Erratum for

Title: Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours

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Contributions of authors

Tracey Jones-Hughes	Led the critique of the company's decision problem and clinical effectiveness evidence. Wrote the Summary, Background, Decision problem, Clinical effectiveness and Overall conclusions. Compiled the report. Provided overall project management.
James Dunham	Contributed to the critique of the economic model and contributed to writing the Cost-effectiveness and End-of-life sections.
Sophie Robinson	Led the critique of the company's literature searching for this submission. Wrote the review of the literature searches for the report. Contributed to the writing and editing of the report.
Mark Napier	Provided clinical advice on soft tissue sarcoma and its management within the NHS. Reviewed and revised a draft version of the report.
Martin Hoyle	Contributed to writing the Cost-effectiveness and End-of-life sections. Contributed to the critique of the economic model and is the guarantor of the report.

for 16.8% of patients and distributed across all system organ classes. Five deaths were reported as related to regorafenib treatment by investigators (cardiac arrest, acute hepatic failure, acute kidney injury, colonic perforation, and thromboembolic event).

The most serious adverse drug reactions in patients receiving regorafenib were haemorrhage, severe liver injury, and gastrointestinal perforation and the most common adverse events included hand-foot skin reaction (HFSR), hypertension, diarrhoea, mucositis and fatigue

1.3 Summary of the ERG's critique of the clinical effectiveness evidence submitted

The methods for the searches and systematic review were adequate and well described, therefore, the ERG concluded that the company did not miss any evidence.

The primary focus of the company's submission was the GRID study. This was an appropriately-designed double-blinded, multi-centre RCT. The treatment arms were balanced and patients were representative of the UK population.

The crossover of 87.9% of placebo-treated patients to open-label regorafenib following disease progression may cause the OS to be overestimated, assuming regorafenib provides a clinical benefit for this outcome. Therefore Bayer applied two correction methods, which have been assessed as appropriate by the ERG, resulting in a statistically significant difference for OS in favour of regorafenib.

1.4 Summary of cost-effectiveness evidence submitted by the company

So far, we have received a total of three versions of Bayer's economic model and cost-effectiveness results.

We received Bayer's economic model and full report on 21st March 2017.

On 25th April 2017, after an earlier request for clarification from us, we received a second version of Bayer's economic model and cost-effectiveness results. This included some updated OS data, as discussed in Section 5.3.6, p**Error! Bookmark not defined.**.

On 16th May 2017, in response to another request for clarification from us, we received a third version of Bayer's economic model and cost-effectiveness results. In addition to the updated OS data, this also included some updated data on treatment duration and mean observed dose of regorafenib (excluding those with a dose of 0 mg) by cycle, as discussed in Section 5.3.8.1, p102.

censoring date within the crossover adjustment calculation" (Bayer response to clarification, p11). This reduction in mean OS substantially improves the cost-effectiveness of regorafenib. For example, assuming the PAS, the ICER for regorafenib vs. BSC decreases from £49,000 to £38,000 per QALY.

However, we have several important concerns with the switching adjustment applied to the 2017 data. Given these concerns, we use the 2015 data-cut for OS in our base case.

We turn now to the extrapolation of OS. Two consultant oncologists, who specialised in the disease area, validated the fittings of various parametric models, on behalf of Bayer. They argued that the loglogistic, Weibull and Gompertz models all looked clinically plausible. However, in their base case, Bayer chose the log-logistic distribution for OS based on the accuracy of the fit the data from GRID.

We surveyed the literature for studies that could help to inform the extrapolation of OS. We found just one relevant study, which suggested, if anything, a reasonably long tail for OS. However, we caution not to rely solely on this study to inform extrapolation, due to limitations in comparability with the GRID study. On balance, in our base case, we model OS as the average of the shorter-tailed Weibull and longer-tailed log-logistic distributions.

Bayer do not explicitly model background general population mortality. In our base case, we include this additional mortality.

1.4.2.3 End of Life criteria

We agree with Bayer that regorafenib meets the End of Life criteria.

1.4.3 Results

In Bayer's base case analysis (without/with PAS), treatment with regorafenib resulted in 1.7333 QALYs at a cost of [redacted]/£47,249, while treatment with the placebo resulted in 0.761 QALYs at a cost of £10,395. The QALY differential was 0.971 and the cost differential was £[redacted]/£36,854. The corresponding ICERs per QALY were £[redacted]/£37,941.

Regorafenib was predicted to result in QALY gains in both PFS and OS, with the benefits roughly similar in both health states. The overall QALY gain depends heavily on the treatment switching adjustments.

Drug acquisition costs were by far the largest cost in the regorafenib arm at £[redacted]/£35,363 which was also the incremental cost as the placebo arm had zero drug costs. Other cost differentials were much smaller; the next largest incremental cost was +£[redacted] for monitoring costs in the regorafenib arm. Remaining costs were very similar between the two treatment arms.

In the probabilistic sensitivity analysis, the ICERs per QALY were similar to the deterministic case at £[redacted]/£38,494 without and with the PAS. Both costs and QALYs were very similar to the base case. At a willingness to pay threshold of £50,000 per QALY, regorafenib had a [redacted]/82% chance of being cost-effective.

Univariate sensitivity analyses were also carried out, indicating that results were sensitive to a number of parameters. Regorafenib drug costs and utility discount rates were the most impactful parameters, with HSUVs and cost discount rates also being significant.

Bayer also carried scenario analyses looking at assumptions for: OS extrapolation, treatment switching, resource use, and utility elicitation method. The most impactful of these were the choice of OS extrapolation, and the method of treatment switching adjustment.

1.5 Summary of the ERG's critique of the cost-effectiveness evidence submitted

The derivation of the PenTAG base case is shown in Table 1 below.

Total uncertainty in the cost-effectiveness of regorafenib versus BSC is high due to:

Substantial uncertainty in the adjustment for widespread treatment switching on diseases progression, from BSC to regorafenib.

Important uncertainty in the extrapolation of OS.

In key plausible scenario analyses, we suggest alternative plausible methods of extrapolating OS, and of modelling costs and QALYs only whilst patients are in PFS.

Table 1. Derivation of PenTAG base case ICERs Regorafenib vs. BSC (£ per QALY)

				Regorafenib price	
				PAS	List
	Bayer base case			**£38,000**	[redacted]
	PenTAG assumption	**Bayer assumption**			
1	OS from 2015 data-cut	OS from 2017 data-cut	(Section 5.3.6.2, p**Error! Bookmark not defined.**)	£49,000	[redacted]

2	Include general mortality from UK population	Do not including general mortality from UK population	(Section 5.3.6.3, p**Error! Bookmark not defined.**)	£41,000	[redacted]

Following adjustment for crossover, both the 2015 and 2017 data indicate a statistically significant difference in overall survival favouring regorafenib. The RPSFT method, based on 2015 data, gave a median OS 17.4 months over the placebo median OS of 11.9 months. Based on 2017 data, the RPSFT method for placebo gave a median OS of 8.4 months. Using the IPE method, placebo gave a median OS of 11.1 months based on 2015 data and 8 months based on 2017 data. The 2017 data show a longer OS benefit compared to placebo (varying from 9 to 9.4 months) than when considering the 2015 data (varying from 5.5 to 6.3 months).

Time to progression

For the cut-off date of 26th January 2012, 57.1% of participants in the regorafenib group experienced disease progression and 93.9% in the placebo group. Median TTP was reported as 165 days in the regorafenib group and 28 days in the placebo group (HR 0.248, [95% CI: 0.170-0.364, p<0.000001]). Therefore, there is a statistically significant difference between arms, in favour of regorafenib for TTP.

Objective Response Rate, Disease Control Rate and Duration of Response

For ORR, although numerically in favour of regorafenib, there was no statistically significant difference between the two arms: 4.5% with regorafenib (PR n= 6/133) vs. 1.5% with placebo (PR n=1/66) and there were no cases reported of complete response.

[redacted]

The disease control rate (DCR) reflects the percentage of patients with metastatic cancer who have achieved complete response, partial response and stable disease, as opposed to ORR which only includes CR or PR. Stable disease was reported by the company to be 71.4% (95/133 patients) in the regorafenib arm as compared to 33.3% (22/66 patients) in the placebo arm. Therefore, DCR for the regorafenib group was 52.6% (n=70/133) compared with 9.1% (n=6/66) in the placebo group (95% CI: –54.72, –32.49; p<0.0001). Bayer suggest this outcome indicates the clinically meaningful tumour control of regorafenib as a third-line treatment in patients with advanced GIST.

With regard to median duration of response, only one patient in the placebo group reported PR, which was 30 days, whereas the median duration of response for patients receiving regorafenib was 99 days.

Maximum percent reduction in the size of target lesions

[redacted]

4.2.2.4.3 Exploratory endpoints

Secondary PFS (SPFS)

Bayer investigated secondary PFS for participants who crossed over from placebo to regorafenib (n=56; 151 days) and for participants who continued on open label regorafenib,

Figure 1. Overall survival by subgroup, IPE correction (data cut-off 08 June 2015)

Source: Bayer submission, Section 4.8, p108

4.2.2.4.5 Adverse events

The GRID study included 198 participants in the safety population, which included 132 in the regorafenib arm and 66 participants in the placebo arm who received at least one dose of regorafenib. The analysis included treatment-emergent adverse events (TEAEs) occurring up to the primary efficacy analysis cut-off date of 26th January 2012.

Secondary analyses included patients who crossed over to regorafenib from placebo (n=132+58) and a subgroup of patients who received regorafenib for over 1 year (n=75).

A summary for all grade adverse events (AEs) is presented in Table 14 which reports the incidences of AEs for > 10 % of people in any treatment arm. The main groups are included, with further detail on individual conditions provided in Appendix 2.

End of life costs were taken from the study conducted by Abel et al [24], a UK hospice-based study. Costs were inflated to 2015/2016 level. The final EoL cost used is £8,736. Finally, Table 43 gives a complete summary of per-cycle variable costs and non-cost parameters.

Table 2. Summary of variables applied in the economic model (per cycle)

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Regorafenib cost	£[redacted]	(£[redacted]-£[redacted])	Table 45
One-time costs for regorafenib	£56	(£45-£67)	Table 54
Regorafenib + BSC while progression-free	£124	(£99-£149)	Table 54
BSC while progression-free	£80	(£64-£96)	Table 54
BSC post-progression	£89	(£71-£107)	Table 54
End of life costs	£8,736	(£8,052-£9,422)	Table 58
Diarrhoea costs	£7	(£6-£8)	Table 55
Hypertension costs	£12	(£9-£14)	Table 56
Progression-free state utility	0.767	(0.718-0.816)	Table 36
Post-progression state utility	0.647	(0.571-0.723)	Table 36
Discount rate (costs)	3.5%	(0-6%)	Table 29
Discount rate (benefits)	3.5%	(0-6%)	Table 29

Source: Bayer submission, Table 60, p.190

5.3.9 Cost-effectiveness results

Bayer's base case ICERs of regorafenib plus BSC compared to BSC alone are £[redacted]QALY and £37,941/QALY without and with the PAS respectively. Table 44 and

5.3.10 Sensitivity analyses

Bayer carried out both one-way sensitivity analyses (OWSA) and probabilistic sensitivity analyses to explore the effect of parameter uncertainty. Scenario analyses were also performed to explore the effects of assumptions in the model.

5.3.10.1 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) is a method of allowing all model parameters which are uncertain to vary simultaneously (for example, the exact HSUV for each state may be uncertain, but the list price of the drug is set by the company and is certain). Uncertain parameters were given suitable parametric distributions and repeatedly sampled 3,000 times and the ICERs recorded for each simulation. The probability of HFSR and diarrhoea were not varied in the PSA as there were 0 events in the GRID study making standard errors difficult to estimate. These probabilities were examined in the OWSA, but were found to have negligible effects on the ICERs per QALY. Table 49 shows the average of the simulated ICERs per QALY.

The base case PSA ICERs were £[redacted]/QALY without PAS and £38,494 with PAS. Results from the Monte Carlo simulations were also plotted in the (incremental cost QALY) space shown in Figure 34 and Figure 35 without and with PAS. The proportion of simulations which fall below the willingness-to-pay threshold (dotted line) gives the probability of the treatment being cost-effective. At a threshold of £50,000, regorafenib had a [redacted]% chance to be cost-effective without the PAS, and an 82% chance with the PAS.