Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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trifluridine/tipiracil (as hydrochloride), 15mg/6.14mg and 20mg/8.19mg film-coated tablets (Lonsurf®) SMC No. (1221/17)

Servier Laboratories Limited

13 January 2017

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 Scotland. The advice is summarised as follows:

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

trifluridine/tipiracil (Lonsurf®) is accepted for use within NHS Scotland.

Indication under review: The treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor agents, and anti-epidermal growth factor receptor agents.

Treatment with trifluridine/tipiracil was associated with an improvement in overall survival when compared with best supportive care in patients who had received, or were intolerant of, first and second-line therapies for metastatic CRC.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of trifluridine/tipiracil. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

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

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

The treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

Dosing Information

Dosage recommendations are based on the trifluridine content of the film-coated tablets.

The recommended starting dose of trifluridine/tipiracil in adults is 35mg/m^2/dose administered orally twice daily on days 1 to 5 and days 8 to 12 of each 28-day cycle as long as benefit is observed or until unacceptable toxicity occurs. The tablets must be taken with a glass of water within one hour after completion of the morning and evening meals.

The dosage is calculated according to body surface area (BSA). The dosage must be rounded to the nearest 5mg increment (see summary of product characteristics for table summarising dosing recommendations according to BSA). The dosage must not exceed 80mg/dose. If doses were missed or held, the patient must not make up for missed doses. Dosing adjustments may be required based on individual safety and tolerability. A maximum of three dose reductions are permitted to a minimum dose of 20mg/m^2 twice daily. Dose escalation is not permitted after it has been reduced.

Trifluridine/tipiracil should be prescribed by physicians experienced in the administration of anticancer therapy.

Product availability date

July 2016
Trifluridine/tipiracil meets SMC end-of-life and orphan-equivalent criteria

Summary of evidence on comparative efficacy

Trifluridine is a thymidine-based nucleoside analogue which is metabolised within cancer cells into a DNA substrate. This is incorporated into and then interferes with DNA function, preventing cell proliferation. Tipiracil acts as an enhancer of trifluridine by inhibiting the function of thymidine phosphorylase, an important enzyme involved in the degradation of trifluridine.[1]

The pivotal evidence for trifluridine/tipiracil in the management of metastatic colorectal cancer (mCRC) is the multi-centre, randomised, double-blind, placebo-controlled phase III study, RECOURSE.[2]

The study recruited adults with mCRC with known Kirsten rat sarcoma oncogene (KRAS) status (mutation or wild-type disease), good performance status (Eastern Co-operative Oncology Group [ECOG] 0 or 1), and adequate organ and haematological function. Patients had at least two prior chemotherapy regimens for their metastatic disease (or an adjuvant regimen if progression occurred within six months). Previous systemic anticancer treatment (SACT) regimen must have

included fluoropyrimidines, oxaliplatin, irinotecan, anti- vascular endothelial growth factor (VEGF) antibody (bevacizumab), and if KRAS wild-type, appropriate epidermal growth factor receptor (EGFR) inhibition (cetuximab or panitumumab). Re-challenge with previous treatment was not an appropriate option for patients if there was either discontinuation due to unacceptable toxicity, or disease progression within three months of the last administration of the standard chemotherapy.[2]

Patients were randomised in a 2:1 ratio to trifluridine/tipiracil (35mg/m^2 of trifluridine, n=534) or placebo (n=266), orally twice daily on days 1 to 5, and days 8 to 12 of each 28-day treatment cycle. In addition, all patients received best supportive care (BSC, such as antiemetics, antidiarrhoeal agents, and haematological support). Treatment was continued until disease progression (as per Response Evaluation Criteria in Solid Tumours [RECIST]), clinical progression, unacceptable toxicity, or withdrawal from the study. Randomisation was stratified by geographic region, KRAS tumour status (mutant or wild-type), and time from first diagnosis of metastatic disease to randomisation (<18 months versus ≥18 months). Dose reductions in 5mg/m^2 decrements (10mg/m^2 per day) were permitted three times (minimum dose 20mg/m^2 twice daily). No crossover was permitted until after the final analysis of the primary endpoint.[2]

The primary outcome was overall survival defined as the time from randomisation to death from any cause, analysed in the intention-to-treat population ie all randomised patients. The primary analysis of overall survival was performed after 72% (574/800) of patients had died, and was at the cut-off date in January 2014 after a median follow-up for censored patients of 8.3 months. Trifluridine/tipiracil was associated with a significant improvement in overall survival when compared with placebo, and this was also demonstrated in an updated analysis including 712 patient deaths (cut-off date in October 2014). Results are presented in Table 1.[2]

Table 1: Overall survival results from RECOURSE[2, 3]

		Trifluridine/tipiracil (n=534)	Placebo (n=266)
Primary analysis (January 2014)	Event rate %(n/N)	68% (364/534)	79% (210/266)
	Median survival	7.1 months	5.3 months
	1-yr survival rate	27%	18%
	HR (95% CI)	0.68 (0.58 to 0.81), p<0.0001	
Updated analysis (October 2014)	Event rate % (n/N)	87% (463/534)	94% (249/266)
	Median survival	7.2 months	5.2 months
	1-yr survival rate	27%	17%
	HR (95% CI)	0.69 (0.59 to 0.81), p<0.0001	

HR = hazard ratio, CI = confidence interval

Pre-specified subgroup analyses showed a consistent effect on overall survival benefit, including KRAS status. 51% of patients had KRAS mutation (407/800) and 49% had KRAS wild-type (393/800); the HR for overall survival in these subgroups were 0.80 (95%CI: 0.63 to 1.02) and 0.58 (95% CI: 0.45 to 0.74)[2].

The secondary outcomes in the study were progression-free survival (PFS), defined as the time from randomisation to first of radiologically-confirmed disease progression, or death from any

cause, and tumour response rates, including objective response (proportion of patients with a best response of complete or partial as per RECIST) and disease control (proportion of patients with best response of stable disease, partial response or complete response).

At the data cut-off (January 2014), 90% of patients had a progression event or had died: 88% (472/534) in the trifluridine/tipiracil group and 94% (251/266) in the placebo group. The hazard ratio (95% confidence interval [CI]) for PFS was 0.48 (0.41 to 0.57), p<0.001. Median PFS was 2.0 months in the trifluridine/tipiracil group and 1.7 months in the placebo group. Separation of the Kaplan-Meier curves was apparent after two months; PFS rates at 4 months were 25% and 4.7% respectively, and PFS rates at 8 months were 8.0% and 1.4% respectively. In the tumour response population (n=760), there was no significant difference between the treatment groups for objective response rate (1.6% [8/502] versus 0.4% [1/258] respectively), but disease control was significantly higher in the trifluridine/tipiracil group: 44% (221/502) versus 16% (42/258) respectively (p<0.001).[2,3]

The time to deterioration to ECOG performance status ≥2 was significantly delayed by trifluridine/tipiracil, hazard ratio (95% CI) of 0.66 (0.56 to 0.78), p<0.0001; median time to deterioration was 5.7 months and 4.0 months, respectively.[2,3]

There were no health-related quality of life outcomes measured in the study.

A multicentre, randomised, double-blind, placebo-controlled phase II study conducted in Japan provides supporting evidence.[4] Eligible patients had received at least two standard chemotherapy regimens and were refractory or intolerant to fluoropyrimidines, irinotecan and oxaliplatin. Other eligibility criteria were similar to the RECOURSE study, except patients with ECOG performance status of 2 could be recruited, and there was no requirement to have had previous VEGF antibody treatment (bevacizumab). Patients were randomised to trifluridine/tipiracil at the licensed dose (n=112), or placebo (n=57); randomisation was stratified by ECOG performance status (0 versus 1 or 2). Treatment was continued until progression, unacceptable toxicity or withdrawal of consent; crossover was not permitted. The primary outcome was overall survival and, at the data cut-off, after a median follow-up of 11.3 months, 73% of patients had died. Trifluridine/tipiracil treatment was associated with a clinically significant improvement in overall survival, HR (95% CI) of 0.56 (0.39 to 0.81), p=0.0011. Median overall survival was 9.0 months and 6.6 months respectively.[4]

Summary of evidence on comparative safety

There are no comparative safety data: the RECOURSE study compared trifluridine/tipiracil plus BSC with placebo plus BSC only. During the study, the mean duration of treatment with trifluridine/tipiracil was 12.7 weeks and with placebo was 6.8 weeks. Adverse events (AEs) were reported for most patients in the RECOURSE study: 98% (524/533) of trifluridine/tipiracil patients and 93% (247/265) placebo patients. Treatment-related AEs were reported in a greater proportion of trifluridine/tipiracil patients: 86% versus 55%. Treatment-related grade ≥3 AEs were reported in 49% and 9.8% of patients respectively. AEs led to discontinuation of study treatment in 3.6% and 1.5% of patients respectively.[3]

In the trifluridine/tipiracil group, treatment-related grade ≥3 AEs were predominantly haematological: anaemia (12% versus 1.9% of placebo patients), neutropenia (20% versus no patients) and thrombocytopenia (1.7% versus 0.4%).[3] Other treatment-related grade ≥3 AEs

which could potentially impact patients' daily lives were infrequent: diarrhoea (2.3% versus no patients), fatigue (2.1% versus 1.9% patients), asthenia (1.7% versus 0.8%). Nausea, vomiting, or stomatitis were each reported in less than 1% of trifluridine/tipiracil patients.[3]

Febrile neutropenia was reported in 3.8% (20/533) of trifluridine/tipiracil patients; there were no incidences of this AE in the placebo group. Granulocyte-colony stimulating factor was given to 9% of patients in the trifluridine/tipiracil group.[2]

In pooled analysis of safety data from RECOURSE and a Japanese phase II study (n=968), dose reductions were required in 15% of trifluridine/tipiracil patients (a single reduction in two-thirds of cases), and in 0.9% of placebo patients. Delays in treatment of at least four days were required in approximately half of the trifluridine-tipiracil patients (56%) and for 49% of all cycles. The main cause for delay were haematological AEs (neutropenia and anaemia).[3]

The trifluridine/tipiracil film-coated tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.[1]

Summary of clinical effectiveness issues

CRC is the third most commonly diagnosed cancer in Scotland, accounting for 12% of cancer diagnoses per year; in 2014 there were 3,721 new cases. CRC is ranked second for mortality in Scotland, with 9.7% of all cancer-related deaths being due to CRC. Median age at diagnosis in 2014 was in the range 70 to 74 years. Age-standardised relative survival at three years for patients diagnosed between 2007 and 2011 was estimated to be 64%. Over the previous ten years, CRC incidence has decreased by 5.4% and mortality has fallen by 17%.[5]

Treatment options for patients with metastatic CRC include surgical resection and 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).[6] Biological therapies such as the monoclonal antibody to EGFR, cetuximab, and the VEGF inhibitor, aflibercept, are in used in selected patients as per extant SMC/Healthcare Improvement Scotland advice. Several other treatments such as the VEGF antibody bevacizumab, the EGFR antibody panitumumab and the multi-kinase inhibitor regorafenib[3] are licensed for metastatic CRC but are not recommended for use in NHS Scotland. The licensed indication for trifluridine/tipiracil positions it as a "last-line" treatment option. Estimations of overall survival for patients in this setting come from the RECOURSE study and from the pivotal study for regorafenib (CORRECT). Median overall survival for patients in these studies managed with best supportive care alone was 5.2 and 5.0 months respectively.[2,7] Trifluridine/tipiracil meets SMC end-of-life and orphan-equivalent criteria.

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely the lack of treatment options available to patients in Scotland for this stage in the disease.

The RECOURSE study provides comparative data against placebo only against a background of best supportive care, which is considered the relevant comparator for current NHS Scotland practice. Trifluridine/tipiracil treatment was associated with a significant improvement in overall survival, hazard ratio 0.69, and this resulted in an improvement in median survival of two months and and in the overall survival rate at one year of 10%. Although the absolute benefit was small,

it was considered clinically relevant in the context of this stage of the disease by the European Medicines Agency. However, the study did not investigate the impact on patients' health-related quality of life (HRQoL). No HRQoL data were presented in the submission.

Differences in median PFS were also small (0.3 month gain with trifluridine/tipiracil), but survival curves separated after median PFS had been reached. At 4 months, the benefit in PFS was more apparent.

RECOURSE study patients were required to have previously been treated with the VEGF antibody, bevacizumab, a treatment option not recommended for use in NHS Scotland. Supportive evidence for trifluridine/tipiracil in patients with no prior history of bevacizumab use is available from the Japanese phase II study. Subgroup analysis of this study suggests that the treatment effect of trifluridine/tipiracil is not adversely altered in patients with no prior bevacizumab use.[4]

Approximately one-fifth of patients had used regorafenib prior to recruitment to RECOURSE. Regorafenib is not routinely available in NHS Scotland; subgroup analyses suggested the treatment effect of trifluridine/tipiracil was maintained in patients who had not previously been treated with regorafenib.[2]

The introduction of trifluridine/tipiracil would help to address an unmet need for effective treatment following the failure and/or intolerance to established SACT of fluoropyrimidines, oxaliplatin, irinotecan and biological agents such as EGFR and VEGF-targeted therapies. Clinical experts consulted by SMC considered that trifluridine/tipiracil is a therapeutic advancement due to the efficacy demonstrated in the robust RECOURSE study. They considered that the place in therapy of trifluridine/tipiracil is in accordance with its licensed indication.

There may be service implications from the point of view of managing AEs, particularly bone marrow suppression and gastrointestinal toxicity and the summary of product characteristics gives recommendations of dose modifications to manage these;[1] in the pre-authorisation studies, delays in commencement of cycles were required for approximately 50% of patients and of treatment cycles, and 15% of patients required dose reduction.[3]

Summary of Patient and Clinician Engagement (PACE)

A PACE meeting with patient group and clinical specialist representation was held to consider the added value of trifluridine/tipiracil, as an end-of-life and orphan-equivalent medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Advanced colorectal cancer has one of the worst survival rates of all cancers with a 5-year life expectancy of 7%. Patients eligible for trifluridine/tipiracil are estimated to have a median survival of six months. This is a devastating diagnosis, exacerbated by the intimate nature of the disease.
- At this stage of the disease, treatment options are extremely limited for patients who fulfil the licensed indication for this medicine. A proportion of patients remains fit and would value a further treatment option. Trifluridine/tipiracil is an oral medicine with a potential survival advantage compared to current treatment options.

- PACE participants considered that capturing quality of life data can be hard at the 3rd line stage. They highlighted that indirect evidence showed the treatment to be well tolerated with low discontinuation rates and similar hospitalisation rates to placebo. The main adverse effects were haematological in nature and therefore unlikely to significantly impact quality of life.
- Whilst adverse events are unlikely to cause hospital admissions, there are regular outpatient attendances required for review and potential repeat visits if treatment delays are needed.
- PACE clinicians considered that patients with a good performance status (ECOG 0 or 1) would be most likely to tolerate trifluridine/tipiracil and would therefore have the best risk: benefit ratio.

Additional Patient and Carer Involvement

We received a patient group submission from Beating Bowel Cancer, which is a registered charity. Beating Bowel Cancer has received 3% pharmaceutical company funding in the last two years, but none from the submitting company. A representative from Beating Bowel Cancer also participated in the PACE meeting. The key points of their submission have been included in the full PACE statement.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing trifluridine/tipiracil to best supportive care (BSC) in patients with metastatic CRC who have been previously treated with, or are not candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents and anti-EGFR agents. Therefore, trifluridine/tipiracil is expected to be used as third-line, or subsequent, therapy. BSC was justified as the comparator due to there being no currently recommended treatment for metastatic CRC patients in the third-line setting. Based on SMC clinical expert feedback, this seems appropriate. A standard three-state partitioned-survival (area under the curve) model was used, with health states consisting of pre-progression (progression free survival), post-progression, and death. A time horizon of 10 years was adopted, and the model used a daily cycle length.

The clinical data used in the model were taken from a phase III study (RECOURSE) and the phase II Japanese study described above. The data from these two studies were pooled for the base case analysis. Extrapolation of PFS and overall survival was performed by fitting parametric functions to the observed pooled data. In the base case, the stratified log-logistic function was used for overall survival and PFS extrapolation for both treatment arms. As no HRQoL data were collected in either of the trifluridine/tipiracil studies, treatment arm specific health state utilities based on the EQ- 5D were derived from the CORRECT study. This study compared regorafenib with BSC/placebo in a similar patient population with previously treated metastatic CRC who had progressed on or after all existing treatments. This resulted in utility values of 0.73 and 0.74 in the pre-progression state for trifluridine/tipiracil and BSC respectively, and a post progression utility of 0.59 for both treatment arms. These values were stated to include a disutility associated with adverse events. Despite coming from a study of a different metastatic CRC treatment, the base case utilities appeared plausible.

Costs in the analysis related to medicines acquisition (for trifluridine/tipiracil), healthcare resource use at each health state treatment stage, end of life costs and adverse event costs were included from an NHS perspective. Costs of trifluridine/tipiracil were based on the distribution of body surface area (BSA) from the RECOURSE study. Dose reductions over time were taken into

account based on the RECOURSE study, and estimated trifluridine/tipiracil treatment duration (time to treatment discontinuation) was based on PFS data adjusted for estimates of treatment initiation delay. Treatment delay time in days was estimated for both the trifluridine/tipiracil and BSC arms. Post-progression therapy costs were estimated for both treatment arms using data from the RECOURSE study, but were similar for trifluridine/tipiracil and BSC. Healthcare resource utilisation pre- and post-progression included outpatient visits, CT scans, GP/nurse visits, and home care visits. Estimates were based on expert clinical opinion and appeared reasonable.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was given on the price of the medicine.

The base case results with PAS for the full population were estimated at an incremental cost-effectiveness ratio (ICER) of £49,225 per quality-adjusted life-year (QALY) gained versus BSC, based on an incremental cost of £8,197, incremental QALYs of 0.17 and incremental life years gained of 0.27. The results of key sensitivity analyses are summarised in table 2.

Table 2: Summary of key sensitivity analysis results

Sensitivity analysis	**ICER with PAS**
Varying the post progression utility value	£44k - £56k
Using the phase III RECOURSE study data only to inform the model	£51k
Reducing the time horizon to 5 years	£51k
BSA based on general population	£51k
Using alternative PFS and overall survival curves	£50k - £54k
Subgroup analysis based on patients with wild-type KRAS	£47k
Subgroup analysis based on patients with mutant KRAS	£53k

The following limitations with the economic analysis were noted:

- The pooling of the phase II data with the RECOURSE data breaks the randomisation of the studies, resulting in issues with internal validity and bias. The impact of any bias is uncertain, although analysis performed by the company suggested that the impact of any heterogeneity between the studies may be limited, supporting the use of pooled data on the grounds of providing a larger patient population base for the extrapolation of PFS and overall survival outcomes. However, the scenario analysis which used only the RECOURSE study data would not have the same risk of bias and resulted in only a modest increase in the ICER. Further scenario and sensitivity analysis for PFS and overall survival estimates using the RECOURSE study data only was provided by the company and this demonstrated an ICER range that was slightly higher compared to using the pooled data. For example, the range associated with varying post-progression utility for BSC was estimated at approximately £46k-£59k/QALY with PAS.
- The visual fit of the base case and alternative parametric functions used to extrapolate PFS was relatively poor. However, scenario analysis involving fitting of alternative parametric functions to PFS and overall survival did not show a large impact on the ICER. As the overall survival data were mature, an exploratory scenario with no extrapolation was provided which resulted in an ICER of £60k/QALY with PAS in the base case, and £63k/QALY with PAS based on the RECOURSE data alone. This provides an upper limit ICER associated with extrapolation uncertainty.

- There are some limitations with the potential generalisability of the RECOURSE study data as an inclusion criterion was that all patients had to have received prior bevacizumab treatment, which is not standard of care for metastatic CRC patients in Scotland. However, analysis of the phase II data indicated that the treatment effect of trifluridine/tipiracil was not adversely altered in patients with no prior bevacizumab use.

The Committee also considered the benefits of trifluridine/tipiracil in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as trifluridine/tipiracil 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, and after application of the appropriate SMC modifiers, the Committee accepted trifluridine/tipiracil for use in NHS Scotland.

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

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network published guideline number 126 'Diagnosis and management of colorectal cancer' in December 2011 and revised in August 2016.[6] For metastatic CRC the following recommendations are made for first-line and second-line treatment.

First-line

- All patients with metastatic CRC should be considered for chemotherapy.
- Combination treatment with either 5-FU/leucovorin/oxaliplatin, or capecitabine/oxaliplatin, or 5-FU/leucovorin/irinotecan is the preferred options in patients with good performance status and organ function. Raltitrexed can be considered in those who are not tolerant of, or unsuitable for 5-FU/leucoverin.
- The choice of first-line chemotherapy for patients with metastatic CRC will depend on patient fitness, co-morbidity, and overall aim of treatment.

Second-line

- Second-line chemotherapy should be considered for patients with metastatic CRC with good performance status and adequate organ function.
- Irinotecan should be used as second-line therapy following first line oxaliplatin (or vice versa).
- The choice of second-line chemotherapy for patients with metastatic CRC will depend on patient fitness, co-morbidity and previous chemotherapy exposure.

Biological therapy

- Cetuximab should be considered in combination with 5-FU/leucovorin/oxaliplatin or 5-FU/leucovorin/irinotecan chemotherapy as first-line treatment with RAS wild type metastatic CRC. The use of cetuximab in combination with oxaliplatin and capecitabine cannot currently be recommended.

No specific recommendation was made for third or further lines of treatment.[6]

The National Institute for Health and Care Excellence published clinical guideline 131, 'Colorectal cancer: the diagnosis and management' in November 2011 and was updated in December 2014; further updates are planned.[8] For metastatic CRC the following recommendations are included:

When offering multiple chemotherapy drugs to patients with advanced and metastatic colorectal cancer consider one of the following sequences of chemotherapy unless they are contraindicated:

- FOLFOX (folinic acid plus 5-FU plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment or
- FOLFOX as first-line treatment then FOLFIRI (folinic acid plus 5-FU plus irinotecan) as second-line treatment or
- XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus 5-FU plus irinotecan) as second-line treatment.
- Decide which combination and sequence of chemotherapy to use after full discussion of the side effects and the patients preferences.

Consider raltitrexed only for patients with advanced colorectal cancer who are intolerant to 5-fluorouracil and folinic acid, or for whom these drugs are not suitable (for example, patients who develop cardiotoxicity). Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer. No specific recommendations were made for third or further lines of treatment.[8]

European Society for Medical Oncology (ESMO) consensus guidelines for the management of patients with metastatic colorectal cancer published in 2016 recommend the following third-line therapy:

- In *RAS* wild-type and *BRAF* wild-type patients not previously treated with EGFR antibodies, cetuximab or panitumumab therapy should be considered.
    - Cetuximab and panitumumab are equally active as single agents.
    - The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan-refractory patients.
    - There is no unequivocal evidence to administer the alternative EGFR antibody, if a patient is refractory to one of the EGFR antibodies.
- Regorafenib is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in *RAS* wild-type patients with EGFR antibodies.
    - Regorafenib is superior to placebo in terms of overall survival, although there are toxicity concerns in frail patients.

Trifluridine/tipiracil is a new option for patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in *RAS* wild-type patients with EGFR antibodies.[9]

- There is no unequivocal evidence to administer the alternative EGFR antibody, if a patient is refractory to one of the EGFR antibodies.

Additional information: comparators

Best supportive care is the most relevant comparator. Regorafenib is licensed for refractory metastatic CRC but is not recommended for use by SMC.

Cost of relevant comparators

Drug	Dose Regimen	Cost per 28-day cycle (£)
trifluridine/tipiracil	**35mg/m^2 orally twice daily on days 1 to 5 and 8 to 12**	**2,000**

Doses are for general comparison and do not imply therapeutic equivalence. Costs based on a body surface area of 1.8m^2. Costs for trifluridine/tipiracil from MIMS online 26 September 2016, costs for regorafenib from eVadis September 2016. Regorafenib is not recommended by SMC.

Additional information: budget impact

The submitting company estimated there would be 204 patients eligible for treatment with trifluridine/tipiracil in year 1, rising to 211 patients in year 5. The estimated uptake rate was 15% in year 1 (31 patients), rising to 30% in year 5 (63 patients) based on clinical expert opinion obtained by the submitting company.

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.

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

References

The undernoted references were supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 11 November 2016.

**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:*
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug 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 drug 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 NHS Scotland 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 NHS Scotland 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.