published data. Similar discrepancies exist for the treatment-emergent drug-related AEs.

AEs were frequent (all patients receiving the study drug experienced at least one AE) (see Table 16) and 93% of regorafenib patients experienced treatment-emergent drug-related AEs compared with 52% of placebo patients. All common AEs were much more frequent in the regorafenib group than in the placebo group. The principal AEs were: hand foot skin reaction (53% in the regorafenib arm compared with 8% in the placebo arm); diarrhoea (41% vs 15%); fatigue (40% vs 32%); hypertension (41% vs 6%); and anorexia (31% vs 15%). The frequency of the most common AEs was consistent with those in the Phase II trial[14], with the exception of hypothyroidism, which occurred in 15% of regorafenib patients in the Phase II trial, but only 6.4% of regorafenib patients in the RESORCE trial (CSR, Table 10-3, page 149). The relative frequency of other events was more consistent.

Table 16: **Incidence of any adverse event with a frequency of ≥10% and ≥5% difference between regorafenib and placebo[6]**

	Treatment-emergent (%)		Treatment-emergent drug-related (%)	
Adverse event	**Regorafenib (n=374)**	**Placebo (n=193)**	**Regorafenib (n=374)**	**Placebo (n=193)**
Any	100	93	93	52
Hand foot skin reaction	53	8	52	7
Diarrhoea	41	15	33	9
Fatigue	40	32	29	19
Hypertension	31	6	23	5
Anorexia	31	15	24	6
Increased blood bilirubin	29	18	19	4
Abdominal pain	28	12	9	3
Increased AST	25	20	13	8
Fever	19	7	4	2
Constipation	17	11	6	2
Anaemia	16	11	6	1
Hypoalbuminaemia	15	8	2	0
Weight loss	14	5	7	2
Oral mucositis	13	3	11	3
Vomiting	13	7	7	3
Thrombocytopenia	10	3	5	1
Hypophosphataemia	10	2	6	1
Hoarseness	10	1	9	0

Rates of AEs of Grade 3 or higher were reported as 79.9% in the regorafenib group compared with 58.5% in the placebo group.[13] More regorafenib patients than placebo patients experienced Grade 3 (46% compared with 16%) and Grade 4 (4% compared with 1%) treatment-emergent drug-related AEs. Some Grade 3 and 4 AEs were also much more frequent in the regorafenib group than in the placebo group (see Table 17). The principal Grade 3 AEs were: hand foot skin reaction (13% in the regorafenib arm compared with 1% in the placebo arm); hypertension (15% vs 5%); increased blood bilirubin (10% vs 8%); increased aspartate aminotransferase (AST, 10% vs 10%); fatigue (9% vs 5%); and hypophosphataemia (8% vs 2%). The only Grade 4 AEs affecting more than 1% of patients all occurred in the regorafenib arm: these were increased blood bilirubin (3%), increased alanine aminotransferase (ALT, 3%) and increased AST (2%).

According to the principal trial publication,[6] serious adverse events (SAEs) occurred in 166 (44%) patients in the regorafenib group and 90 (47%) patients in the placebo group. These SAEs were attributed to the study drug in 39 (10%) regorafenib patients and five (3%) placebo patients.[6] According to the CS[1] (page 79), drug-related treatment-emergent severe AEs (TESAEs) were relatively low in both groups, but higher in regorafenib-treated patients compared with those receiving placebo (10% [n=39] vs. 3% [n=5]). The most common TESAEs (>2%) were general physical health deterioration

([redacted]% in regorafenib patients compared with [redacted]% in placebo patients); ascites ([redacted]%; vs [redacted]%) and hepatic failure ([redacted]% vs [redacted]%).

According to the SmPC,[28] regorafenib has been associated with an increased incidence of haemorrhagic events, which were mostly mild to moderate, but some of which were fatal. As a result, close monitoring is recommended for patients who are predisposed to bleeding. In the RESORCE trial, according to the CS[1] (page 78, Table 29) and Online Table 11,[6] the incidence of haemorrhage events of ≥ Grade 3 was higher in the placebo group (15 patients=8%) than the regorafenib group (21 patients=6%), but the incidence of drug-related haemorrhage events of ≥ Grade 3 was higher in the regorafenib group (6 patients=1.6%) than the placebo group (0 patients).

Table 17: **Incidence of Grade 3 and 4 adverse events (≥2%)[6]**

Adverse event	Treatment-emergent (%)				Treatment-emergent drug-related (%)			
	Regorafenib (n=374)		Placebo (n=193)		Regorafenib (n=374)		Placebo (n=193)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any	56	11	32	7	46	4	16	-
Hand foot skin reaction	13	-	-	-	13	-	-	-
Diarrhoea	3	-	-	-	2	-	-	-
Fatigue	9	-	5	-	6	-	2	-
Hypertension	15	-	5	-	13	-	3	-
Anorexia	3	-	2	-	3	-	-	-
Increased blood bilirubin	10	-	8	3	6	-	2	-
Abdominal pain	3	-	4	-	-	-	-	-
Increased AST	10	-	10	2	4	-	5	-
Ascites	4	-	6	-	-	-	-	-
Anaemia	4	-	5	-	-	-	-	-
Increased ALT	3	-	11	3	2	-	4	-
Hypoalbuminaemia	2	-	8	-	-	-	-	-
Weight loss	2	-	5	-	-	-	-	-
Back pain	2	-	-	-	-	-	-	-
Thrombocytopenia	3	-	-	-	2	-	-	-
Hypophosphataemia	8	-	2	-	4	-	-	-

Empty cells indicate an incidence of <2%

4.2.3.1 Adverse events leading to withdrawal

Rates of dose modification due to AEs were reported as 68.2% in the regorafenib group compared with 31.1% in the placebo group.[6, 13] The rate of permanent discontinuation of the study drug due to any AE was 25% in the regorafenib group compared with 19% in the placebo group (CSR[18] Table 10-2, page 147 and Bruix *et al* 2017[6]). Any drug-related AEs led to discontinuations in 10% of patients in the regorafenib group and 4% of patients in the placebo group (CSR[18] Table 10-2, page 147 and Bruix *et al* 2017[6]). The most frequent AEs leading to discontinuation of regorafenib treatment were reported in the CS[1] (page 80) or Bruix *et al*[6] as general physical health deterioration [redacted]% in the regorafenib group compared with [redacted]% in the placebo group); increased AST (2% vs. 2%); increased blood bilirubin ([redacted]% vs. [redacted]%); hand foot skin reaction (2% vs. 0%); and ALT increase (1% vs 0%).

As reported in the principal trial publication,[6] dose interruptions or reductions due to drug-related AEs occurred in 54% of regorafenib patients and 10% of placebo patients. According to the CS[1] (page 80), dose reductions (not including interruptions) due to AEs occurred in [redacted]% of the patients in the regorafenib group and [redacted]% of the placebo group. These included hand foot skin reaction ([redacted]% in the regorafenib group compared with [redacted]% in the placebo group); diarrhoea ([redacted]% vs. [redacted]%); fatigue ([redacted]% vs. [redacted]%); and increased blood bilirubin ([redacted]% vs. [redacted]%). The most common reason for discontinuing placebo was increased AST ([redacted]% compared with [redacted]% for regorafenib).

4.2.3.2 Deaths

There were 50 deaths (13%) in the regorafenib group and 38 deaths (20%) in the placebo group. Deaths assessed as being related to the study drug were reported for seven (2%) regorafenib patients and two (1.0%) placebo patients. The seven deaths considered related to regorafenib were recorded as (one of each case): duodenal perforation, meningorrhagia, haemorrhagic shock, hepatic encephalopathy, myocardial infarction and one event for which the primary cause of death was an AE associated with clinical disease progression, for which the treating physician assessed the event as being related to the study treatment.[6]

4.2.4 *Ongoing studies*

There are currently no relevant ongoing studies of regorafenib for this indication.

4.2.5 Discussion

The company's systematic review was generally well-conducted. However, some processes could have been reported better and some relevant abstracts and additional analyses relating to the pivotal RESORCE trial should have been identified and included in the CS. This additional literature is cited, where appropriate, in this report. The review only included a single, relevant RCT: the RESORCE trial. This was an international, placebo-controlled Phase III trial evaluating the efficacy and safety of

regorafenib 160mg per day in adult patients with HCC who have previously progressed on sorafenib. RESORCE is a high quality RCT, with a low risk of selection, performance, detection, attrition and reporting bias, and with only small questions to be raised over industry involvement. The trial reported that regorafenib was significantly more effective than placebo across the primary (OS) and secondary (PFS, TTP, ORR) outcomes.

The trial found that patients on regorafenib had increased survival: median OS was reported to be 10.6 months (95% CI 9.1-12.1) in patients randomised to regorafenib compared with 7.8 months (95% CI 6.3-8.8 months) in patients randomised to placebo. The estimated HR for OS (regorafenib compared with placebo) was 0.63, 95% CI 0.50-0.79, one-sided p=0.000020. Median PFS as measured by 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 TTP as measured by mRECIST was also significantly better for regorafenib (3.2 months, 95% CI 2.9–4.2) than for placebo (1.5 months, 95% CI 1.4–1.6): HR, 0.46, 95% CI 0.36-0.55; p<0.0001. The ORR, which includes both CR and PR according to mRECIST, was also significantly higher in the regorafenib group than in the placebo group (11% compared with 4%; p=0.0047). Similar findings were reported across all outcomes when using the RECIST 1.1 criteria. Subgroup analyses demonstrated consistent benefit for patients treated with regorafenib, although an additional analysis found that those who develop a new extrahepatic lesion when they progressed on sorafenib had a considerably worse survival rate than those who did not.[6]

The RESORCE trial also found that HRQoL was consistently worse on treatment than on placebo across different measures: these differences were found to be statistically significant in the case of the FACT-Hep total and the Trial Outcome Index, but did not reach clinical significance according to pre-specified thresholds.

AEs were frequent: 100% of regorafenib patients receiving the study drug experienced at least one AE (compared with 93% on placebo), and 93% of regorafenib patients experienced treatment-emergent drug-related AEs compared with 52% of placebo patients. The principal AEs were: hand foot skin reaction (53% in the regorafenib arm compared with 8% in the placebo arm); diarrhoea (41% vs 15%); fatigue (40% vs 32%); hypertension (41% vs 6%); and anorexia (31% vs 15%). AEs of Grade 3 or higher were reported for 80% of patients in the regorafenib group compared with 59% in the placebo group. Many more regorafenib patients than placebo patients also experienced Grade 3 (46% compared with 16%) and Grade 4 (4% compared with 1%) drug-related AEs. The incidence of haemorrhage events of ≥ Grade 3 was higher in the placebo group (8%) than the regorafenib group (6%), but the incidence of drug-related haemorrhage events of ≥ Grade 3 was higher in the regorafenib group (1.6%)

than the placebo group (0%). According to the CS, drug-related severe AEs 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]

Consequently, given the AE profile of regorafenib, there is a probability that patients who do not match the RESORCE trial population will experience less efficacy and more AEs (because many AEs are hepatic) than patients who match the clinical profile of the RESORCE trial population. The RESORCE trial found that HRQoL was consistently worse on treatment than on placebo across different measures and so this risk/benefit balance might be worse still for the groups without data.[31] The lack of relevant data and its implications are acknowledged in the SmPC[28]: this recognises the potential adverse impact of regorafenib on hepatic function in patients who are Child-Pugh class B and the need to monitor all AEs carefully in this group. There is therefore substantial uncertainty concerning the benefits of regorafenib in patients who do not satisfy the inclusion criteria of the RESORCE trial.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The CS does not contain an evidence synthesis of multiple studies.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The CS does not contain an evidence synthesis of multiple studies.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG did not undertake any additional analyses for the clinical effectiveness review.

4.6 Conclusions of the clinical effectiveness section

The company's systematic review was generally well conducted. The review included a single RCT: the RESORCE trial, which represents the relevant evidence. This was an international, placebo-controlled Phase III trial evaluating the efficacy and safety of regorafenib 160mg per day in adult patients with HCC who have previously progressed on sorafenib. RESORCE is a high quality RCT, with a low risk of selection, performance, detection, attrition and reporting bias. The trial reported that regorafenib was significantly more effective than placebo across the primary (OS) and secondary (PFS, TTP, ORR) outcomes. Subgroup analyses demonstrated consistent benefit for patients treated with regorafenib, but the trial also found that HRQoL was consistently worse on treatment than on placebo across different measures: these differences were found to be statistically significant in the case of the FACT-Hep total and the TOI, but did not reach clinical significance. AEs were frequent. 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 efficacy and safety of regorafenib in other adult HCC patients covered by the NICE scope and the licence, that is, those who are intolerant to sorafenib, or who are Child-Pugh class B or ECOG PS 2, is uncertain.

5 COST EFFECTIVENESS

This chapter presents a summary and critical appraisal of the methods and results of the company's review of published economic evaluations and the *de novo* health economic analysis presented within the CS.[1]

5.1 ERG comment on the company's systematic review of cost-effectiveness evidence

5.1.1 Description of company's systematic review of cost-effectiveness evidence

The company undertook an initial and simultaneous search to identify economic evaluations, cost and resource use and HRQoL of patients with advanced HCC. The following sources were searched: MEDLINE, EMBASE, EconLit, ABI/INFORM [via ProQuest], Cochrane Database of Systematic Reviews [via Wiley], Database of Abstracts of Reviews of Effects [via Wiley], and Cochrane Central Register of Controlled Trials [via Wiley], Cochrane Methodology Register [via Wiley], Health Technology Assessments Database [via Wiley] and NHS Economic Evaluation Database [via Wiley].

The company carried out supplementary searches in several international health technology assessment (HTA) agency websites (NICE, Scottish Medicines Consortium, National Centre for Pharmacoeconomics, Canadian Agency for Drugs and Technology/ pan-Canadian Oncology Drug Review, Haute Autorité de santé, Gemeinsame Bundesausschuss, Institute for Quality and Efficiency in Health Care, Dental and Pharmaceutical Benefits Board Agency).

Conference proceedings websites were searched for abstracts covering the period from 2014 to January 2017 (AACR, ASCO, Gastrointestinal Cancers Symposium, ESMO, ILCA, ESDO, EASL, ESMO World Congress on Gastrointestinal Cancer, JSMO, CSCO, and AASLD).

The company carried out separate update searches for economic evaluations and costs and resource use from July 2016 to May 2017. The HRQoL search was undertaken up to January 2017.

The ERG considers that the search was comprehensive and clearly and fully reported in CS Appendices G-I.[9]

The company's search initially identified 23 publications. Four of these studies were dismissed, leaving 19 economic evaluations. Most of the included studies related to sorafenib for HCC; none of the included studies assessed the cost-effectiveness of regorafenib for HCC.

The ERG conducted an update search in MEDLINE and EMBASE [via Ovid] on 27th July 2017. This search identified one published economic evaluation of regorafenib versus BSC for the treatment of

advanced HCC (Parikh *et al*[35]). This publication was accepted for publication in May 2017, after the company's final literature searches had been performed, hence it could not have been identified by the company's search strategy. The study by Parikh *et al*[35] compares regorafenib versus BSC for patients with unresectable HCC and Child Pugh A cirrhosis from the US health system perspective. The authors estimated that the ICER for regorafenib compared with BSC was $224,362 per QALY gained. As part of their response to the ERG's clarification questions (see company's clarification response,[8] question B17), the company stated that the study reported by Parikh *et al*[35] would have been of little value for the current appraisal as: (i) the evaluation was conducted over a restricted time horizon; (ii) no extrapolation of the data obtained in the RESORCE trial was performed thereby underestimating the survival gain associated with regorafenib, and (iii) the evaluation was performed for the US healthcare system using the US cost for regorafenib without the benefit of the UK PAS. The ERG agrees that this published study cannot adequately address the decision problem set out in the final NICE scope.[36]

5.2 Description of the company's model

5.2.1 Model scope

As part of its submission to NICE, the company submitted a fully executable health economic model programmed in Microsoft Excel®. The scope of the company's economic analysis is summarised in Table 18. The company's model assesses the cost-effectiveness of regorafenib (plus BSC) versus BSC alone for 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 UK NHS and Personal Social Services (PSS). All costs and health outcomes are discounted at a rate of 3.5% per annum. Unit costs are valued at 2015/16 prices.

Table 18: Summary of company's health economic model scope

Population	Adult patients with unresectable HCC who have been previously treated with sorafenib
Intervention	160mg regorafenib once daily for 3 weeks, followed by 1 week off therapy (plus BSC). Dose reductions and treatment interruptions are also included.
Comparator	BSC
Primary health economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	15 years
Discount rate	3.5% per year
Price year	2015/2016

NHS – National Health Service; PSS – Personal Social Services

Population

The population considered within the company's economic analysis relates to adults with HCC who have been previously treated with sorafenib. This is broader than the population recruited into the RESORCE trial,[6] which excluded patients who discontinued sorafenib due to toxicity rather than progression (see Section 4.2) as well as those with Child-Pugh class B disease and those with an ECOG PS of 2 or more. Within the RESORCE trial, patients randomised to the regorafenib group had a mean age of 61.8 years and 87.9% of patients were male; patients randomised to the placebo group had a mean age of 61.1 years and 88.1% of patients were male. A detailed breakdown of patient characteristics is presented in Table 7.

Intervention

The intervention under consideration is regorafenib (given alongside BSC). Regorafenib is assumed to be administered orally at a dose of 160mg once daily (4 x 40mg tablets) for the first 21 days of each 28-day treatment cycle; no treatment is taken during the remaining 7 days of the cycle. The SmPC for regorafenib[28] notes that dose interruptions and/or reductions may be required and should be applied in decrements of 40mg (one tablet), with a lowest recommended daily dose of 80mg. The company's model includes such dose reductions and treatment interruptions based on an analysis of patient-level data from the RESORCE trial,[6] calculated using the mean daily dose of regorafenib prior to and after disease progression.

The SmPC for regorafenib[28] states that *"Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs."* This is consistent with the RESORCE trial in which a proportion of patients who were randomised to the intervention group were allowed to continue treatment with regorafenib post-progression if the treating physician considered that the patient was still experiencing clinical benefit. As such, the company's model includes the costs of post-progression regorafenib use

in the intervention group. The ERG notes that the inclusion of these post-progression regorafenib costs is internally consistent with the experience of the RESORCE trial as the health benefits included in the model are aligned with the resources consumed to generate those benefits. The CS states that many physicians would not treat patients following disease progression,[1] therefore the scenario assessed by the model may deviate somewhat from usual clinical practice in England. The clinical advisors to the ERG did not have a consensus on whether regorafenib would be used in England for patients following progression, in line with the RESORCE trial.[6]

Comparator

The comparator included in the company's model is BSC. This is assumed to consist of concomitant medications, antibiotics, analgesics, radiation therapy for pain control (for bone metastases only), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery or any other symptomatic therapy necessary to provide BSC, except investigational anti-tumour agents, immunotherapy, antineoplastic chemotherapy or antineoplastic hormone therapy (CS,[1] page 33).

The company's base case model does not include post-progression regorafenib treatment in the comparator group as treatment switching was not permitted during the double-blind phase of the RESORCE trial.

Model versions and revisions

Three versions of the company's model were received by the ERG, two of which were submitted following the clarification process. These models include:

(1) The company's original submitted model: this was provided as part of the company's submission. This model is based on the 29th February 2016 DCO of the RESORCE trial.

(2) A revised model (submitted following clarification). This model is also based on the 29th February 2016 DCO of the RESORCE trial. This model includes additional functionality to allow for modelling of independent OS curves for each treatment group and the parametric modelling of time to treatment discontinuation used to estimate regorafenib acquisition costs. This version of the model also includes minor amendments to some of the model parameters, based on issues identified by the ERG during the clarification process (see Section 5.3).

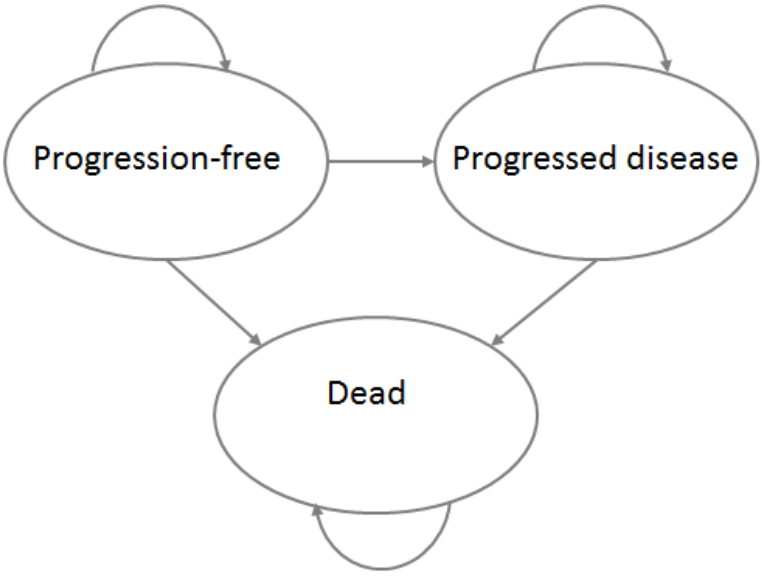
(3) A revised base case model based on the latest DCO of the RESORCE trial (23rd January 2017, submitted following clarification). This model includes updated analyses of time-to-event data; however, the model functionality is restricted to only allow for the modelling of dependent OS curves (including a treatment covariate). Following the identification of a programming error, the company submitted a corrected version of this revised base case model.

The scope of all three models is the same. Throughout this section, the model summary, results and critique relate to the original submitted model, unless otherwise stated. Details of the two models submitted following the clarification process are presented subsequently.

5.2.2 Description of the company's health economic model structure and logic

The general structure of the company's model is presented in Figure 8. The CS states that the company's model adopts a Markov approach; however, this is not an accurate description of the implemented model. Rather, the company's model adopts a partitioned survival approach based on three health states: (1) progression-free; (2) progressed disease, and (3) dead.

Figure 8: Company's model structure



The model operates as follows. Patients enter the model in the progression-free state and receive treatment with regorafenib plus BSC or BSC alone. The probability of being alive and progression-free at any time *t* is taken directly from the observed Kaplan-Meier PFS curves from the RESORCE trial (29 February 2016 DCO, prior to the permitted use of open-label regorafenib).[6] The probability of being alive at any time *t* is modelled using parametric survivor functions (log normal) including a treatment covariate (a hazard ratio [HR] derived from a Cox model) which were fitted to the individual patient-level data (IPD) from the RESORCE trial.[6] The probability of being in the post-progression state at any time *t* is calculated as the difference between the cumulative survival probabilities for OS and PFS. The model is evaluated using 28-day cycles with costs and health outcomes evaluated over a total of 195 cycles (approximately 15 years). Half-cycle correction is applied to account for the timing of events. The model includes post-progression regorafenib treatment for a proportion of patients in the intervention group, based on an analysis of IPD from the RESORCE trial.

HRQoL is principally determined by the presence/absence of disease progression. Disutilities associated with AEs are included for both groups during both the progression-free and post-progression phases. Health utilities are not adjusted by age.

The model includes costs associated with: (i) drug acquisition; (ii) hospitalisation; (iii) medical staff visits; (iv) laboratory test, and (v) radiological tests. Drug costs are adjusted according to the mean daily dose of regorafenib received pre-progression and post-progression. Health state resource use estimates were derived from a survey conducted in 2015 with three leading clinical experts in the field of oncology in the UK. As the model includes post-progression regorafenib treatment for a proportion of patients in the intervention group, costs associated with drug acquisition and associated AEs are included during both the progression-free and post-progression intervals for the intervention group.

The application of different PFS and OS curves, AE rates and treatment costs and other resource use leads to different profiles of costs and health outcomes for the two treatment groups. Incremental cost-effectiveness is calculated as the difference in costs divided by the difference in QALYs for regorafenib and BSC.

Key structural assumptions employed in company's model

The company's model employs the following key structural assumptions:

- The probability of being alive and progression-free over time for regorafenib and BSC is derived from the observed time-to-event PFS outcomes observed within the RESORCE trial.[6] Parametric curves were not fitted to these data as the cumulative PFS probabilities reach zero within the observed period of the trial for both groups.
- Within the company's base case, OS probabilities for each treatment group are modelled using log normal functions. A treatment covariate (an HR) is applied to the regorafenib group (as the baseline) to estimate OS probabilities for the BSC group.
- The company's model includes the costs associated with the use of post-progression regorafenib for a proportion of patients in the intervention group; this reflects the experience of the RESORCE trial.[6] The CS[1] (page 116) notes that the proportion of patients receiving treatment beyond recurrence in the trial is expected to be higher than would occur in clinical practice in England.
- The model includes dose reductions and treatment interruptions to manage AEs based on the experience of the RESORCE trial.[6] This assumption leads to reductions in the acquisition costs of regorafenib. This is assumed to reflect clinical practice in England.
- The model assumes that only AEs of Grade 3/4 severity are associated with impacts on costs and HRQoL. AEs occurring in ≥5% patients in either group of the RESORCE trial population

were included (anaemia, ascites, AST increase, blood bilirubin increase, fatigue, hypertension, hypophosphatemia, and palmar-plantar erythrodysaesthesia syndrome).

- The probability of receiving post-progression regorafenib and the post-progression treatment continuation rate are assumed to be independent of the time of disease progression.

5.2.3 Evidence used to inform the model parameters

Table 19 summarises the evidence sources used to inform the parameters of the company's model. The derivation of the model parameter values using these sources is described in further detail in the following sections.

Table 19: Summary of evidence sources used to inform the model parameters

Parameter type	Parameter	Source(s)
Time-to-event probabilities	PFS – regorafenib	Observed Kaplan-Meier PFS curves from RESORCE[6]
	PFS – BSC	
	OS – regorafenib	Log normal function fitted to IPD for regorafenib group in RESORCE[6]
	OS – BSC	Log normal function fitted to IPD for regorafenib group in RESORCE[6] including a treatment effect covariate (HR)
AEs	AE rate - regorafenib	Analysis of IPD from RESORCE[6]
	AE rate – BSC	Analysis of IPD from RESORCE[6]
HRQoL	Health utility – progression-free state	Tobit regression of data from RESORCE[6]
	Health utility – progressed disease state	
	Disutility – AEs	
Mean dosing	Mean daily regorafenib dose pre-progression	Analysis of IPD from RESORCE[6]
	Mean daily regorafenib dose post-progression	
Treatment continuation rates	Discontinuation probability per cycle whilst progression-free	Based on proportion of patients discontinuing regorafenib for more than one cycle prior to disease progression and median PFS from RESORCE[6]
	Probability of continuing regorafenib post-progression and duration of use	Based on proportion of patients who continued to receive regorafenib after disease progression and post-progression treatment rate in RESORCE[6]
Health state resource use	Visits, tests and hospitalisations. Separate estimates applied for: (1) Progression-free (treated with regorafenib) (2) Progression-free (treated with BSC) (3) Additional resources used at time of progression for regorafenib (4) Post-progression (treated with regorafenib) (5) Post-progression (treated with BSC)	Survey of resource use associated with sorafenib (3 clinical experts)[9]

Parameter type	Parameter	Source(s)
Unit costs	Regorafenib acquisition cost (including PAS)	Bayer[1]
	Unit costs for visits, appointments, hospitalisations, laboratory tests, radiological tests and AEs	NHS Reference Costs 2015/16,[37] Personal Social Services Research Unit (PSSRU) 2016,[38] Akhtar and Chung,[39] Cardiff and Vale Acute Chemistry Repertoire 2016/17 NHS Standards and Indicators,[1] Freedom of Information Act request[1]

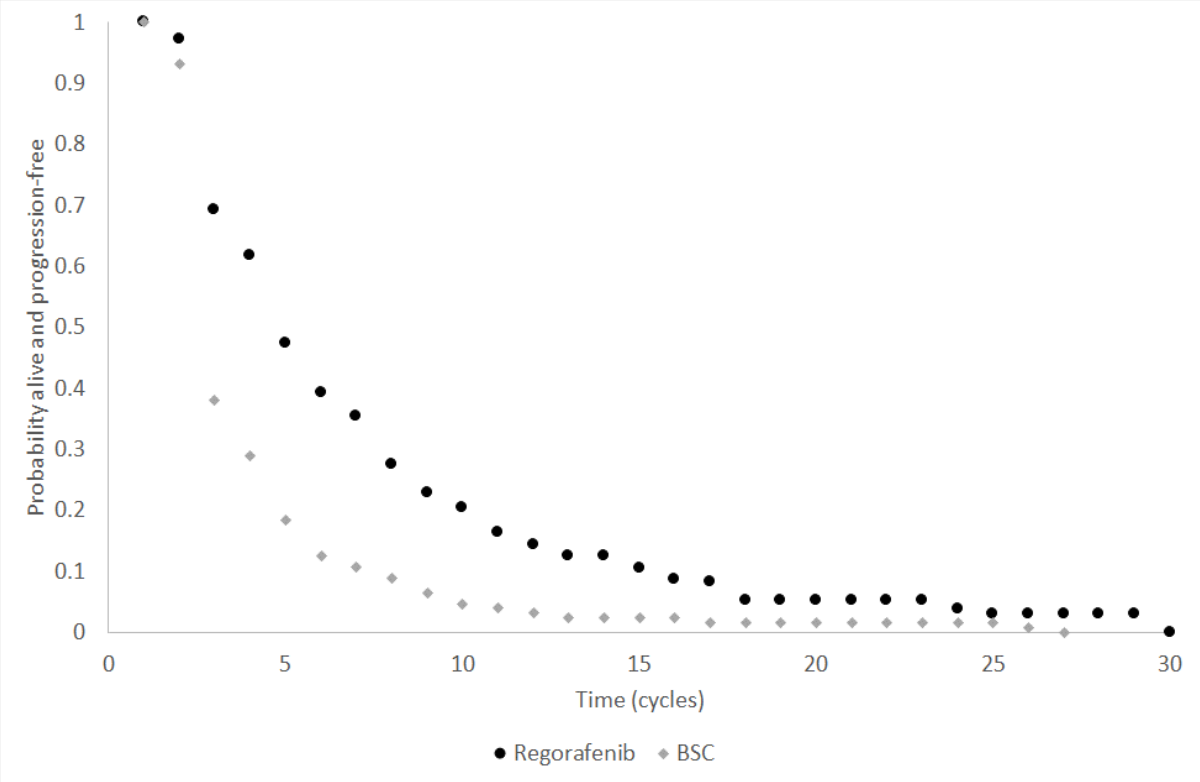
IPD – individual patient-level data; PAS – Patient Access Scheme; PSSRU – Personal Social Research Unit

Time-to-event parameters

Progression-free survival

Within the RESORCE trial, PFS was defined as the time from the date of randomisation to the date of disease progression (radiological or clinical) or death due to any cause (whichever occurred first) (CS,[1] Table 14). Within the company's model, PFS was based on mRECIST criteria. The CS[1] notes that mRECIST "*includes amendments developed for the SHARP trial (27) that require cytopathological confirmation of malignancy to classify pleural effusion or ascites as progression, and that apply more stringent criteria to define progression due to lymph node involvement at the hepatic hilum or new intrahepatic sites (28). It also considers complete tumour necrosis on dynamic imaging studies"* (CS,[1] page 43). Given that the Kaplan-Meier curves for PFS within RESORCE show the complete pattern of PFS for both the intervention and control groups (the cumulative PFS probabilities drop to zero in both groups within the observed period of the trial), the company's model uses these observed time-to-event data directly: parametric survival curves were not fitted to available data. The observed PFS probabilities for each model cycle are presented in Figure 9. Based on these data, the model estimates undiscounted mean PFS durations of 0.47 years for the regorafenib group and 0.23 years for the BSC group.

Figure 9: mRECIST PFS probabilities used in the company's model (derived from company's model)

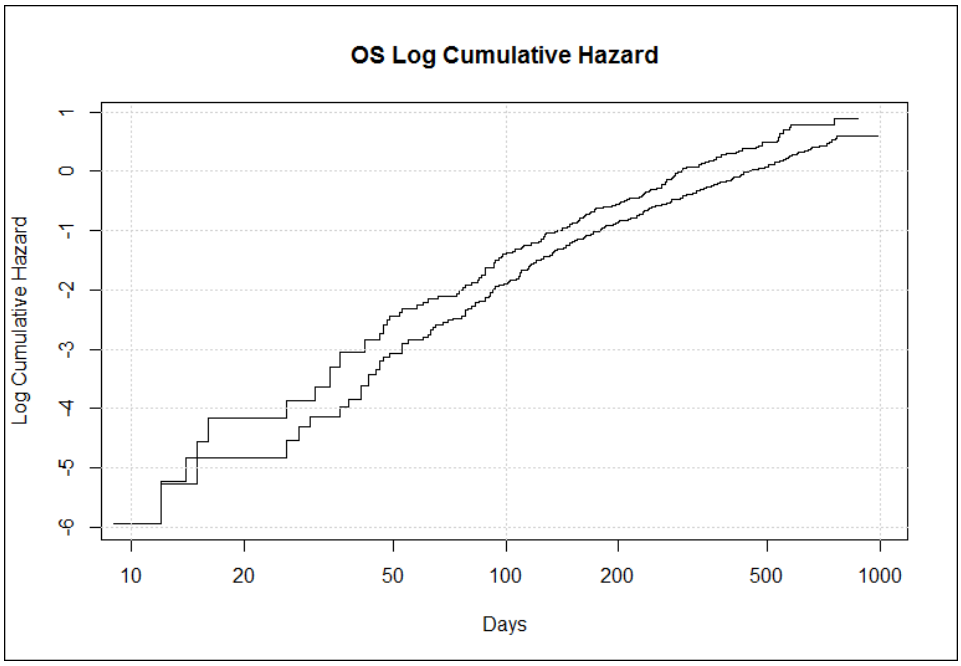


Overall survival

OS is defined as time from the date of randomisation until the date of death due to any cause. Exponential, Weibull, Gompertz, log normal, log logistic and gamma functions were fitted to the available OS time-to-event data. The company explored the use of both independent survival models (fitted separately to each treatment group) and joint models (including a treatment covariate for placebo applied to the regorafenib group as a baseline). Based on an inspection of the log cumulative hazard plots, the company concluded that although the traces for regorafenib and BSC cross at around the 15-day time point, these appear otherwise parallel (see Figure 10). In addition, the company conducted a Grambsch and Therneau test between the Schoenfeld residuals and the log of time: this analysis produced a non-significant *p*-value (p=0.331) which suggests that the proportional hazards assumption is not violated. On the basis of these two pieces of information, the CS argues that the proportional hazards assumption is plausible and the company's base case analysis is based on the jointly fitted model (dependent OS curves). It should be noted however that the treatment effect parameter derived from the jointly fitted models is not used in the company's base case model; instead, an HR derived from a Cox model is used for all parametric model types. The ERG notes that this is inappropriate for accelerated failure time (AFT) models as the treatment effect covariate reflects a constant acceleration factor rather than an HR (see Section 5.3).

Model discrimination was undertaken through examination of goodness-of-fit statistics (the Akaike Information Criterion [AIC] and the Bayesian Information Criterion [BIC]), visual inspection and what is referred to within the CS as "clinical validity." All of these analyses relate only to the jointly fitted model which includes a treatment effect covariate: the CS does not include goodness-of-fit statistics or survival plots for the independently fitted models, although these were provided in response to a request for clarification (presented in Section 5.3). The ERG also notes that the company's exploration of clinical validity does not make reference to the use of subjective clinical judgements about the plausibility of the extrapolation beyond the observed period within the RESORCE trial.[6]

Figure 10: Log cumulative hazard plot for OS (reproduced from CS Figure 14)



Top curve – BSC; bottom curve – regorafenib

The observed and modelled OS predictions parametric OS functions are presented in Figure 11. AIC and BIC statistics for the jointly fitted models are shown in Table 20.

Table 20: Overall survival – AIC and BIC statistics from jointly fitted parametric models (adapted from CS Table 35)

Survivor function	AIC	BIC
Log normal	**5197.513**	**5210.565**
Log logistic	5199.734	5212.787
Gamma	5211.014	5224.067
Weibull	5218.877	5231.929
Gompertz	5238.261	5251.314
Exponential	5239.994	5248.696

Lowest values highlighted in bold

With respect to the statistical goodness-of-fit of the OS models, both the AIC and BIC statistics were lowest for the log normal function (AIC=5197.513, BIC=5210.565). The AIC and BIC were markedly higher for all other models except the log logistic function (AIC=5199.734, BIC=5212.787). The ERG notes that this relates only to the fit of the model to the observed data, which in isolation, represents an insufficient basis for selecting a preferred model.

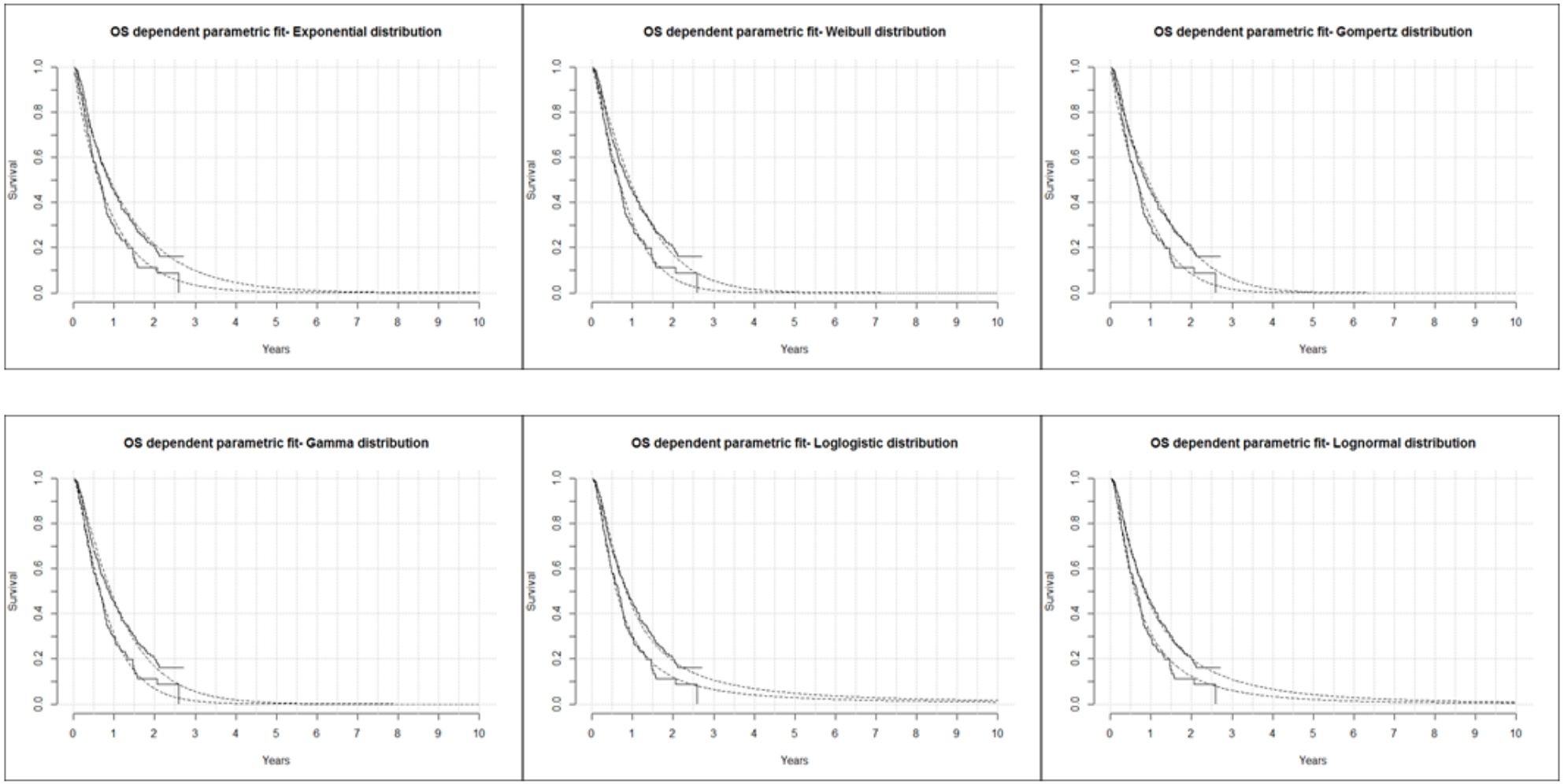
As discussed in the CS, all of the parametric survivor functions considered appear to provide a reasonably good visual fit to the observed OS data, and the log normal and log logistic functions have longer tails than the other candidate parametric functions (see Figure 11).

Within the CS, the company isolates three parametric functions as being potentially clinically valid: the exponential, the log normal and the log logistic models. With respect to the clinical validity of the parametric curve-fitting, the CS notes the following:

- At the 35-cycle timepoint (the last time point for which observed data were available), the log logistic and log normal curves provided the closest fit to the observed Kaplan-Meier curves for both the regorafenib and placebo groups. The exponential curves provide a good approximation for the regorafenib group, but not for the placebo group.
- At the 5-year time point, the log logistic and log normal functions predict a small probability of survival in the BSC arm (log logistic OS probability = 0.03; log normal OS probability = 0.02) and a greater (but small) probability of survival in the regorafenib arm (log logistic OS probability = 0.05; log normal OS probability = 0.04).
- At the 10-year time point, the exponential function predicts approximately zero survival in both the regorafenib and BSC groups, the log logistic function predicts a small survival probability in both groups (OS probability = 0.02 and 0.01 for regorafenib and BSC, respectively) and the log normal function predicts a very small survival probability for regorafenib (OS probability = 0.01 and 0.00 for regorafenib and BSC, respectively).

On the basis of the above information, the log normal model was selected for inclusion in the company's base case analysis. The CS includes sensitivity analyses using each of the alternative parametric OS functions.

Figure 11: Overall survival – parametric curve fits from jointly fitted parametric models (reproduced from CS Figure 15)



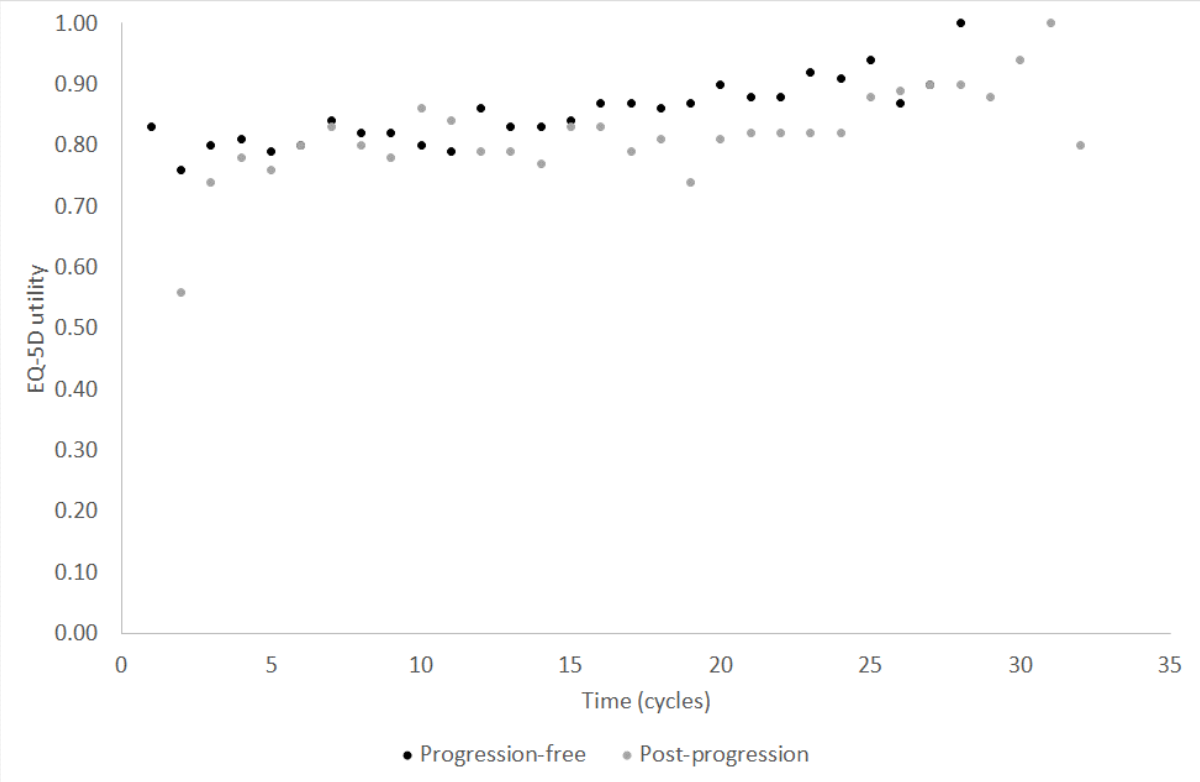
The dotted curves are the fitted extrapolations, and the solid curves are the raw trial data. The upper curves represent the regorafenib arm. The lower curves represent the placebo arm

Health-related quality of life

The company undertook a systematic review of studies reporting HRQoL in HCC (see CS Appendix H[9]). The company considered only those studies which reported HRQoL for HCC patients for both progression-free and post-progressed states (presumably for the sake of consistency, although this is not explicitly stated within the CS). The company's HRQoL review identified only one relevant published study: the placebo-controlled SHARP trial of sorafenib for HCC.[21] The CS notes that the utilities derived from SHARP lack face validity as the value for the post-progression state is higher than that for the progression-free state (progression-free utility=0.6885; post-progression utility=0.7111). These data are not used in the company's base case analysis. Instead, the health utilities employed in the company's model were derived from EQ-5D data collected within the RESORCE trial.[6]

Within the RESORCE trial, EQ-5D questionnaires were self-administered by patients at the start of each treatment visit (the first day of each treatment cycle) whilst the patient was receiving blinded treatment and before they saw the investigator or any study-related procedures were performed. An additional EQ-5D assessment was completed during the "end of treatment" visit.[1] Mean EQ-5D utilities for the pooled treatment population are presented in Figure 12. As shown in the figure, the mean EQ-5D utility at most of the assessment points remains generally high (progression-free utility range = 0.76 to 1.0; post-progression utility range = 0.56 to 0.90).

Figure 12: EQ-5D utility by treatment cycle (both groups pooled, excludes end of treatment visit assessment, point estimates only)



In response to a request for clarification from the ERG (see company's clarification response,[8] question B10), the company provided additional data showing the EQ-5D completion rates for the progression-free and post-progression health states at each assessment visit (see Table 21). The ERG notes that the EQ-5D completion rates were consistently high for the progression-free state, but were subject to considerable attrition following disease post-progression.

Table 21: EQ-5D questionnaire completion rates over time

Cycle	Pre-progression			Post-progression		
	Completed EQ-5D	Alive	Percentage	Completed EQ-5D	Alive	Percentage
1	531	573	93%		0	
2	489	518	94%	4	44	9%
3	283	297	95%	64	224	29%
4	228	255	89%	50	226	22%
5	168	181	93%	60	250	24%
6	123	136	90%	61	248	25%
7	98	118	83%	51	215	24%
8	78	85	92%	48	219	22%
9	65	66	98%	39	211	18%
10	53	56	95%	38	191	20%
11	45	46	98%	37	177	21%
12	33	36	92%	38	159	24%
13	31	31	100%	33	146	23%
14	28	29	97%	24	128	19%
15	20	20	100%	29	116	25%
16	17	20	85%	23	97	24%
17	13	16	81%	20	88	23%
18	10	16	63%	20	79	25%
19	10	10	100%	19	77	25%
20	9	10	90%	16	72	22%
21	9	10	90%	12	54	22%
22	9	10	90%	11	43	26%
23	9	9	100%	11	40	28%
24	6	6	100%	13	35	37%
25	5	6	83%	10	29	34%
26	5	5	100%	7	23	30%
27	3	5	60%	7	20	35%
28	2	3	67%	7	18	39%
29	1	2	50%	6	14	43%
30				5	13	38%
31				3	11	27%
32				1	9	11%

Eight separate regression models were fitted to the available EQ-5D data including combinations of three covariates: (i) treatment group; (ii) progression status, and (iii) AEs. These eight models were each evaluated using: (a) Ordinary Least Squares (OLS) regression; (b) Tobit regression with repeated measurements, and (c) a mixed model for repeated measurements. This resulted in a total of 24 models

being considered. The choice of covariates for inclusion in the final model was explored using a stepwise selection approach. Across the first seven regression models, allocated treatment was not statistically significant (p>0.05), progression status was always significant and AEs were significant in most models. Goodness-of-fit was explored using the adjusted R-squared for the OLS models and using the AIC and BIC for the Tobit and mixed models. The company's preferred analysis was the Tobit model including covariates for progression status and AEs ("Model 8" in CS[1] Table 42). The health utility values applied in the company's model are summarised in Table 22.

Table 22: Health utilities applied in the company's model

Health state / event	Mean utility	SE
Progression-free	0.811	0.00
Progressed disease	0.763	0.01
AEs (disutility)	-0.014	0.01

Regorafenib treatment dose during progression-free phase

The cost of regorafenib treatment during the progression-free and post-progression phases was estimated according to the mean daily dose within the RESORCE trial,[6] based on an analysis of the patient-level data from the trial (see Table 23).

Table 23: Mean daily dose of regorafenib assumed in the company's model

Progression status	Mean daily dose (mg/day)
Progression-free	[redacted]
Post-progression	[redacted]

Regorafenib discontinuation during progression-free phase

During the progression-free phase, [redacted] of the patients are assumed to discontinue regorafenib treatment during each model cycle, based on the proportion of patients who discontinued treatment for more than one cycle prior to disease progression ([redacted]) and the median PFS duration (3.1 months).

Regorafenib continuation during post-progression phase

[redacted] percent of patients who progress are assumed to continue regorafenib treatment after progression, based on the experience of the RESORCE trial.[6] This is applied in the model based on the proportion of progressed patients who received post-progression regorafenib and the sumproduct of the proportion of patients who are new progressors during each cycle and the post-progression regorafenib continuation rate (i.e. the proportion of patients who received 1, 2, 3 etc. additional cycles of regorafenib subsequent to disease progression, see Table 24). This "cycle-cohort simulation"[8] approach assumes that the probability of receiving post-progression treatment and the post-progression treatment continuation rate are independent of the time of disease progression. The ERG 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 24: 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 Table 25.

Table 25: Proportions of patients experiencing adverse events and associated costs

AE type	AE unit cost	Proportion AEs of type - regorafenib	Proportion AEs of type - BSC	AE cost regorafenib	AE cost BSC
Anaemia	£1,283.67 [a]	0.07	0.11	£84.72	£145.05
Ascites	£1,667.00 [b]	0.05	0.17	£83.35	£275.06
AST increase	£1,667.00 [b]	0.16	0.32	£261.72	£533.44
Blood bilirubin increase	£1,667.00 [b]	0.11	0.19	£178.37	£308.40
Fatigue	£1,667.00 [b]	0.08	0.05	£125.03	£85.02
Hypertension	£729.87 [c]	0.25	0.10	£178.82	£75.18
Hypophosphatemia	£1,261.96 [d]	0.14	0.04	£171.63	£51.74
Palmar-plantar erythrodysaesthesia syndrome	£873.37 [e]	0.16	0.02	£142.36	£18.34
Total	-	1.00	1.00	**£1,225.99**	**£1,492.22**

[a] Unweighted mean of total NHS Reference Costs 2015/16[37] for HRG codes SA04G to SA04L (iron deficiency anaemia with CC scores 0 to 14+).

[b] Unweighted mean of total NHS Reference Costs 2015/16[37] for HRG codes GC12G to GC12K (malignant, hepatobiliary or pancreatic disorders, without interventions, with cc score 0 to 6+).

[c] Costed using the total NHS Reference Costs 2015/16[37] for HRG codes EB04Z (hypertension).

[d] Unweighted mean of total NHS Reference Costs 2015/16[37] for HRG codes KC05J to KC05N (fluid or electrolyte disorders with interventions with cc score 0 to 10+).

[e] Costed using the total NHS Reference Costs 2015/16[37] for HRG codes XD57Z (skin conditions, drugs band 1).

Resource use and costs

The company's model includes resource costs associated with: (i) drug acquisition for regorafenib; (ii) health state resource use, and (iii) the management of AEs.

Drug acquisition

Drug acquisition costs for regorafenib were provided by the company. The company has a PAS in place for regorafenib resulting in a price of [redacted] for a packet of 84 x 40mg tablets. The recommended dose of regorafenib is 160mg for each of the first 21 days of a 28-day treatment. Within the company's model, dose reductions and treatment interruptions result in a mean daily dose of [redacted]mg per day during the progression-free phase and [redacted]mg per day during the post-progression phase. Thus, the cost of regorafenib per 28-day treatment cycle including dose reductions and treatment interruptions is [redacted] for patients in the progression-free health state and [redacted] for patients in the post-progression health state. The model assumes that BSC is not associated with any additional drug costs; the ERG notes that this may favour the intervention group as BSC is included in both groups and survival is extended for patients receiving regorafenib. Given that regorafenib is administered orally in tablet form, no administration costs were included in the company's model.

Health state resource use

Health state resource use estimates were based on a physician survey of three leading experts in HCC (conducted in 2015) carried out for sorafenib and assumes that resource use for patients receiving regorafenib is identical to that for patients receiving sorafenib (see Table 26). 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 26: 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 Table 25.

5.2.4 Model evaluation methods

The CS presents the results of the economic analysis in terms of the incremental cost per QALY gained for regorafenib versus BSC. The base case results are presented deterministically based on point estimates of parameters. The CS also includes the results of probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSA) and scenario analyses. The results of the PSA are presented in the form of a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs), based on 1,000 Monte Carlo simulations. The results of the DSA are presented in tabular form with an additional tornado diagram which is limited to the ten most influential model parameters. The distributions applied in the company's PSA are summarised in Table 27.

Table 27: Distributions applied in company's probabilistic sensitivity analyses

Parameter type	Distribution	ERG comment
PFS	Fixed	These parameters are uncertain and should be included in the PSA
OS	Fixed regorafenib baseline, HR for BSC versus regorafenib sampled from normal distribution on log scale	The baseline OS curve is uncertain and should be included in the PSA
AEs	Beta	-
HRQoL	Beta	-
Mean dosing	Gamma	-
Treatment continuation rates	Fixed	These parameters are uncertain and should be included in the PSA
Health state resource use	Gamma	-
Unit costs	Fixed	These parameters are uncertain and should be included in the PSA

5.2.5 Company's model results

Table 28 presents the central estimates of cost-effectiveness derived from the company's original submitted model. Based on the probabilistic version of the model (assuming the log normal function for OS), regorafenib is expected to generate an additional 0.37 QALYs at an additional cost of £12,311 per patient: the corresponding ICER for regorafenib versus BSC is £33,335 per QALY gained. The deterministic version of the model produces a very similar ICER of £33,437 per QALY gained for regorafenib versus BSC.

Table 28: Company's central estimates of cost-effectiveness – regorafenib versus BSC

Probabilistic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. costs**	**ICER (per QALY gained)**
Regorafenib	1.045	[redacted]	0.369	£12,311	**£33,335**
BSC	0.676	[redacted]	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. costs**	**ICER (per QALY gained)**
Regorafenib	1.044	[redacted]	0.367	£12,262	**£33,437**
BSC	0.677	[redacted]	-	-	-

Figure 13 presents the CEAC for regorafenib versus BSC. Assuming a willingness-to-pay (WTP) threshold (λ) of £30,000 per QALY gained, the company's model estimates that the probability that regorafenib produces more net benefit than BSC is 0.21. Assuming a WTP threshold of £50,000 per QALY gained, the company's model estimates that the probability that regorafenib produces more net benefit than BSC is 1.0.

Figure 13: Cost-effectiveness acceptability curves – regorafenib versus BSC (reproduced from CS Figure 17)

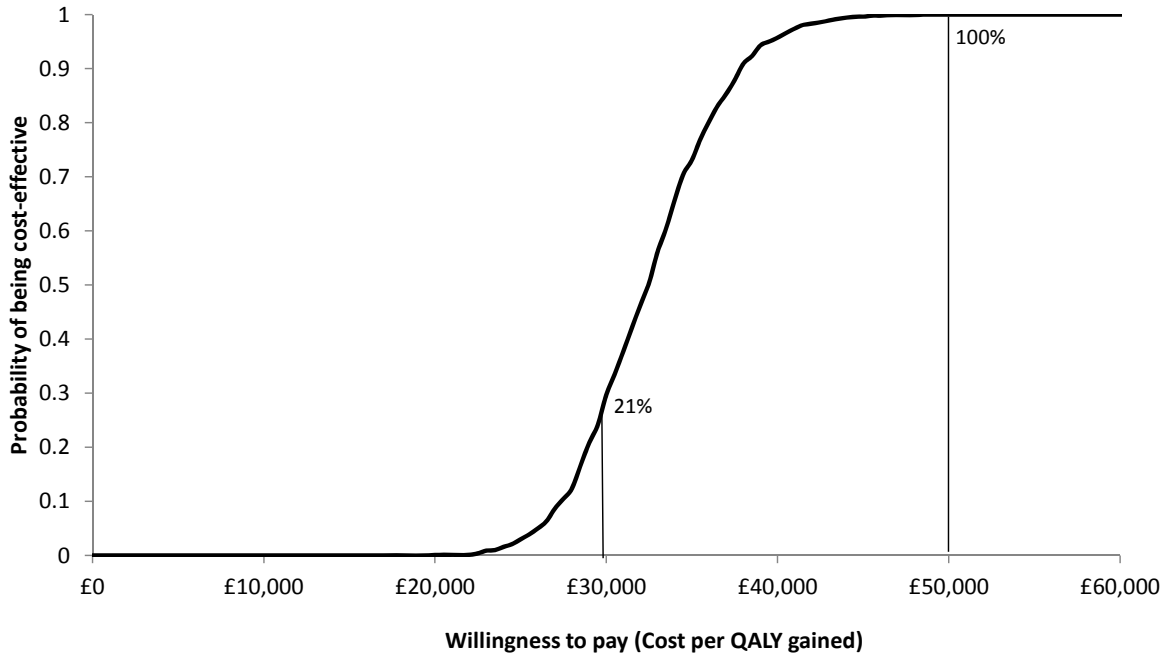
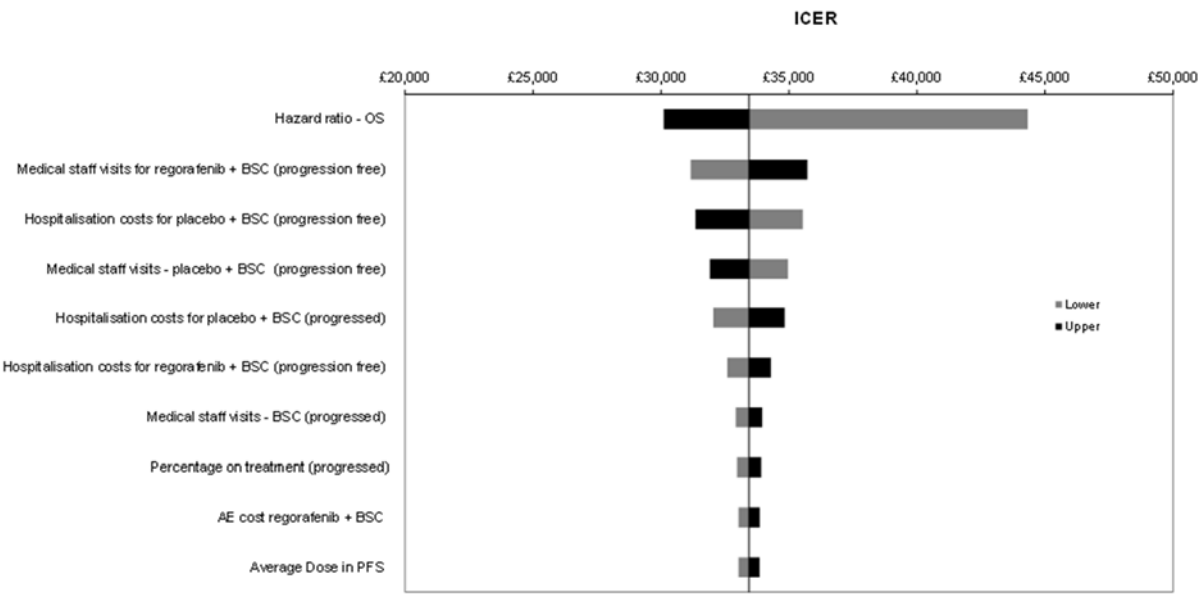


Figure 14 presents the results of the company's DSAs as a tornado diagram (mean parameters varied by +/-30%). Based on this analysis, the most influential model parameters appear to be the HR for OS and assumptions about health state resource use in both treatment groups. Across all analyses, the ICER for regorafenib versus BSC remains lower than £50,000 per QALY gained. It should be noted that the ERG was unable to replicate these analyses using the company's submitted model.

Figure 14: Results of company's deterministic sensitivity analyses – regorafenib versus BSC (reproduced from CS Figure 18*)



** The ERG was unable to replicate the tornado diagram using the submitted model*

Table 29 presents the results of the company's scenario analyses. These analyses indicate that the use of alternative parametric functions to model PFS probabilities has little impact upon the ICER for regorafenib versus BSC. The use of the generalised gamma model for OS produced a notable increase in the ICER for regorafenib plus BSC versus BSC (ICER=£39,466 per QALY gained); the use of all other parametric functions resulted in lower ICERs compared with the base case. The use of health utilities derived from the SHARP trial of sorafenib[21] increased the ICER for regorafenib versus BSC by around £4,000 per QALY gained, however both the company and the ERG have concerns regarding the face validity of these utility estimates. Doubling the disutility associated with disease progression did not have a marked impact upon the model results. The exclusion of dose reductions and interruptions (i.e. assuming a constant fixed dose of 160mg regorafenib per day) increased the ICER for regorafenib versus BSC to £41,206 per QALY gained. The exclusion or restriction of post-progression regorafenib treatment led to decreases in the ICER for regorafenib. The use of shorter time horizons increased the ICER for regorafenib. The ICER for regorafenib versus BSC remained lower than £50,000 per QALY gained across all of the company's scenario analyses.

Table 29: Company's scenario analyses – regorafenib versus BSC (adapted from CS Table 58)

	Inc. costs	Inc. QALYs	ICER (per QALY gained)
Base case	**£12,262**	**0.367**	**£33,437**
PFS – alternative parametric functions			
Log normal	£11,796	0.365	£32,302
Log logistic	£11,915	0.366	£32,571
Weibull	£12,007	0.366	£32,842
Exponential	£12,257	0.367	£33,410
Generalised gamma	£11,842	0.365	£32,456
Gompertz	£12,414	0.368	£33,775
OS – alternative parametric functions			
Log logistic	£12,755	0.395	£32,379
Weibull	£5,747	0.223	£25,726
Exponential	£7,885	0.301	£26,212
Generalised gamma	£9,692	0.246	£39,466
Gompertz	£6,768	0.245	£27,587
Utilities			
Sorafenib utility values (pre-progression = 0.6885; post-progression = 0.7111)	£12,262	0.327	£37,554
Progression disutility doubled	£12,262	0.355	£34,524
Daily average dose of regorafenib			
160mg i.e. no dose reductions or treatment interruptions	£15,111	0.367	£41,206
Post-progression treatment			
None	£10,913	0.367	£29,731*
Maximum of 3 cycles	£11,949	0.367	£32,582
Time horizon			
3 years	£9,647	0.238	£40,555
5 years	£11,004	0.305	£36,112
10 years	£12,029	0.355	£33,862

** The ERG was unable to replicate this ICER. Applying zero duration to the post-progression treatment rates gives a higher ICER of £32,194 per QALY gained*

5.3 Critical appraisal of the company's health economic analysis

This section presents a critical appraisal of the health economic analysis presented within the CS.[1] Section 5.3.1 details the methods used by the ERG to interrogate and critically appraise the company's submitted health economic analysis. Section 5.3.2 summarises the extent to which the company's analysis adheres to the NICE Reference Case.[40] Section 5.3.3 summarises the ERG's verification of the company's implemented model and highlights inconsistencies between the model, the CS,[1] and the sources used to inform the model parameter values. Section 5.3.4 presents a detailed critique of the main issues and concerns underlying the company's analysis.

5.3.1 Methods for reviewing the company's economic evaluation and health economic model

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic evaluation and the underlying health economic model upon which this was based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists[41, 42] to critically appraise the company's model and analysis.
- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.
- Examination of the correspondence between the description of the model reported within the CS[1] and the company's executable model.
- Replication of the base case results, PSA, DSA and scenario analyses presented within the CS.[1]
- Where possible, checking of parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

5.3.2 Adherence of the company's model to the NICE Reference Case

The company's economic evaluation is generally in line with the NICE Reference Case.[40] As discussed in Section 4, the main uncertainty regarding the scope of the company's economic analysis relates to those groups of patients who are included in the marketing authorisation for regorafenib who were excluded from the RESORCE trial.

Table 30: Adherence of the company's model to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The company's model is generally in line with the final NICE scope.[36] However, the ERG notes that the population included in the company's economic analysis relates to patients who have been previously treated with sorafenib, whilst the RESORCE trial[6] which is used to populate the model parameters relates to patients who have progressed on sorafenib. This study specifically excluded patients who discontinued treatment with sorafenib due to toxicity as well as those with Child-Pugh class B disease and those with an ECOG PS of 2 or more.
Comparator(s)	As listed in the scope developed by NICE	The company's choice of comparator is appropriate. BSC the only comparator listed within the final NICE scope.[36]
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains for patients are modelled in terms of QALYs gained.
Perspective on costs	NHS and PSS	The company's economic analysis adopts an NHS and PSS perspective.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's economic evaluation takes the form of a cost-utility analysis. The results of the analysis are presented in terms of the incremental cost per QALY gained for regorafenib (plus BSC) versus BSC alone.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 15-year time horizon. Scenario analyses are also presented for alternative time horizons of 3, 5 and 10 years. The model also includes the functionality to assess the cost-effectiveness of regorafenib over a longer time horizon of approximately 18.3 years, although the impact on the company's ICER is negligible.
Synthesis of evidence on health effects	Based on systematic review	Health outcomes are based on those reported within the RESORCE trial.[6]
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	HRQoL estimates were derived from regression analyses of patient-reported EQ-5D data collected within the RESORCE trial.[6] EQ-5D responses were transformed to preference-based index utilities using the UK tariff.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	

Element	Reference case	ERG comments
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains. The company makes the case that regorafenib should be considered as a life extending treatment given at the end of life (see CS,[1] pages 93-94).
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource components included in the company's model reflect those relevant to the NHS and PSS. Unit costs were valued at 2015/16 prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	All costs and QALYs are discounted at a rate of 3.5%.

5.3.3 Model verification and correspondence between the model, the CS and parameter sources

Double-programming of the deterministic version of the company's model

The ERG rebuilt the deterministic version of the company's base case model in order to verify its implementation. Table 31 presents a breakdown of the health outcomes and costs generated using the company's model and the ERG's rebuilt model.

Table 31: Comparison of company's base case model and ERG's rebuilt model results (undiscounted unless otherwise stated)

	ERG rebuilt model		Company's model	
Outcome	**Regorafenib**	**BSC**	**Regorafenib**	**BSC**
LYGs	1.42	0.90	1.42	0.90
LYGs (discounted)	1.34	0.87	1.34	0.87
QALYs	**1.10**	**0.70**	**1.11**	**0.70**
QALYs (discounted)	1.04	0.67	1.04	0.68
Drug costs – progression-free	[redacted]	[redacted]	[redacted]	[redacted]
Drug costs – post-progression	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation costs	[redacted]	[redacted]	[redacted]	[redacted]
Medical visits costs	[redacted]	[redacted]	[redacted]	[redacted]
Lab tests costs	[redacted]	[redacted]	[redacted]	[redacted]
Radiological tests costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (discounted)	[redacted]	[redacted]	[redacted]	[redacted]

LYG – life year gained

As shown in Table 31, the ERG was able to produce very similar estimates of health gains to those estimated by the company. With respect to the modelled costs, the ERG identified some anomalies:

(i) The ERG identified a programming error whereby the company's formulae to estimate utility decrements due to AEs in the BSC group erroneously refers to the AE probability for patients

receiving regorafenib. This issue was rectified in the company's models submitted following the clarification process.

(ii) The model assumes that there are 13 x 28-day cycles per year. A more appropriate number of cycles is 13.044 (calculated as 365.25/28). This issue was also rectified in the company's revised models submitted following the clarification process.

(iii) Regorafenib treatment costs are calculated using the half-cycle corrected trace of health state occupancy. This assumes that patients who progress or die only receive a half-cycle worth of regorafenib rather than the full cycle's worth of treatment they would be prescribed. The acquisition costs estimated by the ERG are higher than the company's costs as they are based on the health state populations at the beginning of the model cycle.

(iv) The ERG identified some minor issues regarding the calculation of health state hospitalisation costs and medical visit costs. The main discrepancy is a consequence of two sets of programming errors in the company's model. With respect to hospitalisations, the company's model inappropriately applies a zero hospitalisation cost to patients in the regorafenib group who are progression-free but have discontinued treatment (Model worksheet "Model_cost", cells AC284:AC523): the correct hospitalisation cost that should have been applied is £848 (Model worksheet "Live", cell E68 not G68). A similar issue applies to medical visits whereby a zero cost is applied patients in the regorafenib group who are progression-free but have discontinued treatment (Model worksheet "Model_cost", cells AC534:AC773): the correct medical visit cost that should have been applied is £598 (Model worksheet "Live", cell E69 not G69). Even when these errors are corrected, there remains further discrepancy between the costs estimated by the ERG and the company: these discrepancies have the propensity to increase the ICER for regorafenib versus BSC by around £1,000.

(v) The company's model does not include half-cycle correction for the costing of AEs, thereby increasing their costs relative to those estimated by the ERG.

(vi) The AE costs for the BSC group include AEs experienced by a proportion of patients who are assumed to receive regorafenib post-progression. Given that the model does not include the acquisition costs for BSC patients switching to regorafenib, the reasons for the inclusion of these regorafenib-related AE costs are unclear.

In addition, the ERG was unable to reproduce two sets of results reported in the CS using the company's submitted model:

(i) The company's reported DSA which excludes post-progression treatment costs (CS reported ICER = £29,731 per QALY gained [see Table 29]; ERG estimated ICER = £32,194 per QALY gained).

(ii) The company's reported tornado diagram (see Figure 7). The results generated from the tornado diagram in the executable model are very different to those reported in the CS. It is unclear how the reported results were generated using the submitted model.

A further programming error was identified whereby if the Weibull OS model was selected in the company's model, the PFS trace dropped to zero in the second cycle and every cycle thereafter; this affects the company's sensitivity analyses, however the base case ICER remains unaffected.

Notwithstanding these issues and other concerns identified within the critical appraisal (see Section 5.3.4), the ERG is broadly satisfied that the company's model has been implemented as described in the CS.

Correspondence between the model inputs and their original sources

The ERG is satisfied that the inputs applied in the model reflect those described in the CS.[1] However, the ERG did not have access to the raw data used to inform the statistical time-to-event models or the Tobit EQ-5D regression model and therefore cannot verify the accuracy of their implementation.

5.3.4 Main issues identified within the critical appraisal

Box 1 summarises the main issues identified within the ERG's critical appraisal of the company's economic analysis. These issues are discussed in further detail in the subsequent sections.

Box 1: Summary of main issues identified within the company's model

(1) Inappropriate use of a hazard ratio to model treatment effects for OS
(2) Limited consideration of clinical plausibility of extrapolated OS curves
(3) Concerns regarding the modelling of time to treatment discontinuation to estimate regorafenib acquisition costs
(4) Inclusion of potentially unrealistic cost savings due to dose reductions/interruptions
(5) Concerns regarding expert clinician survey to inform health state resource use
(6) Likely overestimation of the cost of a general ward bed day
(7) Use of potentially inappropriate NHS Reference Costs
(8) Questionable reliability of post-progression utility estimate
(9) Inadequate consideration of uncertainty

(1) Inappropriate use of a hazard ratio to model treatment effects for OS

The company elected to use jointly fitted survival models rather than independently fitted OS models based on the argument that the proportional hazards assumption is plausible after examining the log

cumulative hazard plots and undertaking a statistical test using the observed OS data. The company then used the HR for OS reported in the RESORCE study[6] to derive the OS model for the BSC group instead of the treatment effect estimated via the jointly fitted model. The ERG disagrees with the company's approach to model the OS data for several reasons.

Firstly, not all the parametric distributions fitted by the company belong to the family of parametric proportional hazards models. For example, the log normal, log logistic and gamma are AFT models and do not make assumptions of proportional hazards. It is not appropriate to apply an HR to an AFT model. Secondly, where applicable, the validity of the proportional hazards assumption in the observed period does not necessarily hold in the unobserved period; the clinical validity of the proportional hazards assumption should be assessed in the extrapolation period. Thirdly, the goodness-of-fit of the fitted OS curve in the BSC arm using the reported HR in the RESORCE study was not assessed. The AIC and BIC statistics shown in Table 20 and the observed and predicted OS curves shown in Figure 11 were generated using the treatment effect coefficient estimated from the jointly fitted models, not the reported HR. This inappropriate use of the reported HR may have an impact on the ICER for regorafenib versus BSC.

In response to a request for clarification on this matter (see company's clarification response,[8] question B2), the company presented the results of an analysis in which the OS curve for the BSC group was modelled using the log normal function including a constant acceleration factor derived from the jointly fitted model. In this scenario, the ICER is higher than the company's original base case (ICER=£37,239 per QALY gained).

In addition, the company's clarification response also included further analyses in which independent parametric curves were fitted to the available OS data; these independent models do not require a treatment effect covariate and do not impose restrictive assumptions about proportional hazards/odds between competing treatment groups. Within these analyses, the log normal curve resulted in the lowest AIC and BIC, although the AIC for the generalised gamma function was only slightly higher. The curve fits appear similar between the candidate OS functions.

Table 32 presents the results of the company's re-analysis of the OS data using the independently fitted models. As shown in the table, the ICER generated using log normal survival functions fitted independently to the OS data for each treatment group is similar to the ICER generated using the company's base case model.

Table 32: Company's original base case results and results generated using independently fitted OS curves (adapted from company's clarification response, question B2)

Scenario	Inc. costs	Inc. QALYs	ICER (per QALY gained)
Company's original base case - OS modelled using dependent log normal functions with HR treatment effect	£12,262	0.367	£33,437
Independently fitted OS models (no treatment effect covariate)			
Log logistic	£12,040	0.360	£33,463
Log normal	£12,276	0.368	£33,334
Weibull	£6,161	0.244	£25,248
Exponential	£7,670	0.290	£26,428
Generalised gamma	£12,438	0.377	£33,028
Gompertz	£7,165	0.265	£27,033

Inc. – incremental

(2) Limited consideration of clinical plausibility of extrapolated OS curves

The ERG notes that the discussion of clinical validity within the CS relates only to the differences between the observed and predicted OS estimates at cycle 35 (another measure of goodness-of-fit rather than plausibility), and differences between the extrapolated OS estimates derived from the exponential, log normal and log logistic models at the 5-year and 10-year timepoints. The CS does not contain any formal assessment of the clinical plausibility of the extrapolated survival times.

In contrast to the parametric model selected within the company's base case analysis, one clinical advisor to the ERG did not consider the log normal OS distribution to be clinically plausible. They noted that the model-predicted sustained gap in OS between the regorafenib and placebo groups beyond 35-cycles produced by the log normal function was unrealistic within the progressed HCC population. As a consequence, the advisor therefore considered the log logistic and generalised gamma functions to also be clinically implausible. The advisors' preferred curve was the Weibull function, although they noted that both the exponential and Gompertz functions were very similar and were therefore also potentially plausible. The ERG's second clinical advisor did not state a strong preference in favour of any of the individual parametric functions.

(3) Concerns regarding the modelling of time to treatment discontinuation to estimate regorafenib acquisition costs

The ERG has concerns regarding the approach taken to estimate the amount of regorafenib received over time. The company's model estimates time on treatment separately during the progression-free 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 [redacted] 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 ([redacted]) 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" corresponds to the assumptions made in the company's original submitted model. The ERG notes that this approach assumes that all patients who are still on treatment at the DCO immediately discontinue regorafenib. This is clearly inappropriate, hence the subsequent analyses of "Curve A" are not considered further within this ERG report.

Figure 15: "Curve A" – Kaplan-Meier curve for time to treatment discontinuation assuming that patients discontinue treatment at the 29th February 2016 cut-off (reproduced from company's clarification response, question B8)

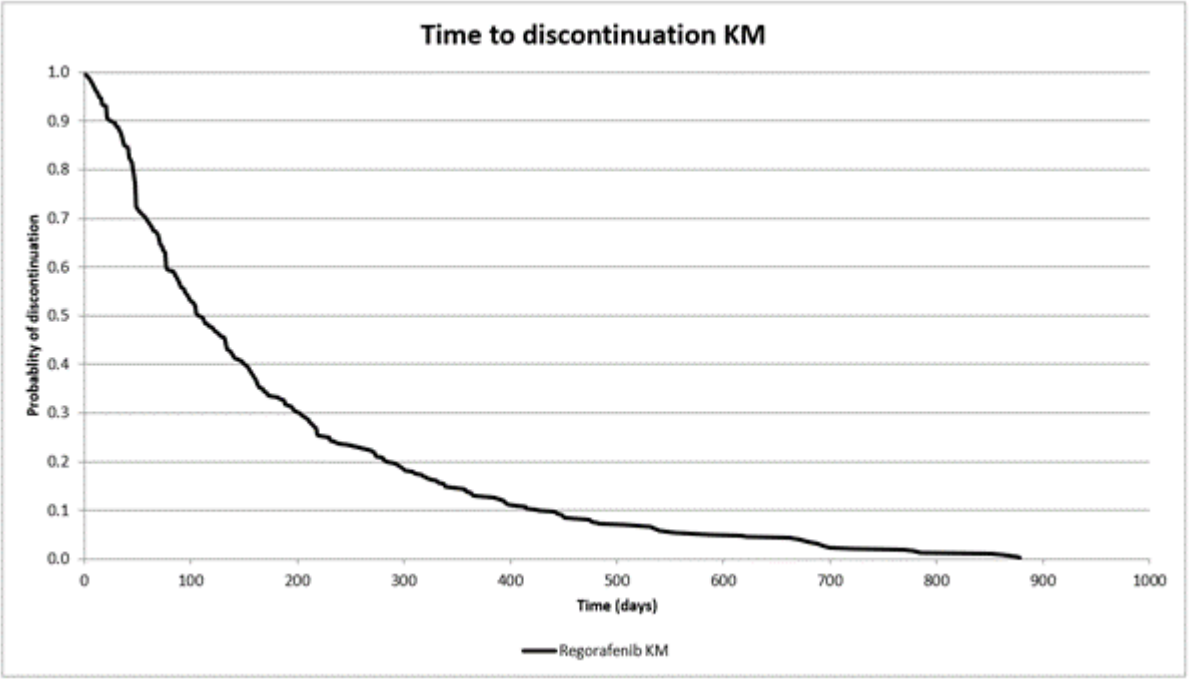
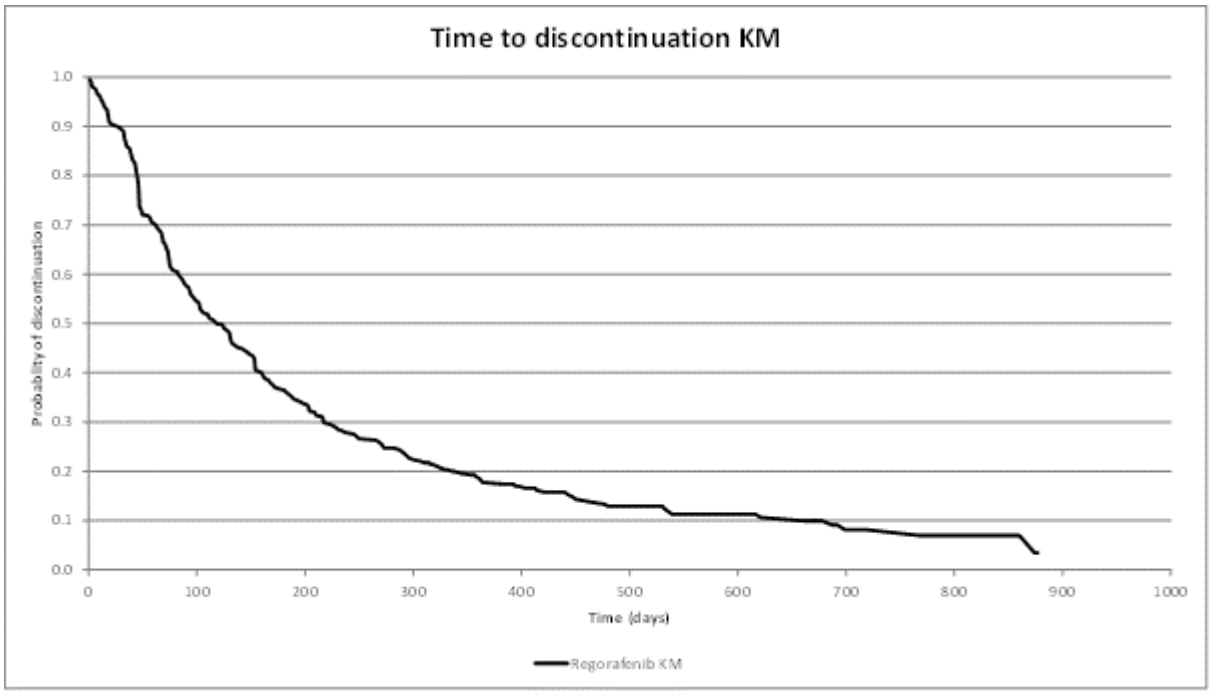


Figure 16: "Curve B" – Kaplan-Meier curve for time to treatment discontinuation assuming that patients on treatment on 29th February 2016 are censored (reproduced from company's clarification response, question B8)



Within their clarification response,[8] the company fitted parametric curves (log normal, log logistic, Weibull, exponential and Gompertz) to the available data on time to treatment discontinuation. The generalised gamma function was not considered; the company's clarification response does not explain this omission. Statistical goodness-of-fit of the candidate parametric models was considered through the use of AIC and BIC statistics (see Table 33). Plots of the fitted parametric curves are shown in Figure **17**. As shown in Table 34, the use of these parametric curves increases the ICER to the range £38,741 to £39,207 per QALY gained.

Table 33: AIC and BIC statistics for parametric models fitted to time to treatment discontinuation data, patients on treatment on 29th February 2016 censored (adapted from company's clarification response, question B8)

Distribution	AIC	BIC
Log logistic	**1145.59**	**1153.44**
Log normal	1148.23	1156.07
Gompertz	1159.86	1167.70
Weibull	1176.79	1184.63
Exponential	1179.11	1183.03

Lowest values highlighted in bold

Figure 17: Parametric models – time to treatment discontinuation, patients on treatment on 29th February 2016 censored (reproduced from company's clarification response, question B8)

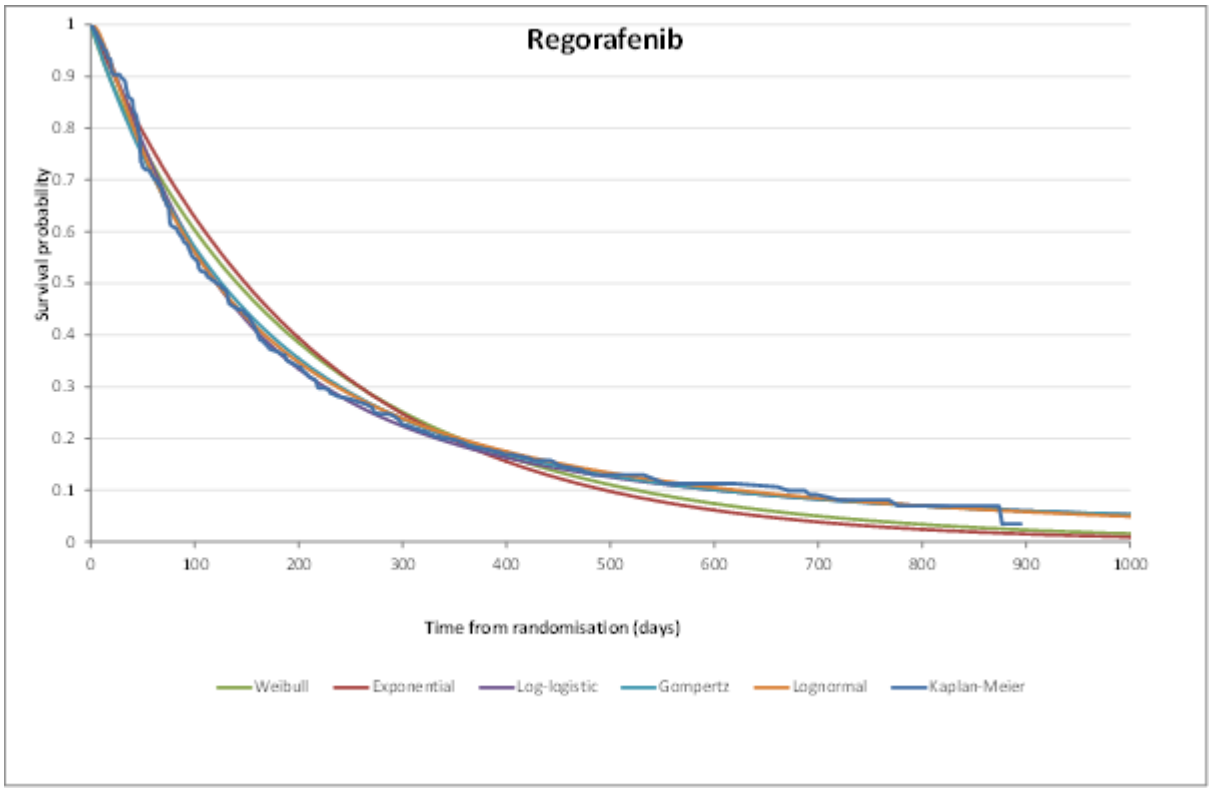


Table 34: Cost-effectiveness results for alternative curves fitted to time to treatment discontinuation, patients on treatment on 29th February 2016 censored (adapted from company's clarification response, question B8)

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. 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 Table 29). 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 35 summarises the completion rates for the 2007 and 2015 surveys.

Table 35: 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 Table 36). 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.

Table 36: Assumed resource use and costs per 28-day treatment cycle

Resource item	Unit cost	Progression-free - proportion using resource				Post progression - proportion using resource			
		Pooled 2007 & 2015 surveys		2015 survey only		Pooled 2007 & 2015 surveys		2015 survey only	
		Sorafenib*	BSC	Sorafenib*	BSC	Sorafenib*	BSC	Sorafenib*	BSC
Hospitalisation									
General ward	£801								
Duration of stay (days)	-								
A&E admission	£138								
Estimated cost per hospitalisation [1]	-								
Hospital outpatient appointments									
Oncologist	£163								
Hepatologist	£253								
Gastroenterologist	£132								
Clinical nurse specialist	£130								
Palliative care team	£131								
Radiologist	£135								
Macmillan nurse	£73								
Follow up visits									
GP visit	£36								
Nurse visit	£36								
Specialist visit	£151								
Tests									
AFP	£3.03								
Liver function	£2.78								
Biochemistry	£1.34								
Complete blood count	£2.65								
International normalised ratio	£3.43								
Endoscopy	£743								
Radiological tests									
CT scan of abdomen	£122								
MRI of abdomen	£238								

** Assumed to apply to regorafenib; [1] Calculated multiplying the estimated length of stay by the estimated cost of a bed day on a general ward (£801); [2] 0.93 at progression; [3] 0.78 at progression; [4] 0.60 at progression; [5] 0.04 at progression; [6] 1.00 at progression; [7] 0.67 at progression*

(5) Likely overestimation of the cost of a general ward bed day

The company's model includes the cost of a general ward bed day of £801: this estimate was derived from a response to a Freedom of Information Act request. According to the CS,[1] this reflects the fully absorbed cost. No further details of the derivation or source of this value are presented within the CS and it is unclear why current NHS Reference Costs[37] have not been used (as was done within the previous sorafenib appraisal). The ERG notes that based on the NHS Reference Costs 2015/16,[37] for non-elective long-stay admissions, the mean cost per bed day weighted by the number of total finished consultant episodes (FCEs) is £572.44. This estimate is lower than the unit cost applied within the company's model.

(6) Use of potentially inappropriate NHS Reference Costs

The ERG notes that some of the costs included in the company's model may not reflect the best use of the available NHS Reference Costs. These are detailed below.

1. The company's model assumes that the cost of an A&E admission is £138.00, based on the total number of FCEs. The ERG notes that the weighted mean cost for patients admitted to A&E excluding episodes relating to emergency dental work and patients who are dead on arrival is £204.11 per episode. The ERG believes that this represents a more appropriate unit cost.
2. The company's model uses a cost of £131.00 for a palliative care team visit; the CS states that this is based on the follow-up cost for a face-to-face consultant-led follow up outpatient appointment for pain management contained in the NHS Reference Costs 2015/16.[37] However, the ERG considers that it may be more appropriate to use a weighted average of outpatient palliative pain management costs (healthcare resource group [HRG] codes SD04A & SD05A); this corresponds to a weighted average of £119.03 per visit. The ERG acknowledges that it asked the company to use a cost of £131 in the clarification process.
3. The company uses a cost £151.12 per specialist follow-up visit. The ERG was unable to identify this value within the NHS Reference Costs 2015/16.[37] The ERG considers that the tariff cost for a medical oncology consultant-led, non-admitted face-to-face visit would be more appropriate (cost=£162.84).
4. The model assumes a cost of £238.00 for an abdominal MRI scan based on HRG code RD03Z. The ERG was unable to find this value within the NHS Reference Costs 2015/16.[37] The ERG believes that the most appropriate tariff value is that of an outpatient MRI scan (cost=£202.70).
5. The company's costing of AEs uses an unweighted average for the costs applicable to each type of AE. The use of weighted mean costs changes the overall AE cost (for those experiencing AEs) to £1,184.11 for regorafenib and £1,365.07 for BSC alone.

(7) Questionable reliability of post-progression utility estimate

The ERG has two concerns regarding the health utilities included in the company's model. These relate to: (i) the questionable reliability of the post-progression utility estimate, and (b) the potential underestimation of the impact on regorafenib treatment on HRQoL.

(a) Questionable reliability of post-progression utility estimate

The ERG has doubts about the face validity of the utility values collected in the RESORCE trial[6] as the utility decrement associated with progression was only -0.048. This point was raised with the company at the clarification stage[8] (question B11). In response, the company stated that: "*We consider the values derived from the RESORCE study to be face-valid.*" The company also stated that the cost-effectiveness of regorafenib was found to be relatively insensitive to doubling the decrement associated with progression (see CS,[1] Table 58).

The ERG believes that the central estimate of the disutility associated with progression is likely to represent an underestimate. As shown in Table 21, the EQ-5D response rate for patients in the pre-progression state was high (typically greater than 90%) and is thus representative of patients in the RESORCE trial,[6] although the ERG notes that the estimated pre-progression EQ-5D score of 0.811 appears high for a population with advanced HCC who have previously progressed on sorafenib. The percentage of patients in the post-progression state completing the EQ-5D was much lower, typically between 20% and 30%, which raises the possibility that only the patients in the best health at that time point completed the EQ-5D questionnaire.

(b) Potential underestimation of utility decrements associated with regorafenib treatment

Within the RESORCE trial,[6] the EQ-5D questionnaire was provided on the first day of each treatment cycle, when a patient had previously spent a week without treatment. The EQ-5D assesses the respondent's health at the time of completion and does not consider patients' health over previous days or weeks. As such, any deleterious effects of regorafenib treatment may not be captured due to the timing of administration of the EQ-5D.

(8) Insufficient consideration of uncertainty

The ERG notes that the company's PSA includes a number of parameters which are held fixed. These include: (a) the PFS curves; (b) the baseline OS curve for the regorafenib group; (c) the post-progression treatment continuation rates, and (d) the unit costs associated with health state resource use (see Table 27). These are all uncertain variables and as such they should have been included in the company's PSA. Consequently, the company's PSA underestimates the uncertainty surrounding the incremental costs and effects of regorafenib. In response to a request for clarification[8] (question B5), the company amended the model to include uncertainty surrounding the PFS curves. However, the other time-to-

event curves (OS and time to treatment discontinuation) remain fixed within the PSA. This may be important as the use of log normal distributions (as used to model OS) tend to increase probabilistic ICERs relative to their deterministic counterparts. Owing to time constraints, the ERG did not modify the company's uncertainty analysis.

5.4 Model amendments and revised base case submitted following clarification

Following the clarification process, two further amended versions of the model were submitted by the company.

Post-clarification model 1: Company's revised model with increased functionality and corrections using RESORCE 29th February 2016 data cut-off

Following the clarification process, the company submitted a revised model that addresses some of the issues identified within this critical appraisal. The key features of this revised model relate to additional functionality to select:

(i) Separate parametric OS curves fitted independently to each treatment group (without a treatment effect covariate)

(ii) The treatment effect covariate generated from the jointly fitted model rather than the Cox-derived HR

(iii) The use of a palliative care team visit cost of £131 (rather than £136, as applied in the original model)

(iv) The use of 13.044 cycles per year (rather than 13.00, as applied in the company's original model)

(v) The correction of the programming error in which the QALY loss for AEs in the BSC group was erroneously linked to the regorafenib AE rate

(vi) The resource use estimates derived from the earlier clinical survey used in the previous sorafenib appraisal (2007 and 2015 surveys combined)[5]

(vii) The use of parametric time to treatment discontinuation curves to estimate drug acquisition costs. A further option is enabled which allows this analysis to be based on all patients on treatment discontinuing at the 29th February DCO or being censored at this DCO. The ERG notes however that the company incorrectly truncated the total treatment costs at 29 cycles, thereby ignoring additional costs incurred due to the tail of the curve.

A single preferred base case analysis was not presented using this version of the model.

Post-clarification model 2: Company's revised base case model using RESORCE 23rd January 2017 data cut-off

Subsequent to the submission of the first post-clarification model, the company submitted a further revised model and revised base case analysis which incorporated updated time-to-event data. The company investigated the possibility of using a longer follow-up period with adjustments made for patients who had started on BSC who subsequently received regorafenib treatment. However, as only four of the 194 patients (2.1%) initially randomised to receive BSC received regorafenib the company did not perform statistical adjustment for treatment switching '*as this represents such a small proportion of patients*'. The ERG notes that this will be unfavourable to regorafenib. However, the company only analysed dependent OS curves including a treatment effect covariate. The company's clarification response[8] (question B1) provides results using this version of the model which include some of the adjustments above (including the use of parametric time to treatment discontinuation curves), but does not, however, have the functionality to apply independently fitted OS curves for each treatment group '*due to time constraints'*; this makes these results difficult to interpret. The key features of the company's revised base case analysis are:

- Use of 23rd January 2017 DCO
- PFS modelled using observed Kaplan-Meier curves
- OS modelled using dependent log normal functions using a revised treatment effect covariate (note: it is unclear whether this is a revised HR or the jointly fitted model treatment effect covariate)
- Time to treatment discontinuation modelled using log logistic function (note: the error relating to the truncation of this curve at 29 cycles also applies within this model version).
- Utilities based on RESORCE trial[6] (as per the original CS[1])
- Correction of the costs of palliative care team visits, the number of cycles per year and the BSC AE rate programming error (see clarification response,[8] questions B16, B22 and B24)
- Use of the 2015 sorafenib resource use survey (as per the original CS[1])

The company's revised deterministic base case results are presented in Table 37: these results also include the correction of a further programming error identified by the company. The company's revised base case analysis leads to a slightly higher ICER compared with their original model: the deterministic ICER for regorafenib versus BSC is estimated to be £36,050 per QALY gained.

Table 37: Company's revised base case cost-effectiveness results – regorafenib versus BSC

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Regorafenib	1.073	[redacted]	0.406	£14,625	**£36,050**
BSC	0.668	[redacted]	-	-	-

Inc. – incremental

The company's clarification response[8] (question B1) and the further revised analyses received following the company's identification of the programming error include additional scenario analyses using their revised base case model. However, as the ERG has concerns which are not reflected in the company's revised base case model (in particular, the inappropriate use of dependent OS curves and the use of an erroneously truncated time to discontinuation curve), the results of these additional scenario analyses are not presented here.

5.5 ERG's exploratory analyses

5.5.1 ERG's exploratory analyses - methods

The ERG undertook seven sets of exploratory analyses. All analyses were undertaken using the deterministic version of the revised model submitted by the company following clarification, which uses the 29th February 2016 DCO (post-clarification model 1). It was not possible to incorporate all of the ERG's preferred assumptions using the model which incorporates data from the January 23rd DCO (post-clarification model 2), hence all exploratory analyses are limited in this respect. Additional sensitivity analyses were undertaken using the ERG's preferred base case scenario. These include the exploration of alternative parametric functions for OS and time to treatment discontinuation, alternative assumptions regarding HRQoL, an alternative interpretation of the resource use survey data, and the optimistic assumption of cost savings associated with a sustained mean daily dose of 120mg regorafenib.

Exploratory analysis 1: Correction of unequivocal model errors and use of alternative unit costs

The following corrections were made to the company's revised model:

- The number of cycles per year was set equal to 13.044*
- The programming error relating to the AE rate for the BSC group was corrected*
- The programming errors relating to the hospitalisation and medical visit costs for patients during the progression-free phase were corrected
- The proportion of BSC patients receiving post-progression regorafenib was set equal to zero.

** These changes were added by the company as options after the clarification process*

In addition, the following unit costs were amended as follows:

- The cost per A&E visit was set equal to £204.11.
- The cost per palliative care team visit was set equal to £119.03.
- The cost per specialist follow-up visit was set equal to £162.84
- The cost per abdominal MRI scan was set equal to £202.70.
- The cost of each AE were set equal to £1,184.11 for the regorafenib group and £1,365.07 for the BSC group.

All subsequent exploratory analyses include these corrections and amendments.

Exploratory analysis 2: Inclusion of more appropriate general ward bed day cost

The general ward bed day cost was amended to reflect the weighted cost of an excess bed day (£572.44 per bed day).

Exploratory analysis 3: Use of full pack dosing

Cost savings due to reduced dosing and treatment interruptions were removed from the model: this was implemented by setting the mean daily dose of regorafenib equal to 160mg per day.

Exploratory analysis 4: Removal of half-cycle correction for drug acquisition costs

Total drug costs were calculated using the proportion of patients alive and on treatment at the beginning of each model cycle. The use of half-cycle correction was retained for all other cost and QALY calculations.

Exploratory analysis 5: Use of combined 2007 and 2015 survey costs

The results of the pooled 2007 and 2015 surveys were used to inform health state resource use. To address the apparent logical inconsistencies in the results of the surveys, it was assumed that the proportions of patients requiring hospitalisation for those on regorafenib and BSC were correct and that these patients were only hospitalised once per month. This is the same approach used by the company in their sensitivity analyses provided post-clarification.

Exploratory analysis 6: Use of independent Weibull functions to model OS

The model was amended to use the independent Weibull functions for OS (excluding a treatment effect covariate).

Exploratory analysis 7: Use of a fully extrapolated log logistic time to discontinuation curve (patients on treatment at 29th February 2016 censored)

In line with the company's revised base case, the log logistic model was selected to model time to treatment discontinuation, based on the time-to-event data which includes censoring of patients remaining on treatment at the 29th February 2016 DCO. A new worksheet was added by the ERG which estimates discounted drug acquisition costs per cycle based on the log logistic function. The worksheet includes full extrapolation up to 10-years (the last timepoint from the company's parametric curve-fitting). A logical consistency constraint was also added to ensure that the probability of being alive and on treatment could not be greater than the survival probability predicted by the selected OS curve. This analysis also includes the assumption of full pack dosing.

Exploratory analysis 8: ERG's preferred base case

The ERG's preferred base case includes exploratory analyses 1 to 7.

5.5.2 Results of the ERG's exploratory analyses

Table 38 presents the results of the ERG's exploratory analyses.

Table 38: Results of the ERG's exploratory analyses

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		-	-	-
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		-	-	-
*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		-	-	-
*Exploratory analysis 3: Use of full pack dosing**					
Regorafenib	1.048	[redacted]	0.368	£15,508	**£42,151**
BSC	0.680		-	-	-
*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		-	-	-
*Exploratory analysis 5: Use of combined 2007 and 2015 survey costs**					
Regorafenib	1.048	[redacted]	0.368	£20,297	**£55,166**
BSC	0.680		-	-	-
*Exploratory analysis 6: Use of independent Weibull functions to model OS**					
Regorafenib	0.896	[redacted]	0.265	£10,242	**£38,683**
BSC	0.632		-	-	-
*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		-	-	-
*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		-	-	-

Inc. – incremental

** Exploratory analyses 2-8 also include corrections and amendments made in exploratory analysis 1*

The correction of model errors and the use of more appropriate unit costs does not have a marked impact upon the ICER for regorafenib versus BSC (ICER=£34,406 per QALY gained). In addition, the use of a lower cost per hospital bed day also has only a marginal impact upon the ICER (ICER=£34,276 per QALY gained). The removal of the half-cycle correction of acquisition costs, the full costing of all prescribed packs of regorafenib, the use of the pooled 2007 and 2015 resource use surveys and the use of a fully extrapolated log logistic function to estimate time to treatment discontinuation each

individually result in a less favourable ICER relative to the company's base case scenario (ICER range = £36,235 to £59,120 per QALY gained). The use of independent Weibull functions to model OS also increase the ICER for regorafenib versus BSC (ICER=£38,683 per QALY gained). The ERG's preferred base case, which includes all of the above amendments (exploratory analyses 1 to 7), results in an ICER for regorafenib versus BSC of £81,081 per QALY gained. The ERG notes that this base case includes data from the 29th February 2016 DCO of the RESORCE study: this is because the company's revised base case model which uses the January 23rd 2017 DCO does not include the functionality for modelling independently fitted OS curves. The ERG prefers the use of independent curves and believes that the company's revised base case which uses the later DCO were less appropriate due to the use of dependent curves. The ERG's base case ICER for regorafenib using both the ERG's preferred assumptions and the later DCO of the RESORCE study is unknown and cannot be assessed using the available versions of the company's model.

5.5.2 Additional sensitivity analyses using the ERG's preferred base case model

Table 39 presents additional sensitivity analyses undertaken using the ERG's preferred base case.

Table 39: Additional sensitivity analyses undertaken using ERG preferred base case model

Scenario	Inc. QALYs	Inc. costs	ICER (regorafenib versus BSC)
ERG base case	0.265	£21,468	£81,081
Alternative OS functions			
OS - exponential	0.311	£22,690	£72,959
OS – log normal	0.369	£27,617	£74,744
OS – log logistic	0.361	£27,363	£75,792
OS – Gompertz	0.286	£20,757	£72,642
OS – generalised gamma	0.378	£27,893	£73,826
Alternative time to treatment discontinuation functions			
TTTD - exponential	0.265	£19,625	£74,122
TTTD – Weibull	0.265	£19,942	£75,317
TTTD – log normal	0.265	£21,606	£81,602
TTTD – Gompertz	0.265	£21,633	£81,703
Alternative utility values			
Utilities from SHARP trial	0.232	£21,468	£92,719
Disutility due to progression doubled (state utility=0.715)	0.260	£21,468	£82,689
Disutility due to progression tripled (state utility=0.667)	0.254	£21,468	£84,362
Alternative interpretation of company's resource use survey			
Number of hospitalisations per month estimated per month assumed to apply to the entire population.	0.265	£22,006	£83,114
Inclusion of dose reductions			
Indefinite dose reduction to 120mg/day	[redacted]	[redacted]	[redacted]

Inc. – incremental

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 regorafenib which accounts for dose reductions and treatment interruptions observed within the RESORCE trial.

Based on the probabilistic version of the company's original model (assuming the log normal function for OS), regorafenib is expected to generate an additional 0.37 QALYs at an additional cost of £12,311: the corresponding ICER for regorafenib versus BSC is £33,335 per QALY gained. The deterministic version of the company's base case model produces a very similar ICER of £33,437 per QALY gained. Assuming a willingness-to-pay (WTP) threshold (λ) of £30,000 per QALY gained, the company's model indicates that the probability that regorafenib produces more net benefit than BSC is 0.21. Assuming a WTP threshold of £50,000 per QALY gained, the probability that regorafenib produces more net benefit than BSC is 1.0.

The ERG critically appraised the company's economic analysis and double-programmed the deterministic version of the company's model. The ERG's critical appraisal identified a number of issues relating to the company's economic analysis and the evidence used to inform it. The most pertinent of these include: (i) the inappropriate use of an HR to model relative treatment effects on OS; (ii) limited consideration of the clinical plausibility of the extrapolated OS curves; (iii) concerns regarding the modelling of time to discontinuation of regorafenib; (iii) the inclusion of potentially unrealistic cost savings due to dose reductions and treatment interruptions; (iv) the use of the 2015 survey of three experts to inform health state resource use (and the exclusion of the earlier survey used to inform the earlier sorafenib appraisal); (v) concerns regarding the appropriateness of several unit cost estimates; (vi) the questionable reliability of the post-progression utility estimate and (vii) the inadequate representation of parameter uncertainty.

Following the clarification process, the company submitted two further versions of the model: (i) a revised model which includes additional functionality to address some of the issues identified within the ERG's critical appraisal, and (ii) a revised base case model which includes less functionality but uses the latest January 23rd 2017 DCO of the RESORCE trial. The company's revised base case analysis leads to a slightly higher deterministic ICER for regorafenib versus BSC of £36,050 per QALY gained compared with their original submitted model. Given that additional issues were identified by the ERG after receipt of this revised model (for example, the use of dependent OS curves and an erroneously truncated time to discontinuation curve), the ERG suggests that the results produced from this iteration of the company's model are not useful for informing decision-making.

The ERG undertook seven sets of exploratory analyses using the deterministic version of the company's revised model (using the 29th February 2016 DCO of the RESORCE trial). The ERG's preferred base case includes the following amendments: (i) the correction of model errors and use of alternative unit

costs; (ii) the inclusion of a more appropriate general ward bed day cost; (iii) the use of full pack dosing (no cost savings due to dose reductions or treatment interruptions); (iv) the removal of half-cycle correction for regorafenib acquisition costs; (v) the use of the combined 2007 and 2015 survey resource use estimates; (vi) the use of independent Weibull functions to model OS, and (vii) the use of a fully extrapolated log logistic time to discontinuation curve (patients on treatment at 29th February 2016 censored). The ERG's preferred base case, which includes all of these amendments, results in a deterministic ICER for regorafenib of £81,081 per QALY gained compared with BSC. The ERG notes that this ICER will be higher if a greater disutility associated with progression is assumed within the model. It should also be noted 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. The 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. It is probable that the company will have information relating to whether dose reductions were due to clinically-planned reductions or due to other reasons: having this information would allow a more accurate estimation of the ICER.

6 END OF LIFE

NICE end of life supplementary advice should be applied in the following circumstances and when both the criteria referred to below are satisfied:

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

In the company's base case (Table 31) the mean expected life years associated with the use of BSC was estimated to be 0.90 years (10.8 months). This is markedly lower than stated 24-month cut-off. In the company's base case, regorafenib treatment was associated with a mean extension of life of 0.52 years (6.24 months) which is in excess of the stated 3-month cut-off. The changes made by the ERG relating to the choice of parametric OS functions do not change the conclusion with respect to the end of life criteria.

7 OVERALL CONCLUSIONS

The company's systematic review was generally well conducted. The review included a single, high-quality RCT: the RESORCE trial, which represents the relevant evidence. The trial reported that regorafenib was significantly more effective than placebo across the primary (OS) and secondary (PFS, TTP, ORR) outcomes, but also found that HRQoL was consistently worse on treatment than on placebo across different measures. AEs were frequent. 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 England. The RESORCE trial did not include some groups of adult HCC patients covered by the NICE scope and the licence, that is, those who are intolerant to sorafenib, or who are Child-Pugh class B or ECOG PS 2. The efficacy and safety of regorafenib in these groups is therefore uncertain.

The exploratory analyses undertaken by the ERG increase the ICER for regorafenib versus BSC from £36,050 per QALY gained (the company's revised base case) to an ERG-preferred ICER of £81,081 per QALY gained. The ERG notes that this ICER would increase slightly if a higher disutility for progressed disease is assumed. 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. However, 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. Key differences in assumptions between the ERG and the company relate to: (1) the use of a fully extrapolated log logistic function to model time to treatment discontinuation; (2) the anticipated number of hospitalisations per month for those receiving regorafenib and for those on BSC, and (3) whether the acquisition costs of regorafenib pills not taken by a patient could be recouped.

7.1 Implications for research

The resource use, in particular frequency of hospitalisation, for patients on BSC after sorafenib should be recorded. If preferential rates are to be assumed for regorafenib, this should come from a large robust survey. If possible, the utility associated with patients who have progressed following treatment with regorafenib and with BSC should be estimated more robustly than was done in the follow-up of patients in the RESORCE study. Long-term data on OS and time to treatment discontinuation would improve the accuracy of the estimate of the cost-effectiveness of regorafenib.

8 REFERENCES

1. Bayer PLC Ltd. Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]. Company submission to the National Institute for Health and Clinical Excellence. Bayer: Reading, UK; 2017:1-179.
2. Cancer Research UK. Liver Cancer Statistics in the UK 2017. 2017. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer#heading-Zero (Accessed 18/01/2017).
3. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *Journal of Hepatology* 2012;56:908-43.
4. Cholongitas E, Papatheodoridis GV, Vangeli M, Terreni N, Patch D, Burroughs AK. Systematic review: the model for end-stage liver disease – should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? *Alimentary Pharmacology & Therapeutics* 2005;22:1079-89.
5. National Institute for Health and Care Excellence. Sorafenib for treating advanced hepatocellular carcinoma (Cancer Drugs Fund reconsideration of TA189) - Final Appraisal Determination. London; 2017.
6. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, *et al.* Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet* 2017;389:56-66.
7. PRISMA. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA); 2009 (available from: http://www.prisma-statement.org/).
8. Bayer PLC Ltd. Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]. Response to ERG clarification questions. Bayer: Reading, UK;2017.
9. Bayer PLC Ltd. Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]. Company submission to the National Institute for Health and Clinical Excellence - Appendices. Bayer: Reading, UK; 2017:1-364.
10. Higgins J, Altman D, Gøtzsche P, Jüni P, Moher D, Oxman A, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
11. Lundh A, Lexchin J, Mintzes B, Schroll J, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2017:Art. No.: MR000033. DOI: 10.1002/14651858.MR000033.pub3.
12. Stamatakis E, Weiler R, JP. I. Undue industry influences that distort healthcare research, strategy, expenditure and practice: a review. *European Journal of Clinical Investigation* 2013;43:469-75.
13. Bruix J, Merle P, Granito A, Huang Y-H, Bodoky G, Yokosuka O, *et al.* Efficacy, safety, and health-related quality of life (HRQoL) of regorafenib in patients with hepatocellular carcinoma (HCC) progressing on sorafenib: Results of the international, double-blind phase 3 RESORCE trial. *Annals of Oncology* 2016;S6:LBA28.
14. Bruix J, Tak W-Y, Gasbarrini A, Santoro A, Colombo M, Lim H-Y, *et al.* Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: Multicentre, open-label, phase II safety study. *European Journal of Cancer* 2013;49:3412-19.
15. Solms A, Reinecke I, Fiala-Buskies S, Keunecke A, Drenth HJ, Bruix J, *et al.* Exposure-response relationship of regorafenib efficacy in patients with hepatocellular carcinoma. *European Journal of Pharmaceutical Sciences* 2017;19 [epub ahead of print].
16. Bruix J, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, *et al.* Analysis of overall survival (OS) by pattern of progression of hepatocellular carcinoma (HCC) during prior sorafenib

treatment in the randomized phase 3 RESORCE trial comparing regorafenib with placebo. *Hepatology International* 2017;11 (1 Supplement 1):S63.

17. Pugh R, Murray-Lyon I, Dawson J, Pietroni M, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *British Journal of Surgery* 1973;60:646-49.

18. Bayer PLC Ltd. RESORCE - Clinical Study Report; 2016.

19. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Seminars in Liver Disease* 2010;30:52-60.

20. Eisenhauer E, Therasse P, Bogaerts J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European Journal of Cancer* 2009;45:228-47.

21. Llovet JM, Ricci S, Mazzaferro V. Sorafenib in advanced hepatocellular carcinoma. *New England Journal of Medicine* 2008;359:378-90.

22. Cella D, Tulsky D, Gray G, Sarafian B, Linn E, Bonomi A. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *Journal of Clinical Oncology* 1993;11:570-79.

23. Heffernan N, Cella D, Webster K, Odom L, Martone M, Passik S. Measuring health-related quality of life in patients with hepatobiliary cancers: the functional assessment of cancer therapy-hepatobiliary questionnaire. *Journal of Clinical Oncology* 2002;20:2229-39.

24. Pickard A, Neary M, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health and Quality of Life Outcomes* 2007;5:70.

25. Bruix J, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet JM. Prognostic Factors and Predictors of Sorafenib Benefit in Patients With Hepatocellular Carcinoma: Analysis of Two Phase 3 Studies. *Journal of Hepatology* 2017 [epub ahead of print].

26. King J, Palmer J, Johnson P, Ross P, Hubner R, Sumpter K, *et al.* Sorafenib for the Treatment of Advanced Hepatocellular Cancer - a UK Audit. *Clinical Oncology* 2017;29:256-62.

27. Steel J, Eton D, Cella D, Olek M, Carr B. Clinically meaningful changes in health-related quality of life in patients diagnosed with hepatobiliary carcinoma. *Annals of Oncology* 2006;17:304-12.

28. European Medicines Agency. Summary of product characteristics – regorafenib. EMA: London. 2017. In. EMA: London; 2017.

29. Grothey A, Van Cutsem E, Sobrero A, Siena S. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *The Lancet* 2013;381:303-12.

30. Li J, Quin S, Xu R, Yao T, Ma B, Pan H, *et al.* Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology* 2015;16:619-29.

31. Gyawali B, Prasad V. Health policy: Me-too drugs with limited benefits - the tale of regorafenib for HCC. *Nature Reviews Clinical Oncology* 2017;18:18.

32. Frenette CT. The role of regorafenib in hepatocellular carcinoma. *Gastroenterology and Hepatology* 2017;13:122-4.

33. Prasad V, Massey P, Fojo T. Oral anticancer drugs: how limited dosing options and dose reductions may affect outcomes in comparative trials and efficacy in patients. *Journal of Clinical Oncology* 2014;32:1620-29.

34. Bruix J, Raoul J, Sherman M, Mazzaferro V, Bolondi L, Craxi A, *et al.* Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *Journal of Hepatology* 2012;57:821-29.

35. Parikh ND, Singal AG, Hutton DW. Cost effectiveness of regorafenib as second-line therapy for patients with advanced hepatocellular carcinoma. *Cancer* 2017; http://dx.doi.org/10.1002/cncr.30863.

36. National Institute for Health and Clinical Excellence. Regorafenib for previously treated unresectable hepatocellular carcinoma. Final scope. In. NICE: London, UK.; 2017: 1-3.

37. Department of Health. NHS Reference Costs 2015/16. 2016. https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016

38. Curtis L, Burns A. Unit Costs of Health and Social Care 2016.; 2016.

39. Akhtar W, Chung Y. Saving the NHS one blood test at a time. *BMJ Quality Improvement Reports* 2014;2:u204012.w1749.

40. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013; 2013.

41. Drummond M, Sculpher M, Claxton K, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. 4th edition. edn. Oxford, England: Oxford University Press.

42. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, *et al.* Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2003;6:9-17.

43. Grimm S BI, Carroll C, Wong R. Cancer Drugs Fund Rapid Review of Nice Guidance Ta189: Sorafenib For The Treatment of Advanced Hepatocellular Carcinoma. 2016. https://www.nice.org.uk/guidance/gid-ta10055/documents/committee-papers (Accessed

9 APPENDICES

Appendix 1: Questions posed to the company and the answers provided regarding the resource use survey undertaken by the company.

During the STA process, but subsequent to the formal clarification process the ERG noticed that there is a key discrepancy in the results of the survey used by the company in its submission. The ERG informed NICE of this and NICE formulated and sent an additional question to the company. (Question 1). The company responded to NICE's question with Answer 1. The ERG were not satisfied with the company's answer and provided a more detailed explanation of the discrepancy (Question 2). The company responded to Question 2 with Answer 2.

Questions 1 and 2, and Answers 1 and 2 are replicated in this Appendix. Following these, the thoughts of the ERG in relation to Answer 2 are provided.

Question 1. "In Table 121 of Appendix 0 in the top right hand cell of the table, clinicians were asked to provide the 'number of admissions per month'. However, the ERG have identified that in all uses of this parameter the number is less than 1. The number of admissions per month must logically be 1 or above"

Answer 1. "The questionnaire asks for the number of admissions per month. Throughout the questionnaire physicians were instructed to enter a decimal if the unit of interest occurred less frequently than once per month. For example, if the frequency was once every three months they were instructed to enter 0.33 (1 divided by 3). On this basis parameter values less than one are logical and in this case indicate that patients on average are hospitalised less than once per month."

Question 2. "The ERG believes that the implementation of the survey resources is unlikely to be consistent with the way in which it was intended. They demonstrate this using the costs of hospitalisation, assuming that the 2015 survey is appropriate. For pre-progression patients having sorafenib the cost of a general ward stay is calculated using four elements:

- P – the proportion of patients requiring hospitalisation ([redacted]
- D – the duration of an average ward stay ([redacted] days)
- H – the number of hospitalisations ([redacted])
- C – cost per bed day (£801)

The model calculates the cost per cycle as P * D * H * C

This formula is only conceptually correct if P is dividing the population into those who are susceptible to hospitalisation and those who are immune. In this instance, H would be therefore only be applied to P.

If, however, P is the proportion of the total population who are hospitalised then H is not needed, unless the model is taking multiple hospitalisations into account.

If multiple hospitalisations are not included the formula should be P*D*C

If multiple hospitalisations are included, then P*D*H*C is correct but H would need to be ≥ 1. (In the submitted model H<1 in all cases)

A similar problem applies for other costs. For example, in cell N84 of the costs sheet it is assumed that for best supportive care, [redacted] of patients do not have INR tests, and that the remaining [redacted] of patients average 0.67 tests.

The instructions to the questionnaire states that the expert should assess the 'average or typical' patient. As such, it is unlikely that they would be answering assuming a proportion of susceptible patients. Can you clarify what the clinicians were intended to be asked? Can you also provide plausible reasons for why P * D * H * C, with H < 1 is correct?"

Answer 2

"The survey question to which this query relates is in the box below. 'A' and 'B' have been added to the table in order to try to make our response clearer.

Acute Care

Q6a Still thinking about a typical 'pre-progression' advanced HCC patients, what proportions of patients receiving treatment or taking no other active treatment (BSC) require each of the following resources as part of acute care?

Table 121. Acute care for 'pre-progression' patients with advanced HCC for patients treated with sorafenib

Acute Care	Average proportions for 'pre-progression' patients	Number of admissions per month
Proportion requiring a hospitalisation (per month)	A	B

The intention of this question was to isolate what has been described above as 'susceptible' patients i.e. the subset of patients who are hospitalised. Looking at this group of patients the questionnaire was structured to allow for multiple hospitalisations as our *a priori* assumption was that for population 'A' the number of admissions 'B' would have a lower bound of 1 (as put forward by the ERG). According to the intention of the questionnaire the appropriate inclusion in the model is P*H*D*C.

The ERG queries whether the questionnaire has been answered as intended given the response to the number of hospitalisations is less than 1.

We believe the response indicates that [redacted] of patients are hospitalised in the pre-progressed health state and that the number of admissions per month relates to this group, as was the intention. We appreciate that for this to be the case the respondents would need to have not seen the time period of 'one month' as indicated in the first column of the table – however, we suspect this is what has happened. We have sought expert clinical opinion regarding this which supports our interpretation (see 'Expert Opinion' overleaf). The responses therefore indicate that [redacted] of patients are 'susceptible' in the pre-progressed health state and that admissions occur less frequently than monthly for this specific population.

We believe it is possible that the survey question immediately preceding question 6a (see box below) may have had an influence. In question 5 respondents were guided to enter decimals when frequencies were less than once per month (i.e. once every three months).

Medical Staff Visits

Q5 Furthermore, when thinking about a typical 'pre-progression' advanced hepatocelluar carcinoma patients, on average how many and which type of physician, nurse and GP visits do they receive per month. If the test is likely to be performed less than once a month enter a decimal e.g. if performed once every 3 months enter 0.333 (1 divided by 3). Please keep in mind that this section is referring to any visits that would be planned (elective).

Table 120. Medical staff visits for 'pre-progression' patients with advanced HCC

Physician visits	Average number of visits (per month) and specialty if required
Pre-progression patients treated with sorafenib	
Specialist visit (e.g. oncologist, gastroenterologist etc.)	
Nurse visit (e.g. clinical nurse specialist, palliative care nurse etc.)	
GP visit	
Other physician visit (please specify)	
Pre-progression patients on BSC	
Specialist visit (e.g. oncologist, gastroenterologist etc.)	
Nurse visit (e.g. clinical nurse specialist, palliative care nurse etc.)	
GP visit	
Other physician visit (please specify)	

Expert opinion

Ideally it would have been possible to contact the original respondents to seek clarification on their answers. However, according to the market research code of practice re-contacting respondents is only allowed if permission is formally provided – such permission was not obtained by the medical research agency. We therefore sought advice from a clinical expert experienced in the management of advanced HCC. Based on their clinical experience they consider that the questionnaire is likely to have been answered as we thought since this is the level of hospitalisation they would expect i.e. [redacted] of patients have [redacted] admissions per month.

Sensitivity analysis

We have presented a sensitivity analysis assuming that [redacted] of patients are hospitalised with an admission frequency of once per month i.e. P*D*C. No changes have been made to the laboratory/radiological tests as the 2015 resource survey asks for the proportion of patients requiring each resource and the frequency 'of these' patients receiving each resource – the implementation in the model is correct."

Table 5. Sensitivity analysis – [redacted] of patients are hospitalised once/month

	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case	14,625	0.406	36,050
Sensitivity analysis	15,538	0.406	38,303

The ERG's thoughts on Answer 2.

The ERG does not believe it likely that the post-hoc justification provided by the company regarding how the questions on hospitalisations were filled in by the clinicians is correct. This is for two reasons: (i) it would appear simpler for a clinician to try and estimate the proportion of the whole population that is hospitalised each month, rather than to assume that only a certain proportion of patients could be hospitalised, whilst the remainder would not, and then to estimate a rate of hospitalisation for those susceptible and (ii) clinical advice provided to the ERG states that the risk of hospitalisation would not be zero for any of the population considered. The ERG believe that the sensitivity analysis conducted by the company, where the number of admissions per month (denoted 'B' by the company) are set to 1 are more suitable for decision making than the company's base case analyses.

Appendix 2: Technical appendix – implementation of ERG exploratory analyses

This appendix details the amendments made to the company's model within the ERG's exploratory analyses.

Exploratory analysis 1: Correction of unequivocal model errors and use of alternative unit costs
The values in the following cells were changed:

- "Model Summary" sheet cell O25 changed from no to yes.
- "Model Summary" sheet cell O26 changed from no to yes.
- "Model Summary" sheet cell O27 changed from no to yes.
- "Patient cohort" sheet cell BK30 amended to:
  =IF(IF(effect!$E$329=2,Pat_cohort!BM30,IF(effect!$J$274=1,BF30,IF(effect!$J$274=2,BE30,IF(effect!$J$274=3,BG30,IF(effect!$J$274=4,BH30,IF(effect!$J$274=5,BI30,IF(effect!$J$274=6,BD30,BJ30)))))))>CN30,CN30,IF(effect!$E$329=2,Pat_cohort!BM30,IF(effect!$J$274=1,BF30,IF(effect!$J$274=2,BE30,IF(effect!$J$274=3,BG30,IF(effect!$J$274=4,BH30,IF(effect!$J$274=5,BI30,IF(effect!$J$274=6,BD30,BJ30)))))))
- "Costs" sheet cell L32 changed from 64.6% to 0%.
- "Costs" sheet cell F37 was changed from £138 to £204.11.
- "Costs" sheet cell F43 was changed from £131 to £119.03.
- "Costs" sheet cell F49 was changed from £151 to £162.84.
- "Costs" sheet cell F59 was changed from £238 to £202.70.
- "Live" sheet cell C96 was changed from £1,225.99 to £1,184.11.
- "Live" sheet cell C100 was changed from £1,225.99 to £1,184.11.
- "Live" sheet cell E96 was changed from £1,493.22 to £1,365.07.

In addition, the formulae in the following cells on the "Model_cost" sheet were changed:

- The formulae in cells AC284 to AC523 were amended to refer to "Live" sheet cell E68 rather than Live sheet cell G68
- The formulae in cells AC534 to AC773 were amended to refer to "Live" sheet E69 rather than G69.

All amended cells are highlighted in red in the ERG's revised model.

<u>All subsequent exploratory analyses are based on this amended version of the model.</u>

Exploratory analysis 2: Inclusion of more appropriate general ward bed day cost
Worksheet "Costs" cell F36 was changed from £801 to £572.44.

This amendment can be implemented by entering a value of "yes" into worksheet "Model Summary" cell O37 in the ERG's revised model.

Exploratory analysis 3: Use of full pack dosing
The values in the following cells were changed:

- "Live" sheet cell C36 was changed to 160mg.
- "Live" sheet cell C37 was changed to 160mg.

This amendment can be implemented by entering a value of "yes" into worksheet "Model Summary" cell O38 in the ERG's revised model.

Exploratory analysis 4: Removal of half-cycle correction for drug acquisition costs
Within the worksheet "Model_cost", the following cells were amended:

- The formulae in cells Q34:Q273 which referred to cells Q275:Q514 in the "patient cohort" worksheet were changed to refer to cells Q29:Q270 in the "patient cohort" sheet.
- The formulae in cells R34:R273 which referred to cells U275:U514 in the "patient cohort" sheet were changed to refer to cells U29:U270 in the "patient cohort" sheet.
- The formulae in cells S34:S273 which referred to cells S275:S514 in the "patient cohort" sheet were changed to refer to cells S29:S270 in the "patient cohort" sheet.
- The formula in cells AS34:AS273 which referred to cells AD275:AD514 in the "patient cohort" sheet were changed to refer to cells AD29:AD270 in the "patient cohort" sheet.
- The formula in cells AT34:AT273 which referred to cells AH275:AH514 in the "patient cohort" sheet were changed to refer to cells AH29:AH270 in the "patient cohort" sheet.
- The formula in cells AU34:AU273 which referred to AF275:AF514 in the "patient cohort" sheet were changed to refer to cells AF29:AF270 in the "patient cohort" sheet.

This amendment can be implemented by entering a value of "yes" into worksheet "Model Summary" cell O39 in the ERG's revised model.

Exploratory analysis 5: Use of combined 2007 and 2015 survey costs
Within the "Costs" worksheet, cells H68, L68, O68 and S68 were changed to values of 1.00.

Within the "summary" worksheet, cell O29 was changed from "no" to "yes". Selecting "yes" automatically triggers the amended values described above in the ERG's revised model.

Exploratory analysis 6: Use of independent Weibull functions to model OS

The option selected from the "survival curves" box on the worksheet "effect" was changed from "dependent curves" to "independent curves" for OS. The Weibull model was selected from the relevant drop down box for OS.

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)

Please refer to new worksheet "ERG_TTD." This replaces the company's cost estimates generated in worksheet "KM discontinuation."

- Columns B:E are linked to the log logistic time to treatment discontinuation curve in worksheet "KM discontinuation."
- Columns G:I summarise the probability of being alive, based on the currently selected OS model.
- Columns K:O introduce a logical consistency constraint which ensures that the modelled time to treatment discontinuation curve never exceeds the OS curve.
- Column Q estimates the total drug cost based on the probability of a patient being alive and still on treatment at the beginning of each cycle and the regorafenib acquisition cost per treatment cycle (cell D2).
- Column R discounts the per-cycle treatment cost at a rate of 3.5% per annum.
- The total discounted treatment cost calculated in cell U3 is linked to worksheet "Output" cell I33.

This amendment can be implemented by entering a value of "yes" into worksheet "Model Summary" cells O30 and O42 in the ERG's revised model.

Exploratory analysis 8: ERG's preferred base case (including all individual amendments)

All changes detailed above were implemented together.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]

You are asked to check the ERG report from ScHARR to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Friday 22 September 2017** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Inclusion of potentially unrealistic cost-savings due to dose reductions/interruptions

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
On page 79 it is stated that one clinical advisor said regorafenib would be prescribed monthly according to a fixed delivery schedule (the opinion of the other advisor is not stated). It was stated that 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. Consequently the ERG does not believe that the cost reductions included in the company's model would not be fully realised in clinical practice and instead has costed regorafenib at its full maximum dose of 160mg per day for the entire duration of treatment.	The dose reductions/interruptions used in the company model are appropriate and should represent the base case. Reduced dose/treatment interruptions The average dose from the RESORCE study should be included as the basecase. Wastage in last cycle Patients receive their medication at the start of the treatment cycle. Removal of half-cycle correction for treatment costs ensures that any wastage in the last cycle of treatment is accounted for. Exploratory analysis 3 from table 38 should not be incorporated into exploratory analysis 8 as it doesn't reflect medicines management in the NHS.	During the sorafenib CDF reappraisal, Bayer sought to understand how avoiding medicines wastage for oral cancer medicines is managed in two of the largest tertiary centres in the UK. Both centres advised that medicines supply is actively managed. Extracts of the process to manage wastage are included below and the two statements have been attached as separate documents. Both of these statements were submitted previously as part of the sorafenib CDF reappraisal and formed part of the committed papers (https://www.nice.org.uk/guidance/ta474/documents/committee-papers-2). Regorafenib, also an oral medicine, can reasonably be expected to be managed in exactly the same way. Pharmacist from Christie Hospital "patient supply of sorafenib is actively managed where possible i.e. through pack splitting where appropriate. The clinician, pharmacist and patient work closely to reconcile what medicines were used within the month and where the patient has not used some tables, only the remainder of another month's supply will be issued to reduce wastage (i.e. the pack will be split and only the outstanding amount issued).…….Whilst this process cannot eradicate wastage entirely, wastage of sorafenib is generally small…"	The new data provided by the company is a welcome addition, however, these do not seem to support the company's assertion that there would be no wastage. Both pharmacists state that '*the process cannot eradicate wastage entirely*'. Even were a strict monitoring system in place that takes into account missed doses, when a patient dies in receipt of regorafenib tablets it is unlikely that these tablets would be taken back and be provided for other patients. It is also uncertain how generalisable are the experiences of large tertiary centres to other hospital settings. Both our clinicians, one based in London and one based in Sheffield indicated that the costs of any pills not taken would not be recouped. We have amended the text to now include that the second clinical expert also stated that the costs of unused pills are unlikely to be recouped. The following text has been added. *'The second clinician stated that 'the*

Based on our understanding of prescribing practices in the largest centres in the UK we do not believe this is representative of practice in the NHS i.e. the NHS does realise the costs of reduced doses/interruptions to treatment of existing oral medicines.		<u>Pharmacist from Queen Elizabeth Hospital Birmingham</u> "the clinician, pharmacist and patient work closely to reconcile what medicines were used in the month (patients are advised to bring their medicines pack and any unused tablets to the appointment). Where the patient has not used some tablets, only the remainder of another month's supply will be issued to reduce wastage. The supply is actively managed by splitting packs where appropriate to ensure on the outstanding amount is issued…. …whilst this process cannot eliminate wastage entirely, wastage of sorafenib is generally uncommon…" The approach of assuming full dose for the entire duration of treatment is not representative of the management of high cost medicines or best practice (e.g. BOPA 2004 (1), NPSA 2008(2)). Having this as a base case assumption is not appropriate as it is not a factually accurate representation of practice in England. 1) British Oncology Pharmacists Association (BOPA) (2004). Position statement on the care of patients receiving oral chemotherapy. Pharmaceutical Journal; 272:422-423 2) National Patient Safety Agency (NPSA) Rapid Response Report. 'Risks of Incorrect Dosing of Oral Anticancer Medicines.' 22nd January 2008. Available at http://www.npsa.nhs.uk/patientsafety/alerts-	*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'* The ERG are comfortable in that we have provided bounds for the ICER, under assumptions that no costs are recouped and that all patients are reduced to [redacted]. Both ICERs are presented, albeit with one marked as CIC (see issue 6). As such, we do not feel there is a need to amend the report and are willing to discuss both scenarios (as much as can be publically divulged) in the committee meeting. It is noted that in the cancer drugs fund re-appraisal of sorafenib the company allowed wastage of 'up to seven days'. It is unclear why similar assumptions were not made by the company for regorafenib.

		and-directives/rapidrr/risks-of-incorrect-dosing-of-oral-anti-cancer-medicines/ In addition, accounting for reduced dose and treatment interruptions is standard in appraisals of cancer medicines.	

Issue 2 The selection of the Weibull parametric curve for OS extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
On page 75 it is stated that the clinical advisor(s) considered the lognormal, loglogistic and generalised gamma overall survival functions to be clinically implausible. There was a preference for the Weibull function but it was noted that both the exponential and Gompertz functions were very similar and therefore also potentially plausible. The report describes a preference for the Weibull but this cannot be considered conclusive given the comments that the exponential and	We believe the input from the advisors would be more closely represented by: Giving more prominence to the cost-effectiveness estimates generated by the Gompertz and exponential curves in table 39 and elsewhere in the report i.e. 1) Exploratory analysis 6 from table 38 should be extended to include results for the Gompertz and exponential curves 2) Exploratory analysis 8 from table 38 should be extended to include results using the Gompertz and exponential curves 3) Table 39 should be modified with row headings for 'Alternative clinically plausible OS functions' and 'Alternative	From the description in the ERG report it appears as if either of three curves (Weibull, Gompertz, exponential) are clinically plausible based on the input of the clinical advisors. We don't believe the clinical input, as it has been described in the report, is accurately reflected by singling out one parametric curve as the basecase. If the intent is to incorporate the expert input as accurately as possible we believe the proposed amendment(s)	The text of the ERG report has been amended to reflect the process undertaken by the ERG. The added text is "*The ERG deemed that the Weibull function was the most appropriate based on the clinical opinion on the plausibility of the extrapolated curves, the goodness-of-fit to the observed data and also the empirical hazards provided by the company within the clarification period (Figure 2 of the clarification response received on the 15th August 2017).*" Uncertainty in selecting the most appropriate parametric distribution

Gompertz curves were similar and were also clinically plausible. The clinical advice has highlighted the uncertainty inherent in selecting the 'most clinically plausible' curve for extrapolation.	less plausible OS functions'. Alternatively, as each of the three curves were considered clinically plausible the base case could be modified to be a weighted average of the three curves.	would achieve this. Currently, based on the narrative on page 75 the selection of one curve is overly conclusive and definitive	is explored in the sensitivity analyses (Table 39). It is anticipated that the Committee will ask questions on this where both the company and the ERG can clarify their views and the Committee can decide on the most appropriate curve.

Issue 3 Treatment beyond progression

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
On page 49 it is stated that the clinical advisors did not have a consensus on whether regorafenib would be used in England for patients following progression. We note that are two clinical advisors listed as authors and therefore assume that there can only be a lack of consensus if one advised patients would be treated post-progression and the other	The base-case should be amended to better represent treatment in England. An even-handed approach might be to assume 50% treatment post-progression.	The lack of consensus between the two advisors mirrors our understanding of the variation of treatment practices in England. The current base-case assumption of fully extrapolated treatment is not reflective of clinical practice in England	The statement regarding treatment beyond progression reflects what may happen in practice should regorafenib be recommended. However, within the RESORCE trial, a proportion of patients received treatments post-progression and this treatment strategy likely generated additional health outcomes. The ERG considers that it would be inappropriate to include these additional health gains without also

didn't. In this context employing full extrapolated treatment as the ERG base-case is not an even-handed representation of the advisors input and doesn't reflect variation in treatment practice – it is therefore not a factually accurate representation for modelling.			including the costs associated with generating them.

Issue 4 The combination of the Weibull OS function with Loglogistic treatment extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
The ERG favours the Weibull curve (which has the lowest duration of predicted survival) but jointly favours the loglogistic extrapolation for treatment (which predicts the longest duration of treatment). On face value this appears to be a little uneven handed.	We request more prominent consideration of scenarios where curves predicting shorter (longer) survival are 'matched' with treatment curves predicting shorter (longer) treatment.	Even-handed presentation of the evidence.	There is no reason to assume that the two curves would have the same functional form. If the company wanted to explicitly model correlation between curves then this would need to be done using individual patient level data, to which the ERG does not have access.

Issue 5 The summary of the main issues identified within the company's model includes changes/corrections with marginal impact on the ICER

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Box 1 on page 73 includes nine 'main' issues identified within the company's model. Two of these (NHS reference costs and cost of a general ward bed day) have a minor effect on the ICER - from the results presented in table 38 it appears that the ICER decrease compared to the company's base case.	We suggest removing these two issues from the list of 'main concerns' or to categorise these as 'minor' issues in light of their minimal impact on the ICER.	With the understanding that the ERG are of the opinion these are still 'main concerns' then there is no factual inaccuracy. However, we suggest that their removal from the list will enable the reader to better focus on the concerns that are most impactful without being distracted by what appear to be relatively minor changes based on ICERs.	We are happy to state in the Appraisal Committee meeting that the impact on the ICER is relatively minor for the two issues highlighted. However, the list contains the main concerns identified by the ERG prior to examining their effect on the ICER. As such this list has not been changed.

Issue 6 Incorrect AIC/BIC information

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
There is some incorrect reporting of AIC/CIC information in the document. 1) The median overall survival estimates are not AIC (pages 1, 28, 42) 2) The median time to progression as measured by mRECIST is not	Please change AIC to CIC as appropriate. Please mark the ICER and incremental costs for the 120mg scenario as CIC	Relates to AIC and CIC data.	1) AIC marking related to median OS has been removed 2) AIC marking related to median time

AIC (page 1, 42) 3) Table 23 page 61 – the mean daily doses are CIC (not AIC) 4) Page 63 - the mean daily doses are CIC (not AIC) 5) [redacted]			to progression as measured by mRECIST has been removed 3) The data in Table 23 have been changed to CIC 4) The data identified have been changed to CIC 5) We are unclear exactly which of the data should be CIC so have marked all data relating to the scenario as CIC

1.1.1 Hospital statements

The Christie (Manchester)

Chief pharmacist: [redacted]

- It is Christie policy to issue **only one month of sorafenib** (in all indications including HCC) therapy at a time

- **Prescribing of sorafenib is aligned with a patient's monthly follow-up** where a clinical decision is made in regard to patient suitability for treatment for the following month. Only when this is satisfied is sorafenib prescribed

- It is advised that patient supply of sorafenib is actively managed where possible i.e. **through pack splitting where appropriate**. The clinician, pharmacist and patient work closely to reconcile what medicines were used within the month and where the patient has not used some tablets, only the remainder of another month's supply will be issued to reduce wastage (i.e. the pack will be split and only the outstanding amount issued)

- Whilst this process cannot eradicate wastage entirely, **wastage of sorafenib is generally small and is not believed to be a major issue for the Christie**.

- The number of patients on sorafenib therapy is relatively small (approximately 10 patients/month across all indications) - this does not differ significantly month by month therefore stock going out of date has not been an issue over the past 3-4 years of use in the centre.

University Hospitals Birmingham

Chief Pharmacist: [redacted]

- **Only one month of sorafenib therapy is prescribed at any given time**; treatment is initiated by a cancer specialist and patients are fully informed about appropriate use of their oral anticancer therapy (both verbally and written)

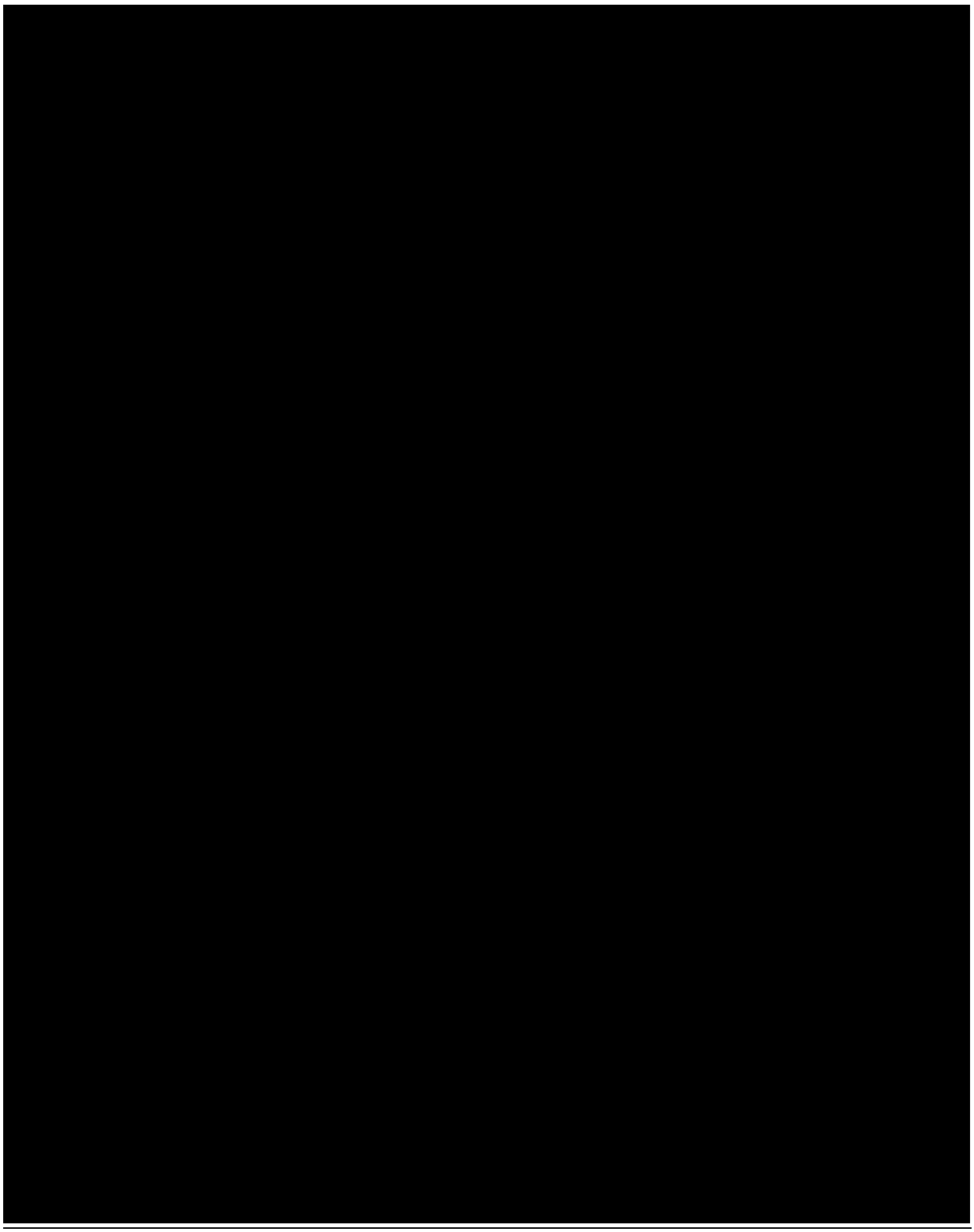
    - In cases where patients are determined to be high risk, a decision may be taken to issue only **one week's supply** and make a reassessment after one week of therapy, this however rarely occurs with sorafenib due to long-term clinical practice with the drug.

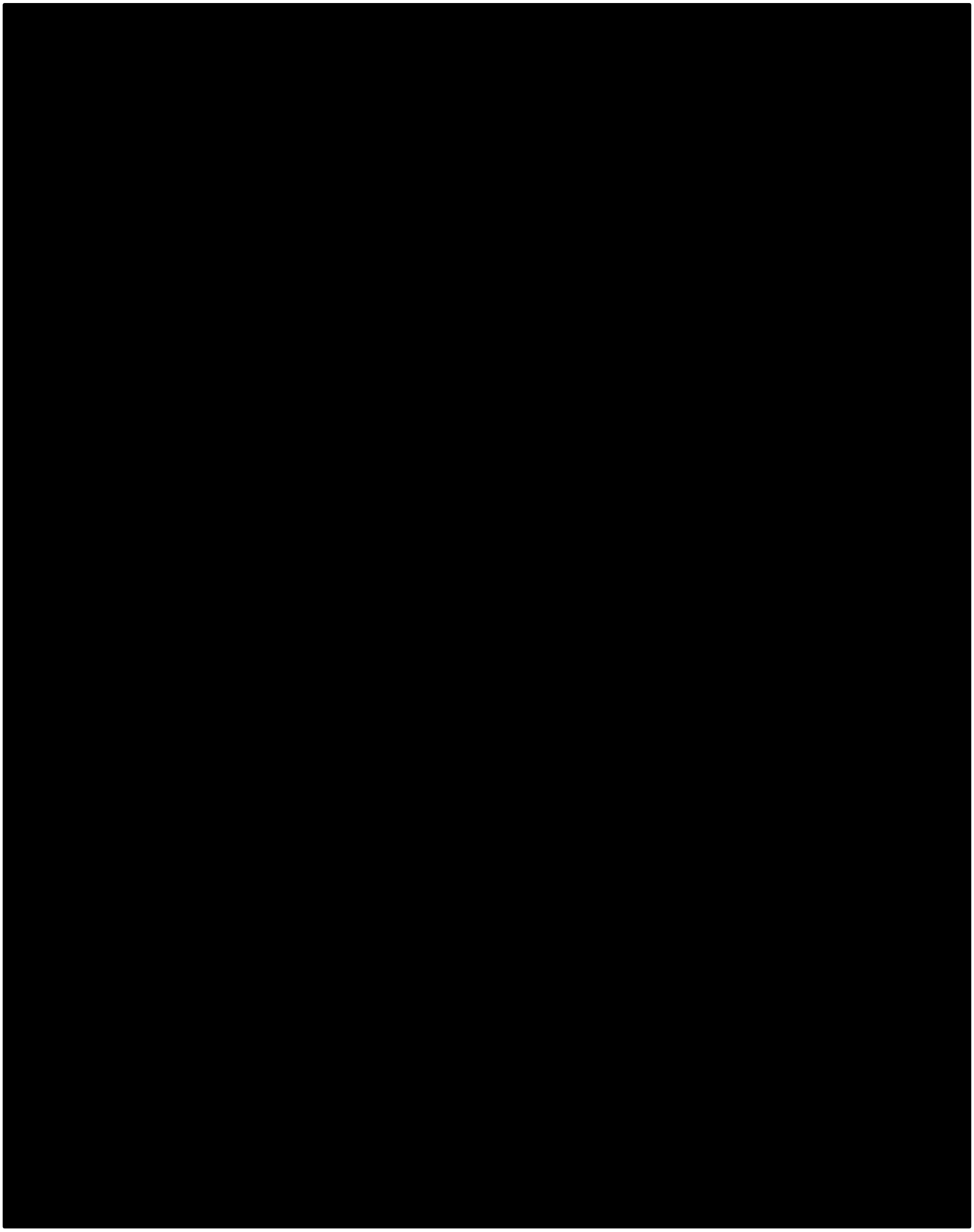
- Prescribing of sorafenib will occur at patient's monthly follow-up appointment where a clinical decision is made regarding the patient's suitability for treatment in the following month. Based on a standard evaluation of the patient including blood tests, where appropriate a following month's supply of sorafenib will be prescribed.

- The clinician, pharmacist and patient work closely to reconcile what medicines were used in the month (patients are advised to bring their medicines pack and any unused tablets to the appointment). Where the patient has not used some tablets, only the remainder of another month's supply will be issued to reduce wastage. **The supply is actively managed by splitting packs where appropriate** to ensure only the outstanding amount is issued.

- Whilst this process cannot eliminate wastage entirely, wastage of sorafenib is generally uncommon and not considered to be a major issue within the Trust.

Appendix A: Pharmacist statements: treatment wastage





ERRATUM

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

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	14th September 2017

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Declared competing interests of the authors

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.

Standard copyright statement on the front page of the ERG/AG report:

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 –

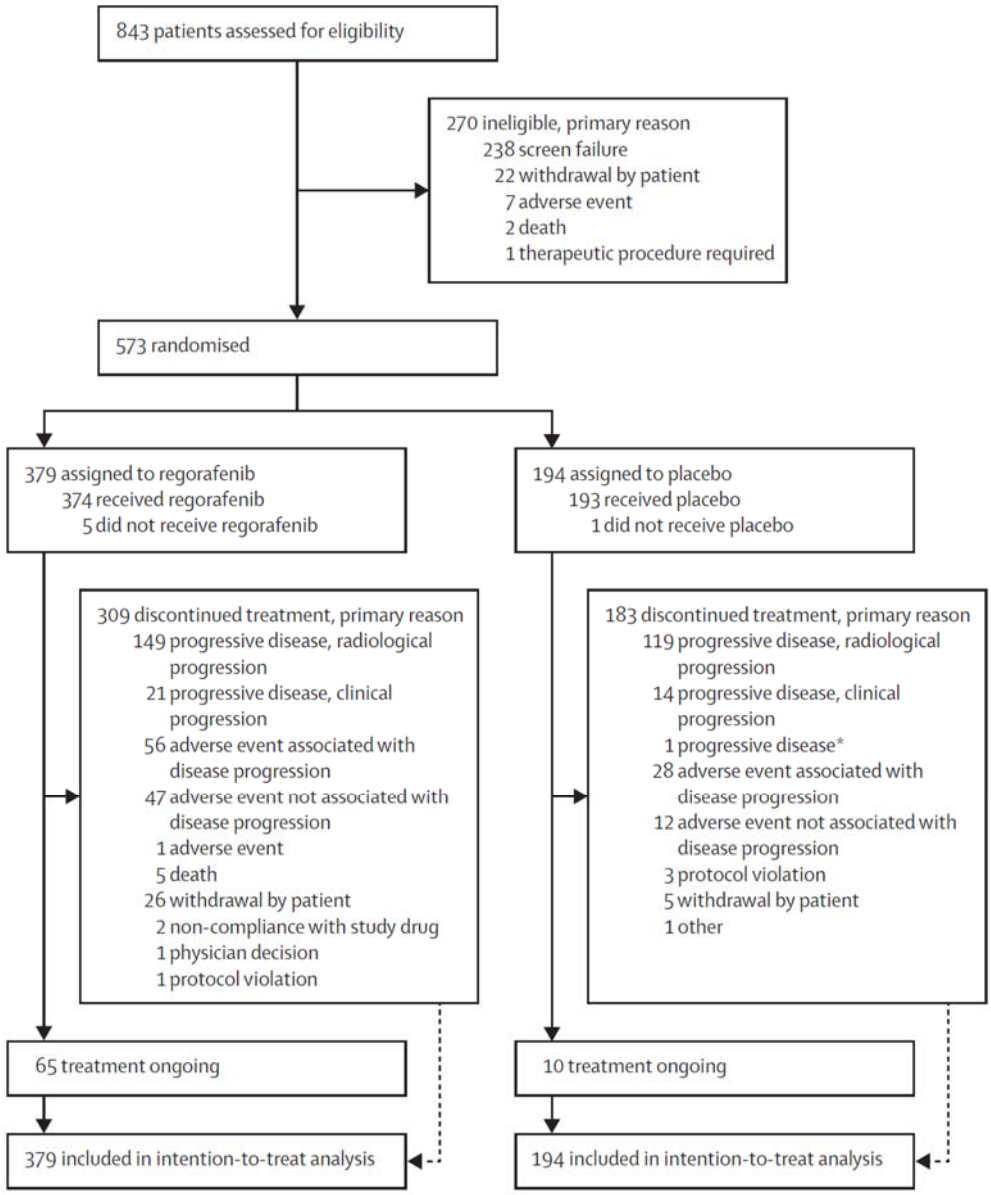
sorafenib for HCC); (6) the use of independent Weibull functions to model OS, and (7) the use of a fully extrapolated log logistic time to treatment discontinuation curve (with full pack dosing). These exploratory analyses were then combined to form the ERG's preferred base case (analysis 8).

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

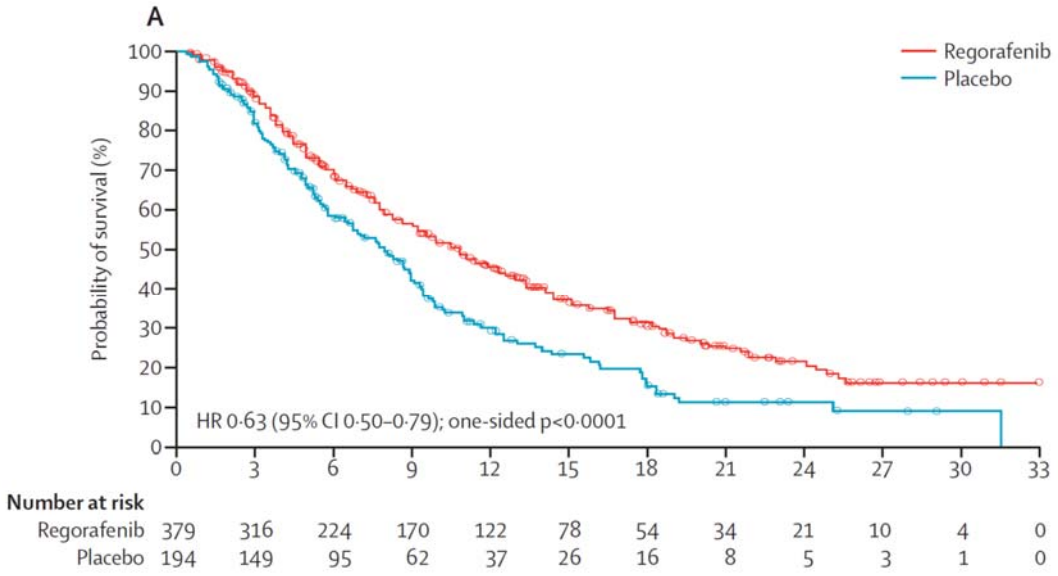
median OS compared to placebo ([redacted]) (see CS,[1] Table 17, page 51). Details are presented in **Error! Reference source not found.** and the Kaplan-Meier curve is reproduced in Error! Reference source not found..

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"

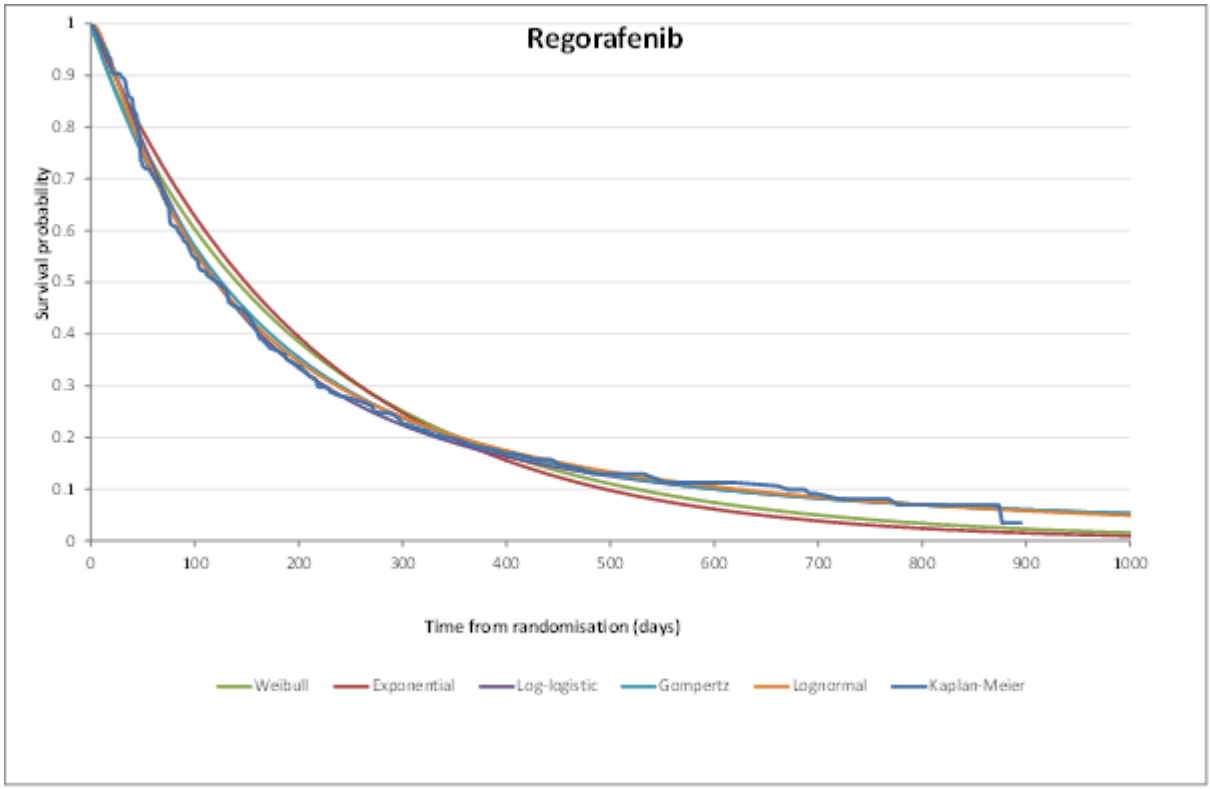


Table 6: Cost-effectiveness results for alternative curves fitted to time to treatment discontinuation, patients on treatment on 29th February 2016 censored (adapted from company's clarification response, question B8)

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

ERG request

We note that post-clarification model 2 includes the updated data cut (23rd January 2017) but does not include the increased functionality that was incorporated into the post-clarification model 1. After some internal discussion, we believe it would be helpful if the committee can use the most up-to-date information in their decision making. For this reason, we would be grateful if you could provide an economic model which includes both the additional functionality and the newest data cut. We are requesting the second model (the one with all functionality) which includes the independent model fits to the latest RESORCE data-cut. The new model submitted must include no other amendments and must be able to produce the ICER from the second model (post-clarification model 1).

We have attached the model as requested (**Regorafenib_ID991_ACIC_EconomicModel_combined_02Oct17_Final**). We have checked that when selecting the original dataset in the model the results sent on 15th August 2017 (Document: Regorafenib_ID991_ACIC_Clarification_15Aug17_FINAL) are reproduced. We have similarly checked that when the extended dataset is selected the results sent on 18th August 2017 are also reproduced (Document: Regorafenib_ID991_ACIC_ClarificationQuestion_B1_18Aug17_Final).

Please note however that in order for the ICERs to match those in the clarification responses it has been necessary to leave the model inputs as originally submitted. Consequently this model retains errors that Bayer has identified and notified to the ERG since the 18th August. In addition it retains inputs that the ERG have changed/corrected - see ERG report. This was necessary for us to comply with the request that the model must "be able to produce the ICER from the second model (post-clarification model 1)".

In table 1 we have listed the changes that have been highlighted since 18th August either by ourselves or in the ERG report. We have attached a version of the model which is identical to (Regorafenib_ID991_ACIC_EconomicModel_combined_02Oct17_Final) but with the addition drop-down boxes on the Model_Summary tab where these corrections can be implemented one at a time (**Regorafenib_ID991_ACIC_EconomicModel_combined_02Oct17_Final_DropdownCorrections**).

Table 1. List of changes/corrections since 18th August

Bayer		
Change/error identified/correction	**Relevant date and document (if applicable)**	**Correction in Regorafenib_ID991_ACIC_EconomicModel_combined_02Oct17_ Final_DropdownCorrections**
Implementation of extra treatment cycles for OS and PFS	1st September: Regorafenib_ID991_ACIC_ClarificationQuestion_1Sep17_Final Regorafenib_ID991_ACIC_EconomicModel_1Sep17	Drop-down option – see tab Model Summary and cells O39 Please see model submitted on 1st September (Regorafenib_ID991_ACIC_EconomicModel_1Sep17)
If Weibull, Gompertz or Exponential overall survival function selected the PFS trace drops to zero in from the second model cycle	1st September: Regorafenib_ID991_ACIC_ClarificationQuestion_1Sep17_Final Regorafenib_ID991_ACIC_EconomicModel_1Sep17	We ran a scenario whereby the same extrapolation curve for PFS and OS was selected
ERG report – page 87		
Number of cycles set equal to 13.044	Highlighted in clarification questions	Drop-down option – see tab Model Summary and cells O26
Programming error relating to the AE rate for the BSC group	Highlighted in clarification questions	Drop-down option – see tab Model Summary and cells O27
Programming error relating to the hospitalisation and medical visit costs for patients during the progression-free phase		Drop-down option – see tab Model Summary and cells O36
Proportion of BSC patients receiving post-progression	ERG report	No correction has been implemented via a drop-down box as we are unsure what the ERG has done.

regorafenib was set equal to zero		
The cost of A&E visit was set to £204.11	ERG report	See drop-down box on Model Summary tab cell O31
The cost per palliative care team visit was set to £119.03	ERG report	See drop-down box on Model Summary tab cell O25
The cost per specialist follow-up visit was set to £162.84	ERG report	See drop-down box on Model Summary tab cell O32
The cost per abdominal MRI scan was set equal to £202.70	ERG report	See drop-down box on Model Summary tab cell O33
The cost of each AE were set equal to £1,184.11 for the regorafenib group and £1,365.07 for the BSC group	ERG report	See drop-down box on Model Summary tab cell O34
Incorrect truncation of treatment costs at 29 cycles	ERG report	See drop-down box on Model Summary tab cell O38
General ward bed day cost changed to £572.44 (exploratory analysis 2)		See drop-down box on Model Summary tab cell O37
Removal of half-cycle correction for drug acquisition costs	ERG report	See drop-down box on Model Summary tab cell O35

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

Addendum: ERG exploratory analyses based on 2016 and 2017 data cut-offs

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4th October 2017

This addendum presents the ERG's exploratory analyses using the original RESORCE data cut-off (29th February 2016 cut-off, Table 1) and using the later data-cut off (23rd January 2017, see

Table ***2***). Additional sensitivity analyses using the later 23rd January 2017 data cut-off are presented in Table 3. As shown in the results, the use of the newer data cut-off reduces the ICER for regorafenib versus BSC.

Table 1: ERG exploratory analyses using 29th February 2016 data-cut-off

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
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		-	-	-
*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		-	-	-
*Exploratory analysis 3: Use of full pack dosing**					
Regorafenib	1.048	[redacted]	0.368	£15,508	**£42,151**
BSC	0.680		-	-	-
*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		-	-	-
*Exploratory analysis 5: Use of combined 2007 and 2015 survey costs**					
Regorafenib	1.048	[redacted]	0.368	£20,297	**£55,166**
BSC	0.680		-	-	-
*Exploratory analysis 6: Use of independent Weibull functions to model OS**					
Regorafenib	0.896	[redacted]	0.265	£10,242	**£38,683**
BSC	0.632		-	-	-
*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		-	-	-
*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		-	-	-

Table 2: ERG exploratory analyses using 23rd January 2017 data-cut-off

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Exploratory analysis 1: Correction of unequivocal model errors and use of alternative unit costs					
Regorafenib	1.072	[redacted]	0.405	£13,637	**£33,703**
BSC	0.668	[redacted]	-	-	-
*Exploratory analysis 2: Inclusion of more appropriate general ward bed day cost**					
Regorafenib	1.072	[redacted]	0.405	£13,536	**£33,456**
BSC	0.668	[redacted]	-	-	-
*Exploratory analysis 3: Use of full pack dosing**					
Regorafenib	1.072	[redacted]	0.405	£16,594	**£41,012**
BSC	0.668	[redacted]	-	-	-
*Exploratory analysis 4: Removal of half-cycle correction for drug acquisition costs**					
Regorafenib	1.072	[redacted]	0.405	£14,309	**£35,365**
BSC	0.668	[redacted]	-	-	-
*Exploratory analysis 5: Use of combined 2007 and 2015 survey costs**					
Regorafenib	1.072	[redacted]	0.405	£22,099	**£54,619**
BSC	0.668	[redacted]	-	-	-
*Exploratory analysis 6: Use of independent Weibull functions to model OS**					
Regorafenib	0.967	[redacted]	0.319	£11,553	**£36,241**
BSC	0.648	[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	1.072	[redacted]	0.405	£22,305	**£55,128**
BSC	0.668	[redacted]	-	-	-
*Exploratory analysis 8: ERG's preferred base case (including all individual amendments)**					
Regorafenib	0.967	[redacted]	0.319	£23,768	**£74,559**
BSC	0.648	[redacted]	-	-	-

Table 3: New sensitivity analyses using 23rd January 2017 data-cut-off

Scenario	Inc. QALYs	Inc. costs	ICER (regorafenib versus BSC)
ERG base case	0.319	£23,768	£74,559
Alternative OS functions			
OS - exponential	0.348	£23,836	£68,462
OS – log normal	0.410	£28,851	£70,409
OS – log logistic	0.412	£28,987	£70,424
OS – Gompertz	0.343	£23,296	£67,835
OS – generalised gamma	0.408	£28,764	£70,551
Alternative time to treatment discontinuation functions			
TTTD - exponential	0.319	£21,461	£67,320
TTTD – Weibull	0.319	£22,832	£71,622
TTTD – log normal	0.319	£23,977	£75,214
TTTD – Gompertz	0.319	£24,192	£75,888
Alternative utility values			
Utilities from SHARP trial	0.281	£23,768	£84,597
Disutility due to progression doubled (state utility=0.715)	0.311	£23,768	£76,441
Disutility due to progression tripled (state utility=0.667)	0.303	£23,768	£78,422
Alternative interpretation of company's resource use survey			
Number of hospitalisations per month estimated per month assumed to apply to the entire population.	0.319	£24,481	£76,793
Inclusion of dose reductions			
Indefinite dose reduction to 120mg/day	[redacted]	[redacted]	[redacted]