SMC2562

regorafenib film-coated tablets (Stivarga®)

Bayer Plc.

08 September 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

regorafenib (Stivarga®) is accepted for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy.

In two phase III studies, regorafenib was associated with statistically significant benefits in overall survival versus placebo.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Regorafenib is an oral tumour deactivation agent that blocks various protein kinases involved in tumour angiogenesis, oncogenesis, metastasis and tumour immunity. In particular, regorafenib inhibits mutated KIT, an important oncogenic driver in gastrointestinal stromal tumours. The recommended dose of regorafenib is 160mg taken orally once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle. Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs.[1] In 2015, in the absence of a submission from the market authorisation holder, regorafenib was not recommended for use within NHS Scotland by SMC for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies (SMC1118/15).

1.2. Disease background

Colorectal cancer (CRC) is the third most common cancer in Scotland, accounting for 12% of cancer diagnoses per year; in 2017, there were 3,800 new cases. CRC is ranked second for mortality in Scotland, with 11% of all cancer-related deaths being due to CRC. Non age-standardised relative survival at 5 years for patients diagnosed between 2007 and 2011 was 60%. From 2007 to 2017, the incidence decreased by 19% and from 2008 to 2018 mortality reduced by 7.8%. In most cases, the initial diagnosis is carried out at the late stages of the disease, which is associated with poor prognosis. At present, there is no cure for metastatic CRC.[2, 3]

1.3. Treatment pathway and relevant comparators

Treatment options for patients with metastatic CRC include surgical resection and systemic anti-cancer therapy (SACT). The backbone of SACT is fluoropyrimidine chemotherapy (eg 5-fluorouracil or capecitabine), commonly given in combinations with oxaliplatin or irinotecan (FOLFOX, FOLFIRI, CapOX regimens). There are a number of targeted therapies available for use in the appropriate patients as per extant SMC/Healthcare Improvement Scotland advice. Trifluridine/tipiracil has been accepted for use by SMC as per the licensed indication, in patients who have received prior therapies or they are not suitable. The most relevant comparators for this submission are trifluridine plus tipiracil and best supportive care.

1.4. Category for decision-making process

Regorafenib meets SMC end of life and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of regorafenib for the treatment of metastatic colorectal cancer comes from two studies- CORRECT and CONCUR. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies

Criteria	CORRECT[2, 4]	CONCUR[5]
Study design	Phase III, randomised, double-blind, placebo-controlled, multicentre study	
Eligible patients	• Age ≥18 years • Histologically or cytologically confirmed metastatic CRC • Disease progression during or within 3 months following the last administration of approved standard therapies which had to include fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if KRAS wild type), unless contraindicated or stopped before disease progression due to unacceptable toxicity or not registered in the country where the study was performed • Patients treated with oxaliplatin in an adjuvant setting were to have progressed during or within 6 months of completion of adjuvant therapy • Patients who had progressed more than 6 months after completion of oxaliplatin-containing adjuvant treatment were to be retreated with oxaliplatin-based therapy to be eligible • Patients with unknown KRAS status at screening were to have received prior anti-EGFR treatment • ECOG Performance Status score of 0 or 1 • Life expectancy of at least 3 months • Measurable or not measurable disease but evaluable by RECIST version 1.1	• Asian adults (≥18 years of age) • Histologically or cytologically confirmed adenocarcinoma of the colon or rectum • Measurable or non-measurable metastatic disease according to RECIST version 1.1. • Patients had to have received at least two previous treatment lines • Disease progression during or within 3 months (or within 6 months of stopping adjuvant oxaliplatin) following the last administration of approved standard therapies which had to include a fluoropyrimidine plus oxaliplatin or irinotecan, unless stopped before disease progression due to unacceptable toxicity. Previous treatment with bevacizumab, cetuximab, or panitumumab was allowed but not mandatory. • ECOG performance status of 0 or 1 • Life expectancy of at least 3 months
Treatments	Regorafenib 160mg once daily orally for 3 weeks followed by 1 week off therapy (cycle of 4 weeks) or placebo. Treatment was to continue until disease progression according to RECIST 1.1, clinical progression, unacceptable toxicity, and/or consent withdrawal.	Regorafenib 160mg once daily orally for 3 weeks followed by 1 week off therapy (cycle of 4 weeks) or placebo. Treatment was to continue until disease progression, death, unacceptable toxic effects, withdrawal of consent by the patient, or decision by the treating physician that discontinuation would be in the patient's best interest. Patients with disease progression could continue treatment at the investigator's discretion.
Randomisation	Randomisation was in a 2:1 ratio and was stratified according to prior treatment with VEGF targeting drugs (yes/no), time from diagnosis of metastatic disease (≥18 months versus <18 months), and geographic region (region 1: North America, Western Europe, Israel, and Australia versus region 2: Asia versus region 3: South America, Turkey, and Eastern Europe).	Randomisation was in a 2:1 ratio and was stratified according to number of metastatic sites (single versus multiple organs), and time from diagnosis of metastatic disease (≥18 months versus <18 months).

Primary outcome	The primary outcome was overall survival, defined as the time between date of randomisation and death due to any cause.
Secondary outcomes	Progression-free survival, objective response rate, disease control rate.
Statistical analysis	No imputation was made for missing data. There was no hierarchical testing procedure.
Abbreviations: CRC = colorectal cancer; ECOG = Eastern Cooperative Oncology Group; RECIST = Response Evaluation Criteria in Solid Tumours	

The primary and selected secondary outcome results for CORRECT and CONCUR have been presented in Table 2.2 below.

Table 2.2 Results from CORRECT and CONCUR (ITT populations).[2, 4, 5, 6]

	CORRECT		CONCUR	
	Regorafenib (n = 505)	**Placebo (n = 255)**	**Regorafenib (n = 136)**	**Placebo (n = 68)**
Primary outcome: overall survival				
Data-cut	July 2011		November 2013	
Median follow-up	-		7.4 months	
Number of events	275	157	95	60
Median overall survival	6.4 months	5.0 months	8.8 months	6.3 months
Hazard ratio (95% CI)	0.77 (0.64 to 0.94) p=0.005		0.55 (0.40 to 0.77) p <0.001	
Overall survival rate at 6 months	52%	44%	*	*
Secondary outcome: investigator-assessed progression-free survival (RECIST 1.1 criteria)				
Data cut	July 2011		November 2013	
Number of events	430	241	*	*
Median PFS	1.9 months	1.7 months	3.2 months	1.7 months
Hazard ratio (95% CI)	0.49 (0.42 to 0.58)		0.31 (0.22 to 0.44)	
PFS rate at 6 months	13%	2.1%	*	*
Abbreviations: CI = confidence interval; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; PFS = progression-free survival * Results considered confidential by company.				

*Other data were also assessed but remain confidential.**

Results from a later data-cut (November 2011) where 74% of patients in CORRECT had died were consistent with the primary data-cut; overall survival HR 0.79 (95% CI 0.66 to 0.94).[2]

2.2. Health-related quality of life outcomes

In CORRECT and CONCUR, Health Related Quality of Life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D questionnaires. No clinically meaningful differences in quality of life were observed between treatment groups from baseline to end of treatment.[4, 5] The regulatory body noted however a numerical trend towards lower scores (worse quality of life) for patients treated with regorafenib over time in single domain evaluations in CORRECT.[2]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing regorafenib with trifluridine plus tipiracil, the submitting company presented an indirect treatment comparison. This has been used to inform the economic base case.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	NMA and supplementary Bucher ITCs and anchored MAICs
Population	Patients with relapsed/refractory metastatic colorectal cancer previously treated with two lines of standard therapies such as fluorouracil, capecitabine, oxaliplatin, irinotecan or cetuximab monotherapy, or combination therapy
Comparators	Trifluridine plus tipiracil, BSC
Studies included	Regorafenib: CORRECT[4], CONCUR[5] Trifluridine plus tipiracil: RECOURSE[7], TERRA[8], Yoshino 2012[9]
Outcomes	Overall survival and PFS
Results	The results of the NMAs suggest there is no evidence of a difference between regorafenib and trifluridine plus tipiracil for overall survival (HR = 0.99; 95% CrI: 0.84 to 1.17) or PFS (HR = 0.93; 95% CrI: 0.85 to 1.03). Sensitivity analysis, including the Bucher ITCs and MAICs, were generally consistent with the results of the NMA.
Abbreviations: BSC = best supportive care; CrI = credible intervals; HR = hazard ratio; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; NMA = Network Meta-Analysis; PFS = progression-free survival;	

3. Summary of Safety Evidence

In the CORRECT study, the median duration of treatment in the regorafenib group (n=500) was 7.27 weeks and in the placebo group (n=253) was 6.98 weeks. Any treatment-related adverse event (TRAE) was reported by 93% (465/500) of patients in the regorafenib group and 61% (154/253) in the placebo group. In the regorafenib and placebo groups respectively, patients reporting a grade 3 or higher TRAE were 55% versus 14%, patients with a reported serious TRAE were 12% versus 3.6%, patients with a dose modification due to treatment emergent TRAEs were 56% versus 9.1%, and patients permanently discontinuing therapy due to an AE was 8.2% versus 1.2%.[2]

The most frequently reported TRAEs of any grade with an incidence >10% in the regorafenib group versus the placebo group were: fatigue (47% versus 28%), hand-foot skin reaction (47% versus 8%), diarrhoea (34% versus 8%), anorexia (30% versus 15%), voice changes (29% versus 6%), hypertension (28% versus 6%), oral mucositis (27% versus 4%), rash or desquamation (26% versus 4%), nausea (14% versus 11%), weight loss (14% versus 2%), and fever (10% versus 3%).[4]

Overall, the safety profile of regorafenib was consistent across studies and was in line with what is expected for an angiogenetic and multi-tyrosine kinase inhibitor. Hypertension, skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhoea, mucositis) were prominent, whereas hematologic toxicities were limited.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Evidence comes from two phase III, double-blind studies.
- Regorafenib was associated with statistically significant benefits in overall survival versus placebo in both CORRECT and CONCUR. The survival data can be considered mature.
- Regorafenib is an oral treatment which can be administered at home, an important consideration for late-stage cancer.

4.2. Key uncertainties

- Although statistically significant, the overall survival gain from treatment with regorafenib was modest. In CORRECT, median overall survival was approximately 1.5 months greater than placebo. Median PFS gain was about seven days. Overall response rate (ORR) was very low in all treatment groups, which suggests survival benefit is driven by disease stabilisation.[2, 4] The risk/benefit ratio of treatment is closely balanced considering the toxicity profile of regorafenib.
- There may be issues that impact the generalisability of the study results to the Scottish population. CORRECT and CONCUR recruited between 2010 and 2013, and since then the treatment pathway for patients with metastatic colorectal cancer has changed considerably as more targeted treatments based on biomarker status are now available. Moreover, 100% and 60% (approximately) of patients in CORRECT and CONCUR respectively had previously received bevacizumab, a treatment that has not been accepted for use by SMC. It is not known how these differences would affect treatment outcomes with regorafenib in the third or later line. Further generalisability issues arise from the exclusion of patients with an ECOG score >1, and that no UK centres were part of CORRECT.[2]
- Quality of life outcomes did not meaningfully differ between regorafenib and placebo, however the instruments used may not have been sensitive to adverse events associated with regorafenib for example, hand-foot skin reaction.[2]
- There is no direct evidence versus the most relevant comparator in Scottish clinical practice, trifluridine plus tipiracil. The indirect evidence had the following limitations: there was heterogeneity across the studies included in the NMA in terms of phase of study, ethnicity of patients and prior targeted biologic treatments. The scenario analyses presented by the company suggest that differences in these characteristics had a minimal effect on results. The analyses did not assess safety or health-related quality of life, which may be clinically relevant when considering the risk/benefit of treatments. Despite these limitations, it would seem reasonable to conclude that both treatments have similar efficacy.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that regorafenib is a therapeutic advancement. Clinical experts felt this would either displace trifluridine plus tipiracil in the third-line or be used in the fourth line where patients at present would receive best supportive care (BSC).

4.4. Service implications

The introduction of regorafenib is not anticipated to have major service implications. As an oral medication for the treatment of late-stage cancer, this will likely have benefits for patients who prefer home-based care. An oral medication also has benefits for the service as it does not require day-care chair time.

5. Patient and clinical engagement PACE

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of regorafenib, as an orphan-equivalent and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- A diagnosis of metastatic colorectal cancer is life-changing, with profound effects on both physical and mental health. Physically, many experience pain and extreme fatigue, which can limit the ability to work and care for family members. Most find the side effects of treatments hard to cope with as well. Mentally, patients face a daily struggle, with severe anxiety, fear, and stress commonly reported. They can also feel guilt for their inability to care for young or elderly family members. These physical and mental impacts are even more acute for patients who have been through several lines of treatment, where the condition is harder to treat and chance of survival is low. A diagnosis of metastatic colorectal cancer is devastating for everyone involved with that person: family, loved ones, and carers.
- In the third line or later, there is only one licensed, SMC-approved treatment, trifluridine plus tipiracil. If patients are contra-indicated to trifluridine plus tipiracil, or if patients had an inadequate response to trifluridine plus tipiracil, there are no other active treatment options available. It is not uncommon for patients in this setting to exhaust all treatment options and yet still be fit for treatment. There is therefore a large unmet need for more effective treatment options in advanced metastatic colorectal cancer.
- Regorafenib has the potential to prolong life, allowing patients more time with their families, and to prolong progression of the disease. In addition, stabilising the cancer may also improve quality of life and symptom control; patients receiving regorafenib have reported more energy and a return to normal daily activities. Regorafenib may allow patients to remain in work or education. It also offers hope for patients; an additional treatment option could alleviate anxiety associated with the thought of running out of treatment options. Regorafenib is also an oral medication, which is convenient, allows patients to administer treatment at home, and avoids unnecessary trips to hospitals.
- In addition to the benefits for the patient, regorafenib may also be beneficial to family

members and carers. A treatment option that may prolong life or improve quality of life can make it easier for carers and families to look after loved ones, and can also allow families to spend more time with their loved one. It would also help to alleviate the stress and anxiety experienced by family and carers. There may also be financial advantages for families if burden of care is reduced.

- Regorafenib is a well-established medicine, having been used in Scotland for other indications for years, and for this indication in other countries. The side effect profile is considered manageable by clinicians; dose adjustments can reduce the side effects experienced by patients and improve outcomes.

Additional Patient and Carer Involvement

We received a patient group submission from Bowel Cancer UK, which is a registered charity. Bowel Cancer UK has received 2% pharmaceutical company funding in the past two years, with none from the submitting company. A representative from Bowel Cancer UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

A summary description of the economic analysis performed is provided in Table 6.1

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility
Time horizon	Lifetime (10 years)
Population	Adult patients with relapsed/refractory metastatic colorectal cancer previously treated with two lines of standard therapies.
Comparators	Trifluridine plus tipiracil (considered primary comparator), best supportive care (BSC).
Model description	Three-state partitioned survival model featuring the states of PFS, progressed disease (PD) and death. Model cycle length was 1 week
Clinical data	The main source of clinical data for regorafenib used in the economic analysis to provide PFS, overall survival, time on treatment, adverse event (grade 3+ with incidence of ≥2%) and utility data were the pooled individual data from the two phase III RCTs of CORRECT and CONCUR.[4, 5] The placebo arms of these studies represented the outcomes for the BSC comparator, and the hazard ratio (HR) results from the NMA (Table 2.2) were used to estimate relative PFS and overall survival outcomes versus trifluridine plus tipiracil (including the RECOURSE[7], TERRA[8], Yoshino 2012[9] studies for the comparator).
Extrapolation	In the base case due to maturity of the PFS data the observed pooled data from CORRECT/ CONCUR were used with the exponential function fitted to the end of data to extrapolate regorafenib and BSC PFS. Several functions were considered for overall survival extrapolation for regorafenib and BSC with the log logistic chosen in the base case on the grounds of good statistical fit, clinical plausibility and for consistency with the function chosen in the NICE appraisal of trifluridine plus tipiracil (TA405).[12] Conditions for proportional hazards were assumed to be met, and hence the HRs from the NMA applied to estimate PFS and OS curves for trifluridine plus tipiracil. Time on treatment (ToT) for regorafenib used the observed data from CORRECT/ CONCUR with extrapolation beyond this using the log logistic function. ToT for trifluridine plus tipiracil (which is treat to progression) was based on applying the HR for PFS from the NMA to the regorafenib ToT curve and assuming this represents the ToT for trifluridine plus tipiracil

Quality of life	Health state utilities were derived from analysis of EQ 5D-3L data from the pooled CORRECT and CONCUR studies. The estimated utilities were 0.72 and 0.59 for PFS and PD respectively. These were not age adjusted due to advanced disease stage, and were adjusted for estimated disutilities associated with adverse events for each treatment arm in the PFS state.
Costs and resource use	Medicine acquisition costs estimated for regorafenib and trifluridine plus tipiracil. No administration costs as both are oral treatments. The dose for regorafenib in the economic analysis was 21 days of 160mg/day over a 28 day cycle. For trifluridine plus tipiracil the licensed weight based dose of 35mg/m^2 given orally twice daily for 10 days in 2 weeks in a 28 day cycle (20 doses) was applied, with UK body surface area (BSA) distribution data in cancer patients from a published source used to estimate weighted average cost per patient.[13] Relative dose intensity (RDI) data were available for regorafenib from the pooled clinical studies but had to be estimated from dose reduction and cycle delay data available for trifluridine plus tipiracil, resulting in higher estimated RDI for trifluridine plus tipiracil. No specific medicine costs are assumed for BSC, but costs captured as part of BSC healthcare resource use costs. Other costs included in the economic analysis were healthcare resource use associated with disease management in the PFS and PD states, adverse event management costs, and one off terminal care costs. Despite up to 43% of patients in the regorafenib clinical studies receiving subsequent post progression therapies no costs were assumed for these in the economic analysis based on feedback from UK clinical experts that there are limited treatment options post 3rd line and few patients will receive active treatment at this advanced disease stage.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price of regorafenib. A PAS discount is in place for trifluridine plus tipiracil and this was included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

The key driver of cost differences in the results are the differences in medicine acquisition costs. QALY gains vs BSC are driven by better PFS and overall survival benefits, and the small difference in QALYs vs. trifluridine plus tipiracil are due to applying the HRs of 0.93 and 0.99 from the NMA for PFS and overall survival respectively in the economic analysis (hence the QALY gain is associated largely with longer time progression-free with regorafenib).

The results used for decision-making included the PAS for regorafenib and the PAS for trifluridine plus tipiracil. SMC is unable to present the results provided by the company which used an estimate of the PAS price for trifluridine plus tipiracil or using the list prices for both medicines due to commercial confidentiality and competition law issues. As such, no results can be reported.

6.3. Sensitivity analyses

The probabilistic results were similar to the deterministic. One way sensitivity analysis performed versus trifluridine plus tipiracil demonstrated that the cost-effectiveness results were most sensitive to varying the overall survival HR estimates.

Scenario analysis were performed by the company covering relative efficacy, extrapolation, AE disutilities, data sources for ITC, including subsequent therapy costs, RDI approach, 5 year time horizon, and no discounting for the trifluridine plus tipiracil comparison. Given the small and non-significant differences in HRs from the ITC assuming a PFS and overall survival HR=1 seems the most appropriate scenario (scenario 1, Table 6.2).

Scenario analysis versus BSC is also shown in Table 6.2, demonstrating that using CORRECT study data only, and applying the generalised gamma parametric function for overall survival extrapolation for BSC has an upward impact on the ICER (Table 6.2).

Table 6.2: Selected scenario analysis

Scenario no.	Scenario description
1	Assuming equal PFS/OS for regorafenib vs trifluridine plus tipiracil (HR=1)
2	CONCUR study only in NMA (Asian population only study)
3	CORRECT study only in NMA (prior anti-VEGF treatment)
4	Log normal extrapolation of overall survival (3rd best fitting for regorafenib)
5	Generalised gamma extrapolation of overall survival (2nd best fitting for regorafenib)
6	Studies with prior anti-VEGF treatment: CORRECT vs RECOURSE (Bucher ITC)
7	Studies in Asian population: CONCUR vs TERRA (Bucher ITC)
8	Include post progression subsequent therapies
9	Equal regorafenib and RDI assumed
10	5 year time horizon
11	Assuming a utility range for PD of 0.54-0.64 (requested for the comparison with BSC)
12a	Combined comparator: Assuming 50% use of trifluridine plus tipiracil and 50% BSC at 3+ treatment lines in clinical practice
12b	Combined comparator: Assuming 25% use of trifluridine plus tipiracil and 75% BSC at 3+ treatment lines in clinical practice

Abbreviations: ICER, Incremental Cost-Effectiveness Ratio; QALY, Quality Adjusted Life Year; BSC, Best Supportive Care; HR, Hazard Ratio; N/A: Not applicable; ITC, indirect treatment comparison; NMA, Network Meta Analysis; RDI, Relative Dose Intensity

6.4. Key strengths

Key strengths of the economic analysis are as follows:

- Mature PFS and overall survival clinical data for use in the economic analysis
- Extrapolation of PFS and overall survival reasonably handled
- Extensive scenario analysis

6.5. Key uncertainties

Key issues relating to the economic analysis are as follows:

- There are limitations and uncertainties over the representativeness of the clinical data from CORRECT and CONCUR used in the economic analysis, in particular the use of prior anti-VEGF in the former study in all patients (which does not reflect Scottish clinical

practice) and the latter study being only in Asian patients, and representing a smaller sample size. There are also uncertainties associated with the representativeness of the trifluridine plus tipiracil clinical evidence used in the ITC and in the economic analysis, which includes one study with prior anti-VEGF treatment (RECOURSE) and two studies in Asian patients (TERRA, Yoshino 2012), one of which is a phase 2 study (Yoshino 2012).

- There are some limitations in the ITCs used in the economic analysis (the fixed effect NMA for base case results and Bucher comparisons used in scenario analyses). However, results from the ITCs where no significant differences in PFS or overall survival are shown in base case and most scenario analyses can be considered to sufficiently demonstrate comparable PFS and overall survival outcomes for regorafenib and trifluridine plus tipiracil, such that assuming equivalent effectiveness and QALY outcomes could be considered appropriate as a base case.
- The company considered trifluridine plus tipiracil to be the primary comparator, with BSC not relevant as a comparator and only included by the company as a form of validation of the economic analysis and results generated. However, based on SMC clinical expert feedback BSC is a relevant comparator for fourth-line patients with no other treatment options. The cost-effectiveness results versus BSC are associated with inherent uncertainty due to limitations with using the CORRECT/ CONCUR placebo arms data as a proxy for BSC (ie the representativeness of these studies which are several years old to current Scottish clinical practice, not specific BSC data for fourth-line, as well as the generalisability limitations expressed in the first bullet above).
- For the comparison with BSC there is uncertainty in the cost-effectiveness results as indicated by scenario analyses performed, with higher ICERs for scenarios in which only the CORRECT study data (the larger regorafenib study) are used (scenario 3), or with extrapolation of overall survival with an alternative but potentially plausible parametric function than used in the base case (the generalised Gamma, scenario 5). In clinical practice it seems likely that regorafenib could potentially displace a mix of trifluridine plus tipiracil and BSC in third and fourth lines. Requested scenario analyses exploring this assuming a proportion of patients receiving BSC in the third line plus setting produced positive ICER estimates (Scenario 12a/b in table 6.2).
- Subsequent post progression therapies were excluded from the base case. Despite expected low use of additional therapies due to advanced disease stage, inclusion of subsequent therapies ideally should be included in the base case. Scenario analysis was performed including subsequent therapies resulting in a small increase in the ICER versus BSC.

7. Conclusion

The Committee considered the benefits of regorafenib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as regorafenib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted regorafenib for use in NHSScotland.

8. Guidelines and Protocols

Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up was published in 2023.[10]

Scottish Intercollegiate Guidelines Network (SIGN). SIGN 126: Diagnosis and management of colorectal cancer was published in 2011 and revised in 2016.[11]

9. Additional Information

9.1. Product availability date

26 August 2013

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle
regorafenib	**160mg orally taken once daily for 3 weeks followed by 1 week off therapy.**	**£3,744**

Costs from BNF online on 31 May 2023. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 518 patients eligible for treatment with regorafenib in year 1, rising to 525 patients in year 5 to which confidential uptake rates were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 14 July 2023**.**

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.