**The Application of Managed Entry Agreement Schemes on Cost-effectiveness Analysis: Regorafenib as a Second-line Treatment for Previously Treated Advanced Hepatocellular Carcinoma in the UK**

**LIST OF ABBREVIATION**

ACD appraisal consultation document

AE adverse event

BSC best supportive care

CEA cost-effectiveness analysis

CEAC cost-effectiveness acceptability curve

CE-plane cost-effectiveness plane

DCF discounted cash flow

ERG evidence review group

EVPPI expected value of partially perfect information

FAD final appraisal determination

FTIS free treatment initiation scheme

HCC hepatocellular carcinoma

HR hazard ratio

HTA health technology assessment

ICER the incremental cost-effectiveness ratio

iNMB incremental net monetary benefit

KM the Kaplan-Meier

LTACS lifetime treatment acquisition cost-capping scheme

LY life year

MEA managed entry agreement

MGS Money-back guarantee scheme

NHS the National Health Service

NICE the National Institute for Health and Care Excellence

NMBnet monetary benefit

OS overall survival

OWSA one-way sensitivity analysis

P post-progression

PAS patients access schemes

PFS progression-free survival

PSA probabilistic sensitivity analysis

PSB payer strategy burden

P-SUB the payer strategy and uncertainty burden

PUB payer uncertainty burden

QALY quality-adjusted life year

SAVI the Sheffield Accelerated Value of Information

SD standard deviation

SDS simple discount scheme

SE standard error

ToT time on treatment

UK United Kingdom

VOI value of information

WTP willingness-to-pay

1. **METHODS**

## **Case study**

We demonstrated how different MEAs could impact NMB from the payer viewpoint and DCF from the manufacturer viewpoint in a selected case study. The case study was inspired by a finished appraisal of regorafenib for patients with advanced HCC who had been previously treated with sorafenib [26] [27]. For this indication, regorafenib was firstly assessed in 2017, and in that appraisal (TA514), NICE did not recommend regorafenib primarily due to cost-effectiveness concerns (despite the existence of an MEA) [26]. In response to that negative decision, Bayer (the manufacturer) submitted additional evidence and an improved MEA, which led to a recommendation after a rapid review (TA555) in 2019 [27]. In the case study, we tried to replicate the model as close to the model that the final committee decision was based on as possible. However, some of the input data were censored from the committee papers due to a confidentiality agreement; we, therefore, used alternative inputs from publicly available sources reported in TA514 and TA555.

* + 1. ***Population***

The population was adult patients with advanced HCC who had been previously treated with sorafenib in the UK [28].

* + 1. ***Intervention***

The intervention consisted of 160mg regorafenib administered once-daily orally for the first three weeks, followed by a one-week break. Chemotherapy continued until disease progression, intolerance or death. However, in the pivotal RESORCE trial, it was observed that a proportion of patients kept receiving regorafenib post-progression if their physicians considered it to yield clinical benefit [29] [28].

* + 1. ***Comparator***

The comparator to regorafenib was best supportive care (BSC) since prior to RESORCE trial, there was no standard treatment for advanced HCC patients who progressed on sorafenib [28].

* + 1. ***Perspective***

Following NICE guidelines, the health care perspective was adopted. Consequently, costs and effects outside of the healthcare (e.g. societal costs, caregiver costs) were not considered.

* + 1. ***Discount rate***

Both costs and health effects incorporated in this study were discounted at a rate of 3.5% per annum in line with NICE guidelines. When calculating the DCF from the undiscounted cash flow, we applied a financial discount rate of 4%. This financial discount rate was in line with 2016 figures for the annual percentage change of pharmaceutical products and reflected the cost of having capital tied up and unable to be invested elsewhere (i.e. if the cash was not tied up then it could be invested and assumed to gain a 4% annual interest) [23].

* + 1. ***Time-horizon***

The time horizon should be sufficiently long to capture all major differences in costs and effects between two treatment arms. Patients with advanced HCC who progressed on sorafenib had short life expectancy [26] [27]. Hence, in this study, we set the lifetime horizon at 15 years.

* + 1. ***Threshold ICER***

A WTP threshold of £50.000 per QALY was considered according to NICE’s recommendation when appraising end-of-life treatments.

* + 1. ***Model structure***

A partitioned survival model was used, in line with the decision- analytical model described in the TA514 and TA555 appraisals. The model consisted of three health states: progression-free (PF), post-progression (P), and death (D) (Figure 4). The input data for the transition probabilities were derived from the published Kaplan Meier (KM) curves from the RESORCE trial [29].

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Figure 4: Representation of the Markov model

* + 1. ***Cycle length***

The cycle length was four weeks in line with the treatment cycle (i.e. three weeks receiving regorafenib and one week off treatment). Half-cycle corrections were applied to most inputs since it was assumed that events occurred in the middle of each treatment cycle (i.e. so that resources used, or utilities were experienced continuously). However, regorafenib was administered on the first day of each cycle; the half-cycle correction was therefore not applied for the treatment acquisition cost.

* + 1. ***Model inputs***

A comprehensive set of input parameters are provided in Appendix 3.

***Transition probabilities:***

Due to the unavailability of patient-level data, we used WebplotDigitizer 4.2 to extract x and y coordinates from the KM curves of progression-free survival (PFS), overall survival (OS) and time on treatment (ToT) as presented in Figure 5, Figure 6 and Figure 7. The method proposed by Hoyle and Henley, was then employed to reproduce patient-level data from the number of patients at risk, together with the estimated number of events and censorships [30].

PFS and ToT curves were not extrapolated since they all reached (or almost reached) zero at the end of the follow-up. Therefore, the probabilities derived from the PFS (determined the percentage of progression-free patients) and ToT (determined the percentage of patients who received the treatment) curves were used directly.

For OS, independently fitted Weibull survival curves were used for the extrapolation. It was assumed that the PFS and ToT curves were always smaller than or equal to the OS at any time. The choices of these extrapolations were based on the preferred committee base-case assumptions, as explained in TA514 [26].

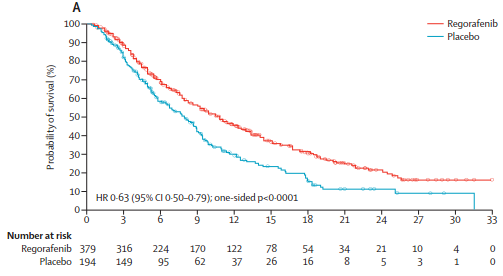


Figure 5: Kaplan-Meier estimates of overall survival from the RESORCE

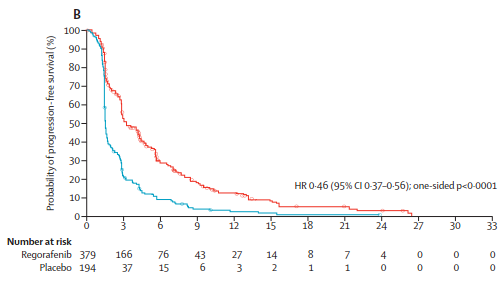


Figure 6: Kaplan-Meier estimates of progression-free survival from the RESORCE trial

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Figure 7: Kaplan-Meier estimates of time on treatment from the RESORCE trial from the January 23rd, 2017 data cut-off point, assuming that patients on treatment on 29th February 2016 are censored

***Adverse events***

In this study, we included the impact of adverse events (AEs) grade 3/4, which occurred in over 5% of patients in either regorafenib or BSC groups in the RESORCE trial [29]. Consequently, the model included the following AEs: anaemia, ascites, aspartate aminotransferase increase, blood bilirubin increase, fatigue, hypertension, hypophosphatemia and hand-foot skin reaction. AEs could occur at any cycle and incurred costs as well as dis-utilities associated with them. The average proportion of AEs was based on observed data from the RESORCE trial and the average per cycle rate of 3/4 AEs in regorafenib, and BSC arms were calculated to be 5.55% and 5.06%, respectively [28].

***Utilities***

Utility inputs for each health state and dis-utility for grade 3/4 AEs were retrieved from the company evidence submission. Health-related quality of life was derived from data collected in the RESORCE trial using the EQ-5D instrument. The utility values for the PF state, the post-progression state and dis-utility due to AEs were 0.811, 0.763 and -0.014, respectively.

***Costs***

*Drug acquisition cost*

Cost of regorafenib was calculated by multiplying the unit price by the recommended dose. The price for a pack of 84 tablets (each tablet contains 40mg regorafenib) is £3,744, which is equal to the cost of a full dose recommended per cycle. Since regorafenib was given orally, no administration costs were included in the model. In the base-case, in order to account for cost savings because of treatment interruptions and dose reductions, a relative dose intensity of 90% (reflecting the mean dose intensity of 144 mg from the RESORCE trial) was applied. In the scenario analysis, the full dose of 160mg regorafenib to estimate the drug acquisition cost was used.

These costs were applied for as long as the patient kept receiving treatment, which was determined by the ToT curve shown in Figure 7. We assumed that the MEAs from the manufacturer would merely impact on drug acquisition cost.

*Adverse event costs*

The average cost associated with AEs per cycle was weighted according to the rate of each event per cycle. The company used individual patient data observed within the RESORCE trial to calculate the proportions of each AE per cycle. On average, the cost associated with AEs per cycle incorporated in the model for regorafenib and BSC arm was £1,244 and £1,502 respectively (detailed calculations are presented in Appendix 1) [26] [27].

*Resource use costs*

Other costs related to health state resource use were estimated according to expert opinions from a physician survey in HCC conducted for sorafenib in 2015. Health state resource uses for patients treated with sorafenib was assumed to be identical to those for patients treated with regorafenib.

The resource use costs per cycle for the progression-free and post-progression state were calculated by multiplying unit costs by the resource use estimates. Additionally, the costs associated with lab tests for patients of the regorafenib arm at progression were applied as a one-off cost. The number of newly progressed patients was assumed to be equal to the proportion of patients leaving the progression-free state at any time (detailed calculations are available in Appendix 2).

* + 1. ***Sensitivity Analysis***

A one-way sensitivity analysis (OWSA) was undertaken to the base case in order to explore the parameter uncertainty in the model and examined the effects of individual parameters on the ICER [25] [31]. The selected parameters were varied one-by-one at a time over the lower and upper limits. The utility, probability and hazard ratio (HR) parameters were varied within their 95% confidence interval. The lower boundary of the “mean dose of regorafenib” was set at 120mg dosing, and the upper boundary was 160 mg dosing. Other parameters were varied within ± 30% of their baseline values.

Furthermore, a probabilistic sensitivity analysis (PSA) was conducted to characterise the combined effect of all parameter uncertainty in the model, which indicated whether regorafenib was cost-effective or not in the presence of the uncertainty inherent around the model parameters [25] [31].

The following list of parameters was simulated using the available standard errors (SE) from the literature. For those inputs that SEs were unavailable in the literature, the standard deviation (SD) and patient number were used to calculate the SE. If SD were unknown, a SE of 20% of the deterministic mean estimate was assumed to present a justifiable level of uncertainty.

Probabilistic distributions were then assigned to each group of input parameters according to their characteristics:

* Assigning the multivariate normal distribution for OS Weibull shape and scale parameters for regorafenib and BSC.
* Cycle-based adverse event probabilities of the regorafenib and BSC arms, as well as utility parameters, were varied based on the beta distribution.
* Cost parameters were varied according to the gamma distribution.
* Using the normal distribution for log-hazard ratio (with mean zero) in order to sample KM based PFS for regorafenib, BSC and KM-based and log-logistic extrapolated ToT for regorafenib.

Random samples were included utilising parameter distributions, and the process was repeated 1,000 times in the form of Monte Carlo simulations using Visual Basic for Applications tool in Microsoft Excel. The cost-effectiveness plane (CE-plane) plotted incremental QALYs versus incremental costs of 1000 iterations, which gave a visual illustration of the uncertainty in incremental costs and incremental QALYs. Furthermore, the CE-plane determined the shape of the cost-effectiveness acceptability curve (CEAC), which showed the probability that an intervention would be cost-effective compared to its comparator at a given threshold [31].

* + 1. ***Scenario Analyses***

The following scenario analyses were conducted to explore the structural uncertainty and assess how MEAs can perform under different levels of structural uncertainty.

* Scenario 1: Using full dose (MDI=100%) substituted for the MDI observed in the clinical trial.
* Scenario 2: Using financial discount rate of 2%.
* Scenario 3: Using financial discount rate of 8%.
* Scenario 4: Applying other distributions for the extrapolation of OS: lognormal distributions substituted for Weibull.
* Scenario 5: Using treatment-invariant health care resource use: The resource use costs in the base-case were treatment and disease state specific and were based on rough estimates from clinician surveys. In this scenario analysis, we use the same resource use for the health states (i.e. the average of regorafenib and BSC specific estimates).

The incremental costs, incremental QALYs, ICER, NMB and DCF results for each of the scenarios above were presented for all the MEAs.

1. **RESULTS**
   1. **Base-case results**
      1. ***Deterministic analysis***

Regorafenib yielded an additional 0.31 QALYs (0.39 additional life years) and incurred discounted incremental costs of £24,011, ultimately resulted in a discounted ICER of £76,754per QALY gained compared to BSC. For the manufacturer, the average DCF was £31,033 per patient. Using the threshold of £50,000per QALY, the iNMB was equal to -£8,369. (Table 1).

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| **DETERMINISTIC RESULTS (BASE CASE)** | | | | |
| **The Payer** | **Description** | **Costs** | **QALYs** | **LY** |
| **Discounted outcomes** | | | |
| Regorafenib | £44,812 | 0.946 | 1.206 |
| BSC | £20,800 | 0.633 | 0.815 |
| Increment | £24,011 | 0.313 | 0.391 |
| ICER | **£76,754** | | |
| iNMB | -£8,369 | | |
| **The Manufacturer** | DCF | £31,033 | | |

Table 1: Base case deterministic results

The disaggregated results (Table 2) showed incremental drug-related costs of £31,181 between regorafenib and BSC arms. The incremental AE management costs and other healthcare resource use costs were £278 and -£7,447, respectively. Incremental QALYs gained in the progression-free state; the post-progression state was 0.25 and 0.06, respectively. Incremental QALYs lost due to adverse events between two arms was insignificant (approximately 0).

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| **Treatment** | **Drug-related  costs** | **Adverse event  management costs** | **Other healthcare  resource use costs** | **QALYs accrued in progression-free state** | **QALYs accrued in post-progression state** | **QALYs lost due to adverse events** |
|
| Regorafenib | £31,181 | £1,086 | £12,545 | 0.442 | 0.505 | -0.001 |
| BSC | £0.00 | £808 | £19,993 | 0.189 | 0.444 | -0.001 |
| **Increment** | **£31,181** | **£278** | **-£7,447** | **0.252** | **0.061** | **0.000** |

Table 2: Disaggregated deterministic results

* + 1. ***Sensitivity analysis***
       1. ***One-way analysis***

The results of OWSA showed that the parameters with the most influence on the ICER were related to “HR for regorafenib ToT”, “mean dose of regorafenib” and hospitalisation costs in both PF and P states for BSC (Figure 8). Apart from the dramatically wide range of ICER (range from £16,602 to £134,308) associated with “HR for regorafenib ToT” variation, the ICER of the base case remained above £55,000/QALY once varying other parameters.

Figure 8: One-way sensitivity analysis results

* + - 1. ***Probabilistic analysis***

The results of probabilistic analysis, including CE-plane and CEAC, are presented in Table 3 and Figure 9. Regorafenib resulted in a probabilistic ICER of £78,073 per QALY gained when compared to BSC, and it yielded a £31,598 DCF for the manufacturer. At a threshold of £50,000, the iNMB was -£8,799, and the probability of regorafenib being cost-effective compared to BSC was 37.4%.

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| **PROBABILISTIC RESULTS (BASE CASE)** | | | | |
| **The Payer** | **Description** | **Costs** | **QALYs** | **LY** |
| **Discounted outcomes** | | | |
| Regorafenib | £45,453 | 0.95 | 1.21 |
| BSC | £20,982 | 0.64 | 0.82 |
| Increment | £24,471 | 0.31 | 0.39 |
| ICER | **£78,073** | | |
| iNMB | -£8,799 | | |
| **The Manufacturer** | DCF | £31,598 | | |

Table 3: Base case probabilistic results

Figure 9: CE-Plane (above) and CEAC (below) for the base case

* 1. **Manage entry agreement results**
     1. ***Deterministic Analyses***
        1. ***Individual manage entry agreement***

For each scheme, the values that would satisfy or marginally satisfy the WTP threshold of £50,000**/**QALY were computed and presented in the column “Value” (Table 4).

For the simple discount scheme, the minimum discount applied to the list price in order to meet the given threshold was 26.84% (resulting in a drug acquisition cost for full dose per cycle was £2,462). For the free treatment initiation scheme, three initial cycles treatment (including cycle 0) were provided for free. For the lifetime treatment acquisition cost-capping scheme, a maximum cap of £23,114 was charged, and for the money-back guarantee scheme, the minimum number of cycles for PFS for payback guarantee was eight cycles (excluding cycle 0).

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| **STRATEGY** | **VALUE** | **COSTS** | | | **QALYs** | | | **ICER** | **iNMB** | **DCF** |
| **Rego** | **BSC** | **Inc. Costs** | **Rego** | **BSC** | **Inc. QALYs** |
| **Base case** | **-** | **£44,812** | **£20,800** | **£24,011** | **0.946** | **0.633** | **0.313** | **£76,754** | **-£8,369** | **£31,033** |
| Simple discount scheme | 26.84% | £36,442 | £20,800 | £15,642 | 0.946 | 0.633 | 0.313 | £50,000 | £0 | £22,703 |
| Free treatment initiation scheme | 3 cycles | £35,945 | £20,800 | £15,145 | 0.946 | 0.633 | 0.313 | £48,411 | £497 | £22,170 |
| Lifetime treatment acquisition cost-capping scheme | £23,114 | £36,442 | £20,800 | £15,642 | 0.946 | 0.633 | 0.313 | £50,000 | £0 | **£22,769** |
| Money-back guarantee scheme | 8 cycles | £35,269 | £20,800 | £14,468 | 0.946 | 0.633 | 0.313 | £46,249 | **£1,174** | £21,507 |
| **Rego**: Regorafenib; **BSC**: Best supportive care; **Inc.**: incremental; **iNMB**: incremental net monetary benefit;  **DCF**: Discounted cash flow | | | | | | | | | | |

Table 4: Deterministic results for the individual manage entry agreements

According to the deterministic results (Table 4), both the simple discount scheme and the lifetime treatment acquisition cost-capping scheme resulted in the ICER of £50,000. The ICER values obtained from the free treatment initiation scheme and the money-back guarantee scheme were £48,411 and £46,249, respectively.

From the payer’s viewpoint, the money-back guarantee scheme resulted in the highest iNMB (£1,174). From the manufacturer’s viewpoint, the DCF from different MEAs were relatively similar, and the lifetime treatment acquisition cost-capping scheme yielded the greatest DCF (£22,769).

* + 1. ***Probabilistic Analyses***

The results of the probabilistic analysis for the individual MEAs and the combination of the simple discount scheme (26.4%) with the money-back guarantee scheme (1 cycle) are showed in Table 9, the CE-Planes and CEACs are provided in Appendix 4.

Generally, all the MEAs reduced the probabilistic ICERs compared to the base case. The probabilistic ICER ranged from £48,584 to £53,377 per QALY. The money-back guarantee scheme was the only scheme that resulted in ICER lower than £50,000/QALY with the value was £48,584.

Given a threshold of £50,000/QALY, the probability of regorafenib being cost-effective ranged from 51.5% to 53.8%, with the lowest likelihood resulted from using simple discount scheme (26.4%) in combination with money-back guarantee scheme (1 cycle) and the highest likelihood achieved by using the money-back guarantee scheme.

For the payer consideration, the money-back guarantee scheme produced positive mean iNMB, while other schemes led to the negative values. Among these schemes, the money-back guarantee scheme yielded the highest iNMB (£440); however, iNMB values varied dramatically in its distribution, and the SD (£16,617) obtained by using the money-back guarantee scheme also got the highest value. For the manufacturer, the DCF results were comparable among explored schemes. The probabilistic mean DCF ranged between £22,222 and £23,923. The lifetime treatment acquisition cost-capping scheme yielded the greatest DCF (£23,923) with the lowest SD (£6,333).

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| **Strategy** | **ICER** | **Prob. CE** | **Incremental Net Monetary Benefit** | | | | | **Discounted Cash Flow** | | | | |
| **Mean** | **2.5th  percentile** | **Median** | **97.5th  percentile** | **SD** | **Mean** | **2.5th  percentile** | **Median** | **97.5th  percentile** | **SD** |
| **Base case** | **£78,073** | **37.4%** | **-£8,799** | **-£38,352** | **-£7,849** | **£17,389** | **£17,101** | **£31,598** | **£6,958** | **£30,408** | **£61,842** | **£16,712** |
| Simple discount scheme (26.84%) | £51,041 | 52.8% | -£325 | -£22,954 | £1,520 | £19,460 | £12,754 | £23,029 | £5,172 | £20,368 | £44,819 | £12,371 |
| Free treatment initiation scheme (3 cycles) | £50,246 | 52.1% | -£77 | -£27,545 | £1,310 | £23,559 | £15,659 | £22,744 | £957 | £21,206 | £50,489 | £15,322 |
| Lifetime treatment acquisition cost-capping scheme  (£23,115) | £53,377 | 51.8% | -£1,048 | -£14,782 | £294 | £10,603 | £7,074 | **£23,923** | £14,715 | £21,780 | £34,863 | £6,333 |
| Money-back guarantee scheme  (8 cycles) | £48,584 | 53.8% | **£440** | -£27,916 | £2,362 | £25,992 | £16,617 | £22,222 | -£1,621 | £19,815 | £50,418 | £16,322 |
| Combination of simple discount scheme (26.4%) with money-back guarantee scheme (1 cycle) | £50,484 | 51.5% | -£149 | -£22,287 | £882 | £19,691 | £12,388 | £22,967 | £5,116 | £21,747 | £44,654 | £11,956 |
| **Prob. CE**: Probability of being cost-effective at WTP threshold of £50,000/QALY; **ICER**: Incremental cost-effectiveness ratio; **SD**: Standard deviation. | | | | | | | | | | | | |

Table 9: Probabilistic results for the individual manage entry agreements

* 1. **The HTA risk analysis and value of information analysis**
     1. ***The HTA Risk Analysis result for the base case***

Using SAVI online tool, we measured the value for PUB, PSB and P-SUB per patient. Those values are illustrated in the below HTA Risk Analysis chart.

Figure 10: HTA risk analysis chart for the base case

In the base case, if regorafenib were adopted, the payer would incur a total amount of burden equal to £11,730 per patient (P-SUB) consisting of a PSB of £8,251 and a PUB of £3,482. By contrast, the payer bore the risk burden linked with a PUB of £3,482 only if selecting BSC.

* + 1. ***The HTA Risk Analysis results for the MEAs***
       1. ***The HTA risk analysis chart***

Compared to the base case, the substantial decreases in the P-SUB results in the regorafenib arm were witnessed in all strategies using the MEAs (Figure 11). In the BSC arm, apart from using the lifetime treatment acquisition cost-capping scheme, the P-SUB values increased in other strategies. The PUB was the major component of the P-SUB for both arms, and the increasing of PUB values were seen in both arms except for the lifetime treatment acquisition cost-capping scheme.

For the simple discount scheme, the P-SUB value for regorafenib and BSC were £5,789 and £5,044, respectively. The free treatment initiation scheme resulted in a P-SUB of £6,479 for regorafenib and £7,250 for BSC. Applying the lifetime treatment acquisition cost-capping scheme led to a P-SUB of £3,511 for regorafenib and £2,385 for BSC. For the money-back guarantee scheme, the P-SUB values were equal to £6,599 and £7,805 for regorafenib and BSC, respectively. When combining the simple discount scheme with MGD, the P-SUB was equal to £5,454 for regorafenib and £5,228 for BSC arm.

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Figure 11: HTA risk analysis chart for the MEAs

* + - 1. ***The value of information analysis***

At a threshold of £50,000, the values of individual EVPI for the base case was lowest (£3,482) and the EVPI reached the highest value of £6,599 by using the money-back guarantee scheme. The illustration of individual EVPI across different WTP thresholds for the base case and the undertaken MEAs are presented in Figure 12. Apart from the base case, the EVPI for all schemes mostly reached a peak at the threshold of £50,000.

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EVPI = £5,044

EVPI = £3,482

EVPI = £2,385

EVPI = £6,479

EVPI = £5,228

EVPI = £6,599

Figure 12: Individual expected value of perfect information results

The full EVPPI results for single parameters are provided in Appendix 5. As can be seen in the OWSA results (Figure 8), “HR for regorafenib ToT” and “mean dose of regorafenib” contributed to most of the parameter uncertainty. Thus, we focused on examining the EVPPI value as well as their corresponding indices to overall EVPI of these two parameters (Table 10). The EVPPI associated with “HR for regorafenib ToT” varied from £1,899 to £6,350 with the lowest value was seen by using the lifetime treatment acquisition cost-capping scheme, and the money-back guarantee scheme resulted in the highest value. The EVPPI for “mean dose of regorafenib” ranged from £479 to £1,255 with the largest value was witnessed by using the combination of the simple discount scheme with the money-back guarantee scheme, and the money-back guarantee scheme resulted in the smallest EVPPI.

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| **Strategy Parameter** | **HR for Regorafenib (time on treatment)** | **Mean dose of Regorafenib** |
| **Base case** | **£3,118** | **£516** |
| Simple discount scheme | £4,736 | £1,089 |
| Free treatment initiation scheme | £6,102 | £960 |
| Lifetime treatment acquisition cost-capping scheme | £1,899 | £624 |
| Money-back guarantee scheme | £6,350 | £479 |
| Combination of the simple discount scheme with the money-back guarantee scheme | £4,861 | £1,255 |

Table 10: Single parameter EVPPI results

* 1. **Scenario Analyses**

Scenario analysis results are presented in Table 11. Without using MEAs, the deterministic ICER varied from £71,315 to £124,320.

In scenario 1, none of the MEAs resulted in the ICER less or equal to £50,000/QALY.

Scenario 2 and 3 did not alter the results of ICER, iNMB compared to the base case (Table 4). However, the results of DCF were varied due to the change in the financial discount rate. Once the rated reduce to 2%, the simple discount scheme yielded the greatest DCF (£23,146), whilst the lifetime treatment acquisition cost-capping scheme resulted in the highest DCF (£22,446) when using a financial discount rate of 8%.

In scenario 4, both incremental costs and incremental QALYs increased, the ICER increased, and iNMB decreased compared to the base case. The lifetime treatment acquisition cost-capping scheme and the money-back guarantee scheme were two schemes that marginally satisfied the £50,000 threshold. Whilst the lifetime treatment acquisition cost-capping scheme yielded the greater iNMB (£1,302), the money-back guarantee scheme resulted in the higher DCF (£23,865).

Assuming the health state resource use were equal between two arms (scenario 5) resulted in the highest ICER, and, thus, this is the most pessimistic scenario. The results showed that the incremental costs grew 162% compared to the base case whilst the incremental QALYs was maintained. As predicted, none of MEAs met the £50,000 threshold.

## 3.5 Scenario analyses:

Five scenario analyses are shown in Table 11, Table 12, Table 13, Table 14 and Table 15.

### 3.5.1 Scenario 1: Using full dose of 160mg regorafenib daily

The ICER values have increased in all MEA schemes in this scenario. The deterministic ICER varied from £50,191 to £87,751 with the lowest ICER obtained by applying the simple discount scheme and the highest ICER was obtained when no MEA was applied.For the payer, all NMB values were negative, and the greatest NMB was equal to -£60 resulted in the lifetime treatment acquisition cost-capping scheme. For the manufacturer, the simple discount scheme yielded the highest DCF of £25,208 (we did not take into consideration the case without MEA).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Type of MEA | Incremental costs | Incremental QALYs | ICER | NMB | DCF |
| Without MEA | £27,451.68 | 0.313 | £87,751.39 | -£11,809.95 | £34,457.38 |
| Simple discount scheme | £18,158.72 | 0.313 | £58,045.74 | -£2,516.99 | £25,208.37 |
| Free treatment initiation scheme | £17,606.86 | 0.313 | £56,281.66 | -£1,965.12 | £24,615.81 |
| Lifetime treatment acquisition cost-capping scheme | £15,701.60 | 0.313 | £50,191.38 | -£59.87 | £22,837.30 |
| PBRSA | £16,855.72 | 0.313 | £53,880.60 | -£1,213.99 | £23,880.38 |

Table 11: The results of scenario 1

### 3.5.2 Scenario 2: The financial interest rate varied from 4% to 2% per annual.

This scenario did not affect the ICER and NMB values, it merely influenced the DCF. Given the results in the table below, the simple discount scheme yielded the highest DCF of £23,146, and the lowest DCF of £22,043 was seen using PBRSA.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Type of MEA | Incremental costs | Incremental QALYs | ICER | NMB | DCF |
| Without MEA | £24,011.21 | 0.313 | £76,753.66 | -£8,369.47 | £31,638.30 |
| Simple discount scheme | £15,641.73 | 0.313 | £50,000.00 | £0.00 | £23,145.99 |
| Free treatment initiation scheme | £15,144.71 | 0.313 | £48,411.23 | £497.02 | £22,762.92 |
| Lifetime treatment acquisition cost-capping scheme | £15,641.73 | 0.313 | £50,000.00 | £0.00 | £22,938.96 |
| PBRSA | £14,468.22 | 0.313 | £46,248.78 | £1,173.51 | £22,043.38 |

Table 12: The results of scenario 2

### 3.5.3 Scenario 3: The financial interest rate varied from 4% to 8% per annual.

Similar to scenario 2, this scenario also only had an influence on the DCF results. The greatest DCF of £21,901 was obtained with the simple discount scheme, and the lowest one was £20,542 in the PBRSA.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Type of MEA | Incremental costs | Incremental QALYs | ICER | NMB | DCF |
| Without MEA | £24,011.21 | 0.313 | £76,753.66 | -£8,369.47 | £31,638.30 |
| Simple discount scheme | £15,641.73 | 0.313 | £50,000.00 | £0.00 | £21,900.94 |
| Free treatment initiation scheme | £15,144.71 | 0.313 | £48,411.23 | £497.02 | £21,095.78 |
| Lifetime treatment acquisition cost-capping scheme | £15,641.73 | 0.313 | £50,000.00 | £0.00 | £22,445.84 |
| PBRSA | £14,468.22 | 0.313 | £46,248.78 | £1,173.51 | £20,542.97 |

Table 13: The results of scenario 3

### 3.5.4 Scenario 4: Assuming a worse prognosis (PFS and OS)

In this scenario, a variation in the hazard ratio was assumed to reflect the real-world effectiveness difference. Therefore, we applied a hazard ratio of 0.9 to the PFS and 0.95 to the OS of regorafenib. These values are selected arbitrarily.

Compared to the base case (Table 5), this scenario lowered both the incremental costs and incremental QALYs. Without applying any MEA, the incremental costs went down from £24,011 (base case) to £22,982, and the incremental QALYs from 0.31 to 0.27.

The PBRSA obtained the lowest ICER of £49,186, and was also the only strategy that yielded a positive NMB (£219), whereas the highest DCF of £22,769 was seen in lifetime treatment acquisition cost-capping scheme.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Type of MEA | Incremental costs | Incremental QALYs | ICER | NMB | DCF |
| Without MEA | £22,982.42 | 0.27 | £85,256.79 | -£9,504.07 | £30,739.39 |
| Simple discount scheme | £14,693.66 | 0.27 | £54,508.37 | -£1,215.31 | £22,488.36 |
| Free treatment initiation scheme | £14,115.92 | 0.27 | £52,365.17 | -£637.57 | £21,875.83 |
| Lifetime treatment acquisition cost-capping scheme | £14,913.64 | 0.27 | £55,324.45 | -£1,435.29 | £22,769.26 |
| PBRSA | £13,258.99 | 0.27 | £49,186.24 | £219.36 | £21,033.01 |

Table 14: The results of scenario 4

### 3.5.5 Scenario 5: Treatment invariant resource use estimates

The costs related to health state resource uses for regorafenib arm were assumed to be equal to those for BSC arm. We set the values of resource uses equal to the average values of both arms (average of the treatment specific resource use estimates from regorafenib and BSC).

According to the results in below table, this scenario altered the incremental costs by varying the health resource uses for both arms. Without applying any MEA, the ICER increased from £24,011 (base case) to £38,892. This led to an increase in the ICER from £76,753.66 (base case) to £124,320. All four proposed MEAs did not meet an ICER of £50.000, and regorafenib was deemed to be not cost-effective compared to BSC. As a result, NMB values are negative in all strategies and we did not necessary to consider DCF.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Type of MEA | Incremental costs | Incremental QALYs | ICER | NMB | DCF |
| Without MEA | £38,891.51 | 0.313 | £124,319.68 | -£23,249.77 | £31,033.18 |
| Simple discount scheme | £30,522.04 | 0.313 | £97,566.02 | -£14,880.30 | £22,703.29 |
| Free treatment initiation scheme | £30,025.01 | 0.313 | £95,977.25 | -£14,383.28 | £22,169.61 |
| Lifetime treatment acquisition cost-capping scheme | £30,522.04 | 0.313 | £97,566.02 | -£14,880.30 | £22,769.26 |
| PBRSA | £29,348.52 | 0.313 | £93,814.79 | -£13,706.79 | £21,507.26 |

Table 15: The results of scenario 5

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**APPENDICES**

Appendix 1:Average cost associated with adverse events per cycle

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Adverse events** | **Cost** | **Rate** | | **AEs costs** | | **Cost Source** | **Weight source** |
| **Regorafenib** | **BSC** | **Regorafenib** | **BSC** |
| Anaemia | £ 1,283.67 | 0.40 | 1.09 | £ 513.47 | £ 1399.20 | NHS National Schedule of Reference Cost 2015-2016 (HRG code SA04G-SA04L) | Company submission (TA514), p.126-127 |
| Ascites | £ 1,667.00 | 0.45 | 1.43 | £ 750.15 | £ 2383.81 | NHS National Schedule of Reference Cost 2015-2016 (Average HRG codes GC12G-GC12K) | Company submission (TA514), p.126-127 |
| Aspartate aminotransferase increase | £ 1,667.00 | 0.74 | 1.08 | £ 1233.58 | £ 1800.36 | NHS National Schedule of Reference Cost 2015-2016 (Average HRG codes GC12G-GC12K) | Company submission (TA514), p.126-127 |
| Blood bilirubin increase | £ 1,667.00 | 0.41 | 0.71 | £ 683.47 | £ 1183.57 | NHS National Schedule of Reference Cost 2015-2016 (Average HRG codes GC12G-GC12K) | Company submission (TA514), p.126-127 |
| Fatigue | £ 1,667.00 | 0.38 | 0.25 | £ 633.46 | £ 416.75 | NHS National Schedule of Reference Cost 2015-2016 (Average HRG codes GC12G-GC12K) | Company submission (TA514), p.126-127 |
| Hypertension | £ 729.87 | 1.15 | 0.37 | £ 839.35 | £ 270.05 | NHS National Schedule of Reference Cost 2015-2016 (HRG code EB04Z) | Company submission (TA514), p.126-127 |
| Hypophosphatemia | £ 1,261.96 | 1.25 | 0.10 | £ 1577.45 | £ 126.20 | NHS National Schedule of Reference Cost 2015-2016 (Average HRG codes KC05J-KC05N) | Company submission (TA514), p.126-127 |
| Hand-foot skin reaction | £ 873.37 | 0.77 | 0.04 | £ 672.49 | £ 34.93 | NHS National Schedule of Reference Cost 2015-2016 (HRG code XD57Z) | Company submission (TA514), p.126-127 |
| **Weighted cost for AEs per cycle** |  | | | **£ 1243.8601** | **£ 1501.9473** |  | |

Table 12:Average cost associated with adverse events per cycle

Appendix 2: Health state resource use for patients in both the progression-free and post-progression states

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Item** | **Unit cost** | **Progression-free** | | **Post-progression** | | **Cost source** | **Resource use source** |
| **Regorafenib** | **BSC** | **Regorafenib** | **BSC** |
| **Hospitalisation** | | | | | | | |
| General ward | £801 | 0.07 | 0.25 | 0.08 | 0.25 | Average fully absorbed inpatient bed day cost in 2012/13. Inflated to 2016 costs using HCHS pay and prices index | Company submission  (NICE committee paper TA514) |
| Duration of stay (day) | - | 5.83 | 7 | 5.25 | 7 |  | Company submission  (NICE committee paper TA514) |
| Cost of hospitalisation [1] | - | £4669.83 | £5607 | £4205.25 | £5607 |  | Company submission  (NICE committee paper TA514) |
| A&E admission | £204.11 | 0.37 | 0.25 | 0.08 | 0.25 | ERG's report (NICE committee paper TA514) | Company submission  (NICE committee paper TA514) |
| **Medical staff visit** | | | | | | | |
| Oncologist | 163 | 1.07 | 0.75 | 1 | 0.75 | NHS Reference Costs (code 370) | Company submission  (NICE committee paper TA514) |
| Hepatologist | 253 | 0.33 | 0 | 0 | 0 | NHS Reference Costs (code 306) | Company submission  (NICE committee paper TA514) |
| Clinical nurse specialist | 130 | 0.67 | 0.5 | 0.5 | 0.5 | PSSRU 2016 | Company submission  (NICE committee paper TA514) |
| Palliative care team | £119.03 | 0 | 2.17 | 0 | 0 | NHS Reference Costs (code SD04A & SD05A) | Company submission  (NICE committee paper TA514) |
| Specialist visit | £162.84 | 0.84 | 0.84 | 0.5 | 0.84 | ERG's report (NICE committee paper TA514) | Company submission  (NICE committee paper TA514) |
| **Lab tests** | | | | | | | |
| Alpha fetoprotein | £3.03 | 1 | 0.84 | 1.84[2] | 0.84 | Cardiff and Vale Acute Chemistry Repertoire 2016/2017 Inflated to 2018 costs using HCHS pay and prices index | Company submission  (NICE committee paper TA514) |
| Liver function | £2.78 | 1 | 0.84 | 1.00[2] | 0.84 | Akhtar, W. and Chung, Y (2014) Inflated to 2018 costs using HCHS pay and prices index | Company submission  (NICE committee paper TA514) |
| Biochemistry | £1.34 | 1 | 0.84 | 1.84[2] | 0.84 | Akhtar, W. and Chung, Y (2014) Inflated to 2018 costs using HCHS pay and prices index | Company submission  (NICE committee paper TA514) |
| **Item** | **Unit cost** | **Progression-free** | **Post-progression** | **Cost source** | **Resource use source** | **Item** | **Unit cost** |
| Complete blood count | £2.65 | 1 | 0.84 | 1.84[2] | 0.84 | Akhtar, W. and Chung, Y (2014) Inflated to 2018 costs using HCHS pay and prices index | Company submission  (NICE committee paper TA514) |
| International normalised ratio | £3.43 | 0.71 | 0.34 | 0.67[3] | 0.34 | NHS Reference Costs | Company submission  (NICE committee paper TA514) |
| **Radiological tests** | | | | | | | |
| CT scan of abdomen | £122.00 | 0.39 | 0.17 | 0.84[3] | 0.17 | NHS Reference Costs (code RD22Z) | Company submission  (NICE committee paper TA514) |
| [1]: Calculated by multiplying the duration of stay by general ward [2]: 1.00 at progression (one-off cost) [3]: 0.67 at progression (one-off cost) | | | | | | | |

Table 13:Resource use for patients in both the progression-free and post-progression state

Appendix 3: List of input parameters and corresponding distributions for deterministic and probabilistic analyses

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PARAMETER DESCRIPTION** | **VALUE** | **DISTRIBUTION** | **STANDARD ERROR** | **SOURCE** |
| **UTILITIES** | | | | |
| Utility for progression-free state | 0.811 | Beta | 0.0046 | NICE (2018), Company Submission TA514 |
| Utility decrement for progression | 0.048 | Beta | 0.005 | NICE (2018), Company Submission TA514 |
| Utility decrement for adverse events | 0.014 | Beta | 0.007 | NICE (2018), Company Submission TA514 |
| **PROBABILITIES** | | | | |
| Probability of adverse events occurrence for Regorafenib | 0.056 | Beta | 0.0111 | NICE (2018), Company Submission TA514 |
| Probability of adverse events occurrence for BSC | 0.051 | Beta | 0.0101 | NICE (2018), Company Submission TA514 |
| **COSTS** | | | | |
| **Cost of treatment** | | | | |
| Cost of Regorafenib per cycle | £3,744 | Fixed | N/A | NICE (2019), Guidance TA555 |
| Mean dose intensity of Regorafenib | £0.90 | Beta | 0.148 | Bruix (2017), RESORCE Trial |
| **Costs of adverse events** | | | | |
| Costs of adverse events per cycle for Regorafenib | £1,243.86 | Gamma | 248.772 | NICE (2018), Company Submission TA514 |
| Costs of adverse events per cycle for BSC | £1,501.95 | Gamma | 300.389 | NICE (2018), Company Submission TA514 |
| **Progression-free costs** | | | | |
| **Hospitalisations** | | | | |
| Hospitalisation cost for Regorafenib | £326.89 | Gamma | 65 | NICE (2018), Company Submission TA514 |
| Accident & Emergency Admin cost for Regorafenib | £75.52 | Gamma | 15 | NHS Reference Costs 2015-2016 and NICE (2018), Company Submission TA514 |
| Hospitalisation cost for BSC | £1,401.75 | Gamma | 280 | NICE (2018), Company Submission TA514 |

Appendix 3 (continued): List of input parameters and corresponding distributions for deterministic and probabilistic analyses

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PARAMETER DESCRIPTION** | **VALUE** | **DISTRIBUTION** | **STANDARD ERROR** | **SOURCE** |
| Accident & Emergency Admin cost for BSC | £51.03 | Gamma | 10 | NHS Reference Costs 2015-2016 and NICE (2018), Company Submission TA514 |
| **Medical staff visits** | | | | |
| Cost of visiting Oncologist for Regorafenib | £174.41 | Gamma | 35 | NHS Reference Costs (code 370) and NICE (2018), Company Submission TA514 |
| Cost of visiting Hepatologist for Regorafenib | £83.49 | Gamma | 17 | NHS Reference Costs (code 306) and NICE (2018), Company Submission TA514 |
| Cost of visiting Clinical nurse specialist for Regorafenib | £87.10 | Gamma | 17 | PSSRU 2016 and NICE (2018), Company Submission TA514 |
| Cost of visiting Specialist for Regorafenib | £136.79 | Gamma | 27 | NHS Reference Costs (code 370) and NICE (2018), Company Submission TA514 |
| Cost of visiting Oncologist for BSC | £122.25 | Gamma | 24 | NHS Reference Costs (code 370) and NICE (2018), Company Submission TA514 |
| Cost of visiting Clinical nurse specialist for BSC | £65 | Gamma | 13 | PSSRU 2016 and NICE (2018), Company Submission TA514 |
| Cost of visiting Palliative care team for BSC | £258.30 | Gamma | 52 | NHS Reference Costs (code 191) and NICE (2018), Company Submission TA514 |
| Cost of visiting Specialist for BSC | £136.79 | Gamma | 27 | NHS Reference Costs (code 370) and NICE (2018), Company Submission TA514 |
| **Lab Tests** | | | | |
| Cost of Alpha fetoprotein test for Regorafenib | £3.03 | Gamma | 1 | NICE (2018), Company Submission TA514 and Cardiff and Vale Acute Chemistry Repertoire 2016/2017 |
| Cost of Liver function test for Regorafenib | £2.78 | Gamma | 1 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |
| Cost of Biochemistry test for Regorafenib | £1.34 | Gamma | 0 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |
| Cost of Complete blood count test for Regorafenib | £2.65 | Gamma | 1 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |

Appendix 3 (continued): List of input parameters and corresponding distributions for deterministic and probabilistic analyses

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PARAMETER DESCRIPTION** | **VALUE** | **DISTRIBUTION** | **STANDARD ERROR** | **SOURCE** |
| Cost of International normalised ratio test for Regorafenib | £2.44 | Gamma | 0 | NICE (2018), Company Submission TA514 and NHS Reference Costs 2015-16 |
| Cost of Alpha fetoprotein test for BSC | £2.55 | Gamma | 1 | NICE (2018), Company Submission TA514 and Cardiff and Vale Acute Chemistry Repertoire 2016/2017 |
| Cost of Liver function test for BSC | £2.34 | Gamma | 0 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |
| Cost of Biochemistry test for BSC | £1.13 | Gamma | 0 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |
| Cost of Complete blood count test for BSC | £2.23 | Gamma | 0 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |
| Cost of International normalised ratio test for BSC | £1.17 | Gamma | 0 | NICE (2018), Company Submission TA514 and NHS Reference Costs 2015-16 |
| **Radiological tests** | | | | |
| Cost of CT scan of abdomen for Regorafenib | £20.74 | Gamma | 4 | NHS Reference Costs (code RD22Z) and NICE (2018), Company Submission TA514 |
| Cost of CT scan of abdomen for BSC | £20.74 | Gamma | 4 | NHS Reference Costs (code RD22Z) and NICE (2018), Company Submission TA514 |
| **One-off costs at progression** | | | | |
| Cost of Alpha fetoprotein test for Regorafenib | £3.03 | Gamma | 1 | NICE (2018), Company Submission TA514 and Cardiff and Vale Acute Chemistry Repertoire 2016/2017 |
| Cost of Liver function test for Regorafenib | £2.78 | Gamma | 1 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |
| Cost of Biochemistry test for Regorafenib | £1.34 | Gamma | 0 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |
| Cost of Complete blood count test for Regorafenib | £2.65 | Gamma | 1 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |

Appendix 3 (continued): List of input parameters and corresponding distributions for deterministic and probabilistic analyses

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PARAMETER DESCRIPTION** | **VALUE** | **DISTRIBUTION** | **STANDARD ERROR** | **SOURCE** |
| Cost of International normalised ratio test for Regorafenib | £2.30 | Gamma | 0 | NICE (2018), Company Submission TA514 and NHS Reference Costs 2015-16 |
| Cost of CT scan of abdomen for Regorafenib | £81.74 | Gamma | 16 | NICE (2018), Company Submission TA514 and NHS Reference Costs (code RD22Z) |
| **Post-progression costs** | | | | |
| **Hospitalisations** | | | | |
| Hospitalisation cost for Regorafenib | £336.42 | Gamma | 67 | NICE (2018), Company Submission TA514 |
| Accident & Emergency Admin cost for Regorafenib | £16.33 | Gamma | 3 | NHS Reference Costs 2015-2016 and NICE (2018), Company Submission TA514 |
| Hospitalisation cost for BSC | £1,401.75 | Gamma | 280 | NICE (2018), Company Submission TA514 |
| Accident & Emergency Admin cost for BSC | £51.03 | Gamma | 10 | NHS Reference Costs 2015-2016 and NICE (2018), Company Submission TA514 |
| **Medical staff visits** | | | | |
| Cost of visiting Oncologist for Regorafenib | £163 | Gamma | 33 | NHS Reference Costs (code 370) and NICE (2018), Company Submission TA514 |
| Cost of visiting Clinical nurse specialist for Regorafenib | £65 | Gamma | 13 | PSSRU 2016 and NICE (2018), Company Submission TA514 |
| Cost of visiting Specialist for Regorafenib | £81.42 | Gamma | 16 | NHS Reference Costs (code 370) and NICE (2018), Company Submission TA514 |
| Cost of visiting Oncologist for BSC | £122.25 | Gamma | 24 | NHS Reference Costs (code 370) and NICE (2018), Company Submission TA514 |
| Cost of visiting Clinical nurse specialist for BSC | £65 | Gamma | 13 | PSSRU 2016 and NICE (2018), Company Submission TA514 |
| Cost of visiting Specialist for BSC | £136.79 | Gamma | 27 | NHS Reference Costs (code 370) and NICE (2018), Company Submission TA514 |
| **Lab Tests** | | | | |
| Cost of Alpha fetoprotein test for Regorafenib | £2.55 | Gamma | 1 | NICE (2018), Company Submission TA514 and Cardiff and Vale Acute Chemistry Repertoire 2016/2017 |

Appendix 3 (continued): List of input parameters and corresponding distributions for deterministic and probabilistic analyses

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PARAMETER DESCRIPTION** | **VALUE** | **DISTRIBUTION** | **STANDARD ERROR** | **SOURCE** |
| Cost of Biochemistry test for Regorafenib | £1.13 | Gamma | 0 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |
| Cost of Complete blood count test for Regorafenib | £2.23 | Gamma | 0 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |
| Cost of Alpha fetoprotein test for BSC | £2.55 | Gamma | 1 | NICE (2018), Company Submission TA514 and Cardiff and Vale Acute Chemistry Repertoire 2016/2017 |
| Cost of Liver function test for BSC | £2.34 | Gamma | 0 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |
| Cost of Biochemistry test for BSC | £1.13 | Gamma | 0 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |
| Cost of Complete blood count test for BSC | £2.23 | Gamma | 0 | NICE (2018), Company Submission TA514 and Akhtar, W. & Chung, Y. (2014) |
| Cost of International normalised ratio test for BSC | £1.17 | Gamma | 0 | NICE (2018), Company Submission TA514 and NHS Reference Costs 2015-16 |
| **Radiological tests** | | | | |
| Cost of CT scan of abdomen for Regorafenib | £20.74 | Gamma | 4 | NHS Reference Costs (code RD22Z) and NICE (2018), Company Submission TA514 |
| Cost of CT scan of abdomen for BSC | £20.74 | Gamma | 4 | NHS Reference Costs (code RD22Z) and NICE (2018), Company Submission TA514 |
| **OTHER PAPAMETERS** | | | | |
| Annual cost and outcome discount rate | 3.50% | Fixed | N/A | NICE guideline |
| Weibull intercept | 2.83 | Normal | (0,1) | Calculation |
| Weibull log(scale) | -0.08 | Normal | (0,1) | Calculation |
| Hazard Ratio for Regorafenib Progression-free | 1 | Log normal | 0.15 | Estimation |
| Hazard Ratio for BSC Progression-free | 1 | Log normal | 0.6 | Estimation |
| Hazard Ratio for Regorafenib Time on treatment | 1 | Log normal | 0.71 | Estimation |

Appendix 4: Cost-effectiveness planes and cost-effectiveness acceptability curves for the individual MEAs and MEAs in combinations

Figure 13:CE-Plane (above) and CEAC (below) for the simple discount scheme

*Appendix 4 (continued): Cost-effectiveness planes and cost-effectiveness acceptability curves for the individual MEAs and MEAs in combinations*

Figure 14:CE-Plane (above) and CEAC (below) for the free treatment initiation scheme

*Appendix 4 (continued): Cost-effectiveness planes and cost-effectiveness acceptability curves for the individual MEAs and MEAs in combinations*

Figure 15:CE-Plane (above) and CEAC (below) for the lifetime treatment acquisition cost-capping scheme

*Appendix 4 (continued): Cost-effectiveness planes and cost-effectiveness acceptability curves for the individual MEAs and MEAs in combinations*

Figure 16:CE-Plane (above) and CEAC (below) for the money-back guarantee scheme

*Appendix 4 (continued): Cost-effectiveness planes and cost-effectiveness acceptability curves for the individual MEAs and MEAs in combinations*

Figure 17:CE-Plane (above) and CEAC (below) for the combination of simple discount scheme with money-back guarantee scheme.

Appendix 5:Expected value of partially perfect information results

1. **The base case**

**Single parameter EVPPI**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Per Person EVPPI (£)** | **Standard Error** | **Indexed to Overall EVPI = 1.00** | **EVPPI for The UK Per Year (£)** |
| Mean dose intensity-Regorafenib | 515.61 | 130.95 | 0.15 | 515600.0 |
| Post-progression hospitalisation cost \_BSC | 0.81 | 4.98 | 0.00 | 807.9 |
| Hazard Ratio time on treatment-Regorafenib | 3117.95 | 124.42 | 0.90 | 3118000.0 |

*Appendix 5 (continued): Expected value of partially perfect information results*

1. **Simple discount scheme (26.84%)**

**Single parameter EVPPI**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Per Person EVPPI (£)** | **Standard Error** | **Indexed to Overall EVPI = 1.00** | **EVPPI for The UK Per Year (£)** |
| Utility for progression-free state | 4.15 | 78.86 | 0.00 | 4.149e+03 |
| Utility for post-progression state | 17.59 | 86.26 | 0.00 | 1.759e+04 |
| Mean dose intensity-Regorafenib | 1088.73 | 168.39 | 0.22 | 1.089e+06 |
| Costs of adverse events -Regorafenib | 5.71 | 72.21 | 0.00 | 5.708e+03 |
| Costs of adverse events -BSC | 10.10 | 81.46 | 0.00 | 1.010e+04 |
| Progression-free - hospitalisation cost \_BSC | 216.12 | 156.15 | 0.04 | 2.161e+05 |
| Progression-free- Cost of visiting Hepatologist -Regorafenib | 60.89 | 119.02 | 0.01 | 6.089e+04 |
| Progression-free -Cost of visiting Clinical nurse specialist -Regorafenib | 259.12 | 173.64 | 0.05 | 2.591e+05 |
| Progression-free - Cost of visiting Oncologist - BSC | 12.49 | 85.08 | 0.00 | 1.249e+04 |
| Progression-free - Cost of visiting Clinical nurse specialist -BSC | 1.21 | 68.82 | 0.00 | 1.212e+03 |
| Progression-free - Cost of Biochemistry test -Regorafenib | 27.15 | 102.10 | 0.01 | 2.715e+04 |
| Progression-free - Cost of International normalised ratio test - Regorafenib | 61.80 | 112.62 | 0.01 | 6.180e+04 |
| Progression-free -Cost of International normalised ratio test - BSC | 18.09 | 92.85 | 0.00 | 1.809e+04 |
| Progression-free -Cost of CT scan of abdomen -BSC | 7.71 | 79.11 | 0.00 | 7.712e+03 |
| At progression \_Cost of International normalised ratio test for Regorafenib | 19.59 | 91.51 | 0.00 | 1.959e+04 |
| Post-progression - Hospitalisation cost - BSC | 599.35 | 183.71 | 0.12 | 5.993e+05 |
| Post-progression - Accident & Emergency Admin cost -BSC | 5.27 | 73.87 | 0.00 | 5.272e+03 |
| Post-progression - Cost of visiting Clinical nurse specialist - Regorafenib | 5.83 | 74.50 | 0.00 | 5.826e+03 |
| Post-progression - Cost of Complete blood count test -Regorafenib | 12.53 | 79.47 | 0.00 | 1.253e+04 |
| Post-progression - Cost of Alpha fetoprotein test - BSC | 82.60 | 121.76 | 0.02 | 8.260e+04 |
| Post-progression - Cost of CT scan of abdomen - BSC | 109.08 | 136.86 | 0.02 | 1.091e+05 |
| OS – Weilbull- intercept-Regorafenib | 281.02 | 158.20 | 0.06 | 2.810e+05 |
| OS- Weilbull- intercept -BSC | 16.07 | 93.31 | 0.00 | 1.607e+04 |
| OS- Weilbull-log(scale)-BSC | 1.69 | 65.29 | 0.00 | 1.687e+03 |
| Hazard Ratio PFS-Regorafenib | 5.54 | 108.24 | 0.00 | 5.536e+03 |
| Hazard Ratio time on treatment-Regorafenib | 4735.93 | 115.03 | 0.94 | 4.736e+06 |

*Appendix 5 (continued): Expected value of partially perfect information results*

1. **Free treatment initiation scheme (3 initial cycles including cycle 0)**

**Single parameter EVPPI**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Per Person EVPPI (£)** | **Standard Error** | **Indexed to Overall EVPI = 1.00** | **EVPPI for The UK Per Year (£)** |
| Utility for progression-free state | 181.80 | 144.67 | 0.03 | 1.818e+05 |
| Utility for post-progression state | 62.11 | 118.06 | 0.01 | 6.211e+04 |
| Utility decrement for adverse events - Regorafenib | 55.87 | 147.83 | 0.01 | 5.587e+04 |
| Utility decrement for adverse events - BSC | 29.57 | 161.33 | 0.00 | 2.957e+04 |
| Probability of adverse events occurrence -Regorafenib | 17.89 | 112.06 | 0.00 | 1.789e+04 |
| Probability of adverse events occurrence -BSC | 43.56 | 123.29 | 0.01 | 4.356e+04 |
| Mean dose intensity-Regorafenib | 959.62 | 323.02 | 0.15 | 9.596e+05 |
| Progression-free -Hospitalisation cost \_Regorafenib | 194.59 | 180.47 | 0.03 | 1.946e+05 |
| Progression-free -Hospitalisation cost \_BSC | 263.68 | 170.18 | 0.04 | 2.637e+05 |
| Progression-free - Accident & Emergency Admin cost BSC | 501.13 | 238.61 | 0.08 | 5.011e+05 |
| Progression-free - Cost of visiting Oncologist - Regorafenib | 272.39 | 179.00 | 0.04 | 2.724e+05 |
| Progression-free- Cost of visiting Hepatologist -Regorafenib | 125.03 | 173.23 | 0.02 | 1.250e+05 |
| Progression-free -Cost of visiting Clinical nurse specialist -Regorafenib | 120.88 | 155.93 | 0.02 | 1.209e+05 |
| Progression-free -Cost of visiting specialist -Regorafenib | 115.07 | 192.63 | 0.02 | 1.151e+05 |
| Progression-free -Cost of visiting Clinical nurse specialist -BSC | 171.62 | 156.29 | 0.03 | 1.716e+05 |
| Progression-free -Cost of visiting Palliative care team - BSC | 87.75 | 151.67 | 0.01 | 8.775e+04 |
| Progression-free - Cost of visiting specialist -BSC | 155.89 | 172.54 | 0.02 | 1.559e+05 |
| Progression-free - Cost of Alpha fetoprotein test - Regorafenib | 3.62 | 140.08 | 0.00 | 3.617e+03 |
| Progression-free - Cost of Biochemistry test -Regorafenib | 6.05 | 109.31 | 0.00 | 6.052e+03 |
| Progression-free - Cost of Complete blood count test -Regorafenib | 124.51 | 164.34 | 0.02 | 1.245e+05 |
| Progression-free - Cost of International normalised ratio test - Regorafenib | 1.39 | 96.03 | 0.00 | 1.391e+03 |
| Progression-free - Cost of Biochemistry test -BSC | 135.96 | 156.96 | 0.02 | 1.360e+05 |
| Progression-free - Cost of Complete blood count test -BSC | 16.65 | 120.76 | 0.00 | 1.665e+04 |
| Progression-free -Cost of CT scan of abdomen -Regorafenib | 23.75 | 115.57 | 0.00 | 2.375e+04 |
| At progression - Cost of Alpha fetoprotein test - Regorafenib | 107.16 | 163.94 | 0.02 | 1.072e+05 |
| At progression - Cost of Liver function test - Regorafenib | 103.29 | 130.66 | 0.02 | 1.033e+05 |
| At progression - Cost of Biochemistry test -Regorafenib | 66.99 | 146.94 | 0.01 | 6.699e+04 |
| At progression - Cost of Complete blood count test - Regorafenib | 106.16 | 186.42 | 0.02 | 1.062e+05 |
| At progression - Cost of International normalised ratio test- Regorafenib | 30.91 | 142.20 | 0.00 | 3.091e+04 |
| Post-progression - Hospitalisation cost - Regorafenib | 27.21 | 142.70 | 0.00 | 2.721e+04 |
| Post-progression - Accident & Emergency Admin cost - Regorafenib | 49.29 | 171.92 | 0.01 | 4.929e+04 |
| Post-progression - Hospitalisation cost - BSC | 514.81 | 233.06 | 0.08 | 5.148e+05 |
| Post-progression - Accident & Emergency Admin cost -BSC | 130.67 | 139.90 | 0.02 | 1.307e+05 |
| Post-progression - Cost of visiting Oncologist - Regorafenib | 48.65 | 136.61 | 0.01 | 4.865e+04 |
| Post-progression - Cost of visiting Clinical nurse specialist -Regorafenib | 108.36 | 121.09 | 0.02 | 1.084e+05 |
| Post-progression - Cost of visiting specialist -Regorafenib | 2.73 | 104.41 | 0.00 | 2.730e+03 |
| Post-progression - Cost of Biochemistry test -Regorafenib | 120.52 | 184.21 | 0.02 | 1.205e+05 |
| Post-progression - Cost of Complete blood count test - Regorafenib | 19.55 | 106.21 | 0.00 | 1.955e+04 |
| Post-progression - Cost of International normalised ratio test- BSC | 134.80 | 153.58 | 0.02 | 1.348e+05 |
| Post-progression -Cost of CT scan of abdomen -BSC | 215.78 | 178.85 | 0.03 | 2.158e+05 |
| OS- Weilbull-intercept -Regorafenib | 216.63 | 162.51 | 0.03 | 2.166e+05 |
| OS- Weilbull -log(scale) -Regorafenib | 2.83 | 93.00 | 0.00 | 2.830e+03 |
| OS- Weilbull -log(scale)-BSC | 36.09 | 145.77 | 0.01 | 3.609e+04 |
| Hazard Ratio PFS-Regorafenib | 238.68 | 209.26 | 0.04 | 2.387e+05 |
| Hazard Ratio time on treatment-Regorafenib | 6102.35 | 117.92 | 0.94 | 6.102e+06 |

*Appendix 5 (continued): Expected value of partially perfect information results*

1. **Lifetime treatment acquisition cost-capping scheme (£23,115)**

**Single parameter EVPPI**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Per Person EVPPI (£)** | **Standard Error** | **Indexed to Overall EVPI = 1.00** | **EVPPI for England Per Year (£)** |
| Utility for progression-free state | 9.12 | 29.98 | 0.00 | 9.121e+03 |
| Probability of adverse events occurrence -Regorafenib | 5.16 | 24.55 | 0.00 | 5.163e+03 |
| Mean dose intensity-Regorafenib | 624.43 | 78.52 | 0.26 | 6.244e+05 |
| Progression-free -Hospitalisation cost \_BSC | 107.77 | 64.38 | 0.05 | 1.078e+05 |
| Progression-free- Cost of visiting Hepatologist -Regorafenib | 17.16 | 26.74 | 0.01 | 1.716e+04 |
| Progression-free - Cost of Liver function test - BSC | 2.73 | 12.24 | 0.00 | 2.727e+03 |
| Progression-free - Cost of Alpha fetoprotein test - BSC | 2.89 | 26.99 | 0.00 | 2.890e+03 |
| Post-progression - Hospitalisation cost - Regorafenib | 6.87 | 27.48 | 0.00 | 6.867e+03 |
| Post-progression - Hospitalisation cost - BSC | 279.87 | 87.15 | 0.12 | 2.799e+05 |
| Post-progression - Cost of Alpha fetoprotein test - BSC | 6.51 | 25.86 | 0.00 | 6.515e+03 |
| OS- Weilbull-intercept -Regorafenib | 225.92 | 90.57 | 0.09 | 2.259e+05 |
| OS- Weilbull-intercept -BSC | 14.23 | 34.64 | 0.01 | 1.423e+04 |
| Hazard Ratio PFS-Regorafenib | 1.29 | 16.35 | 0.00 | 1.292e+03 |
| Hazard Ratio time on treatment-Regorafenib | 1898.80 | 99.81 | 0.80 | 1.899e+06 |
| Hazard Ratio PFS-BSC | 2.21 | 9.23 | 0.00 | 2.213e+03 |

*Appendix 5 (continued): Expected value of partially perfect information results*

1. **Money-back guarantee scheme (8 cycles)**

**Single parameter EVPPI**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Per Person EVPPI (£)** | **Standard Error** | **Indexed to Overall EVPI = 1.00** | **EVPPI for the UK Per Year (£)** |
| Utility for progression-free state | 35.84 | 109.08 | 0.01 | 3.584e+04 |
| Utility for post-progression state | 78.33 | 166.11 | 0.01 | 7.833e+04 |
| Probability of adverse events occurrence -Regorafenib | 153.38 | 130.76 | 0.02 | 1.534e+05 |
| Probability of adverse events occurrence -BSC | 29.16 | 123.35 | 0.00 | 2.916e+04 |
| Mean dose intensity-Regorafenib | 478.63 | 308.95 | 0.07 | 4.786e+05 |
| Costs of adverse events -Regorafenib | 46.73 | 110.44 | 0.01 | 4.673e+04 |
| Costs of adverse events -BSC | 5.70 | 85.04 | 0.00 | 5.697e+03 |
| Progression-free -Hospitalisation cost \_Regorafenib | 268.58 | 198.97 | 0.04 | 2.686e+05 |
| Progression-free - Accident & Emergency Admin cost - Regorafenib | 46.51 | 109.62 | 0.01 | 4.651e+04 |
| Progression-free -Hospitalisation cost \_BSC | 53.04 | 160.89 | 0.01 | 5.304e+04 |
| Progression-free -Cost of visiting specialist -Regorafenib | 12.33 | 91.07 | 0.00 | 1.233e+04 |
| Progression-free - Cost of visiting Oncologist - BSC | 34.16 | 112.17 | 0.01 | 3.416e+04 |
| Progression-free -Cost of visiting Clinical nurse specialist -BSC | 5.66 | 106.44 | 0.00 | 5.658e+03 |
| Progression-free -Cost of visiting Palliative care team - BSC | 12.39 | 84.61 | 0.00 | 1.239e+04 |
| Progression-free -Cost of visiting specialist -BSC | 63.67 | 149.13 | 0.01 | 6.367e+04 |
| Progression-free - Cost of Liver function test -Regorafenib | 6.26 | 78.96 | 0.00 | 6.264e+03 |
| Progression-free - Cost of Complete blood count test -Regorafenib | 93.80 | 150.25 | 0.01 | 9.380e+04 |
| Progression-free - Cost of Liver function test -BSC | 21.49 | 94.96 | 0.00 | 2.149e+04 |
| Progression-free - Cost of Complete blood count test -BSC | 74.46 | 148.07 | 0.01 | 7.446e+04 |
| Progression-free - Cost of International normalised ratio test - BSC | 1.84 | 86.04 | 0.00 | 1.837e+03 |
| At progression - Cost of Liver function test - Regorafenib | 6.74 | 90.02 | 0.00 | 6.743e+03 |
| At progression - Cost of Complete blood count test - Regorafenib | 4.03 | 81.51 | 0.00 | 4.034e+03 |
| At progression - Cost of International normalised ratio test- Regorafenib | 166.56 | 126.61 | 0.03 | 1.666e+05 |
| Post-progression - Hospitalisation cost - Regorafenib | 13.54 | 99.40 | 0.00 | 1.354e+04 |
| Post-progression - Hospitalisation cost - BSC | 43.21 | 183.51 | 0.01 | 4.321e+04 |
| Post-progression - Cost of visiting Oncologist - Regorafenib | 1.59 | 85.80 | 0.00 | 1.594e+03 |
| Post-progression - Cost of visiting Clinical nurse specialist -Regorafenib | 8.08 | 90.43 | 0.00 | 8.085e+03 |
| Post-progression - Cost of visiting specialist -Regorafenib | 5.74 | 85.64 | 0.00 | 5.743e+03 |
| Post-progression - Cost of visiting Oncologist - BSC | 67.25 | 150.04 | 0.01 | 6.725e+04 |
| Post-progression - Cost of Alpha fetoprotein test - Regorafenib | 87.34 | 148.19 | 0.01 | 8.734e+04 |
| Post-progression - Cost of Liver function test - BSC | 154.62 | 172.53 | 0.02 | 1.546e+05 |
| Post-progression - Cost of Biochemistry test -BSC | 29.65 | 135.72 | 0.00 | 2.965e+04 |
| Post-progression - Cost of Complete blood count test - BSC | 19.82 | 88.27 | 0.00 | 1.982e+04 |
| Post-progression - Cost of International normalised ratio test- BSC | 56.63 | 129.41 | 0.01 | 5.663e+04 |
| OS- Weilbull-intercept -Regorafenib | 50.02 | 126.31 | 0.01 | 5.002e+04 |
| OS- Weilbull-intercept -BSC | 263.23 | 216.35 | 0.04 | 2.632e+05 |
| Hazard Ratio PFS-Regorafenib | 81.95 | 137.70 | 0.01 | 8.195e+04 |
| Hazard Ratio time on treatment-Regorafenib | 6349.51 | 109.81 | 0.96 | 6.350e+06 |

*Appendix 5 (continued): Expected value of partially perfect information results*

1. **The combination of simple discount scheme (26.4%) with money-back guarantee scheme (1 cycle)**

**Single parameter EVPPI**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Per Person EVPPI (£)** | **Standard Error** | **Indexed to Overall EVPI = 1.00** | **EVPPI for UK Per Year (£)** |
| Utility for progression-free state | 80.51 | 107.76 | 0.02 | 8.051e+04 |
| Utility decrement for progression | 237.07 | 150.09 | 0.05 | 2.371e+05 |
| Utility for post-progression state | 159.54 | 128.04 | 0.03 | 1.595e+05 |
| Utility decrement for adverse events - Regorafenib | 234.61 | 153.88 | 0.04 | 2.346e+05 |
| Utility decrement for adverse events - BSC | 123.89 | 135.11 | 0.02 | 1.239e+05 |
| Probability of adverse events occurrence -Regorafenib | 104.07 | 114.61 | 0.02 | 1.041e+05 |
| Probability of adverse events occurrence -BSC | 366.99 | 157.14 | 0.07 | 3.670e+05 |
| Mean dose intensity-Regorafenib | 1254.68 | 168.24 | 0.24 | 1.255e+06 |
| Costs of adverse events -Regorafenib | 228.61 | 146.59 | 0.04 | 2.286e+05 |
| Costs of adverse events -BSC | 249.57 | 155.14 | 0.05 | 2.496e+05 |
| Progression-free -Hospitalisation cost \_Regorafenib | 164.57 | 136.23 | 0.03 | 1.646e+05 |
| Progression-free - Accident & Emergency Admin cost - Regorafenib | 138.16 | 138.70 | 0.03 | 1.382e+05 |
| Progression-free -Hospitalisation cost \_BSC | 375.08 | 163.18 | 0.07 | 3.751e+05 |
| Progression-free - Cost of visiting Oncologist - Regorafenib | 330.73 | 130.03 | 0.06 | 3.307e+05 |
| Progression-free- Cost of visiting Hepatologist -Regorafenib | 33.36 | 83.14 | 0.01 | 3.336e+04 |
| Progression-free -Cost of visiting Clinical nurse specialist - Regorafenib | 60.26 | 100.12 | 0.01 | 6.026e+04 |
| Progression-free -Cost of visiting specialist -Regorafenib | 179.72 | 139.88 | 0.03 | 1.797e+05 |
| Progression-free - Cost of visiting Oncologist - BSC | 102.07 | 116.16 | 0.02 | 1.021e+05 |
| Progression-free -Cost of visiting Clinical nurse specialist - BSC | 2.60 | 79.25 | 0.00 | 2.603e+03 |
| Progression-free -Cost of visiting specialist -Regorafenib | 8.19 | 80.41 | 0.00 | 8.188e+03 |
| Progression-free - Cost of Alpha fetoprotein test - Regorafenib | 16.67 | 96.25 | 0.00 | 1.667e+04 |
| Progression-free - Cost of Liver function test -Regorafenib | 129.12 | 118.97 | 0.02 | 1.291e+05 |
| Progression-free - Cost of Biochemistry test -Regorafenib | 133.74 | 132.72 | 0.03 | 1.337e+05 |
| Progression-free - Cost of Complete blood count test -Regorafenib | 17.75 | 81.62 | 0.00 | 1.775e+04 |
| Progression-free - Cost of International normalised ratio test - Regorafenib | 11.03 | 86.90 | 0.00 | 1.103e+04 |
| Progression-free - Cost of Alpha fetoprotein test - BSC | 11.73 | 82.04 | 0.00 | 1.173e+04 |
| Progression-free - Cost of Liver function test - BSC | 60.00 | 95.36 | 0.01 | 6.000e+04 |
| Progression-free - Cost of Biochemistry test -BSC | 0.00 | 73.14 | 0.00 | 0.000e+00 |
| Progression-free - Cost of Complete blood count test -BSC | 67.16 | 93.79 | 0.01 | 6.716e+04 |
| Progression-free - Cost of International normalised ratio test - BSC | 147.49 | 125.60 | 0.03 | 1.475e+05 |
| Progression-free -Cost of CT scan of abdomen -Regorafenib | 108.01 | 113.55 | 0.02 | 1.080e+05 |
| Progression-free -Cost of CT scan of abdomen -BSC | 138.55 | 128.02 | 0.03 | 1.386e+05 |
| At progression - Cost of Liver function test - Regorafenib | 266.48 | 145.92 | 0.05 | 2.665e+05 |
| At progression - Cost of Biochemistry test -Regorafenib | 88.35 | 112.50 | 0.02 | 8.835e+04 |
| At progression - Cost of Complete blood count test - Regorafenib | 6.09 | 78.37 | 0.00 | 6.095e+03 |
| At progression - Cost of International normalised ratio test- Regorafenib | 4.39 | 81.47 | 0.00 | 4.387e+03 |
| At progression - Cost of CT scan of abdomen -Regorafenib | 3.27 | 76.64 | 0.00 | 3.272e+03 |
| Post-progression - Hospitalisation cost - Regorafenib | 398.04 | 190.39 | 0.08 | 3.980e+05 |
| Post-progression - Hospitalisation cost - BSC | 608.09 | 179.83 | 0.12 | 6.081e+05 |
| Post-progression - Cost of visiting Oncologist - Regorafenib | 150.17 | 127.17 | 0.03 | 1.502e+05 |
| Post-progression - Cost of visiting Clinical nurse specialist -Regorafenib | 82.94 | 113.52 | 0.02 | 8.294e+04 |
| Post-progression - Cost of visiting specialist -Regorafenib | 80.22 | 99.67 | 0.02 | 8.022e+04 |
| Post-progression - Cost of visiting Oncologist - BSC | 28.94 | 85.76 | 0.01 | 2.894e+04 |
| Post-progression - Cost of visiting Clinical nurse specialist -BSC | 210.07 | 144.04 | 0.04 | 2.101e+05 |
| Post-progression - Cost of visiting specialist -BSC | 122.57 | 110.49 | 0.02 | 1.226e+05 |
| Post-progression - Cost of Alpha fetoprotein test - Regorafenib | 1.71 | 73.80 | 0.00 | 1.713e+03 |
| Post-progression - Cost of Complete blood count test - Regorafenib | 163.28 | 112.37 | 0.03 | 1.633e+05 |
| Post-progression - Cost of Alpha fetoprotein test - BSC | 147.22 | 129.94 | 0.03 | 1.472e+05 |
| Post-progression - Cost of Liver function test - BSC | 255.32 | 150.27 | 0.05 | 2.553e+05 |
| Post-progression - Cost of Biochemistry test -BSC | 143.06 | 140.01 | 0.03 | 1.431e+05 |
| Post-progression - Cost of Complete blood count test - BSC | 163.32 | 141.18 | 0.03 | 1.633e+05 |
| Post-progression - Cost of CT scan of abdomen -Regorafenib | 93.02 | 109.72 | 0.02 | 9.302e+04 |
| Post-progression - Cost of CT scan of abdomen -BSC | 1.28 | 74.82 | 0.00 | 1.283e+03 |
| OS- Weilbull-intercept -Regorafenib | 619.61 | 187.09 | 0.12 | 6.196e+05 |
| OS- Weilbull-log(scale) -Regorafenib | 87.10 | 109.33 | 0.02 | 8.710e+04 |
| OS- Weilbull-intercept -BSC | 250.99 | 147.20 | 0.05 | 2.510e+05 |
| OS- Weilbull-log(scale) -BSC | 29.36 | 86.47 | 0.01 | 2.936e+04 |
| Hazard Ratio PFS-Regorafenib | 22.85 | 82.40 | 0.00 | 2.285e+04 |
| Hazard Ratio time on treatment-Regorafenib | 4860.66 | 106.43 | 0.93 | 4.861e+06 |
| Hazard Ratio PFS-BSC | 277.16 | 172.53 | 0.05 | 2.772e+05 |