trifluridine/tipiracil film-coated tablets (Lonsurf®)

Servier Laboratories Limited

05 July 2024

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

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

Indication under review: in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.

In an open-label, randomised phase III study, the addition of bevacizumab to trifluridine/tipiracil was associated with significant improvements in overall survival.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are 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

Trifluridine is an antineoplastic thymidine-based nucleoside analogue and tipiracil is a thymidine phosphorylase (TPase) inhibitor. Trifluridine prevents cell proliferation by directly interfering with DNA function. It is given in conjunction with tipiracil to prevent its degradation by TPase. Bevacizumab binds to vascular endothelial growth factor (VEGF) and inhibits its receptors. When used in combination with bevacizumab for the treatment of colorectal cancer (CRC), the recommended dose of trifluridine/tipiracil is 35 mg/m^2/dose (according to body surface area) administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle until disease progression or unacceptable toxicity. When used in combination with trifluridine/tipiracil for the treatment of metastatic CRC, the dose of bevacizumab is 5 mg/kg of body weight given once every 2 weeks.[1, 13]

1.2. Disease background

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. Colorectal cancer 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. Both the incidence and mortality of CRC are related to socioeconomic deprivation, and this relationship is well-established in Scotland.[2, 3]

1.3. Treatment pathway and relevant comparators

There are two treatment regimens available in this setting for the treatment of adult patients with metastatic CRC who have received two prior anticancer treatment regimens (including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti EGFR agents): trifluridine/tipiracil monotherapy (SMC1221/17) and regorafenib (SMC2562). Clinical experts consulted by SMC consider trifluridine/tipiracil monotherapy to be the most relevant comparator.

1.4. Category for decision-making process

Eligibility for a PACE meeting
Trifluridine/tipiracil 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 trifluridine/tipiracil in combination with bevacizumab comes from SUNLIGHT. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies[2, 4]

Criteria	SUNLIGHT
Study design	Open-label, multinational, randomised, phase III study.
Eligible patients	• Age ≥18 years • Histologically confirmed unresectable adenocarcinoma of the colon or rectum • Prior treatment with ≤2 chemotherapy regimens for the treatment of advanced CRC and had progressive disease or if their last regimen had caused unacceptable adverse effects • Prior regimens must have included a fluoropyrimidine, irinotecan, oxaliplatin, an anti-VEGF monoclonal antibody and/or an anti-EGFR monoclonal antibody (in patients with RAS wild type tumours) • Known RAS-mutation status • Measurable or non-measurable disease as defined by RECIST version 1.1 • ECOG performance status 0 or 1 • Adequate bone marrow, renal, hepatic and coagulation function
Treatments	Patients were randomised equally to receive trifluridine/tipiracil orally twice daily at a dose of 35 mg/m^2 on days 1 through to 5 and on days 8 through to 12 every 28 days plus bevacizumab at a dose of 5 mg/kg by intravenous infusion on days 1 and 15 (n=246) or trifluridine/tipiracil monotherapy (n=246). Treatment was to continue until disease progression or unacceptable toxic effects occurred or consent was withdrawn.
Randomisation	Randomisation was stratified according to RAS-mutation status (mutant or wild type); time since first metastasis diagnosis (<18 months or ≥18 months); and geographical location (North America, European Union, or rest of the world).
Primary outcome	Overall survival, defined as time from randomisation to death from any cause. Efficacy was assessed in all patients who had undergone randomisation, in accordance with the intention-to-treat principle.
Secondary outcomes	Progression-free survival (investigator-assessed), best overall response.
Statistical analysis	A hierarchical statistical testing strategy was applied in the study to control the overall type I error rate; progression-free survival would be evaluated only if the primary analysis of overall survival achieved statistical significance.

Abbreviations: ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; RAS = Rat sarcoma viral oncogene homolog; RECIST = Response Evaluation Criteria in Solid Tumours; VEGF = vascular endothelial growth factor.

At data-cut 19 July 2022, there was a statistically significant difference between trifluridine/tipiracil in combination with bevacizumab and trifluridine/tipiracil monotherapy for the primary outcome (overall survival) and key secondary outcome (progression-free survival). See Table 2.2 for details.

Table 2.2. Results from SUNLIGHT (ITT population; data-cut 19 July 2022).[2, 4]

	Trifluridine/tipiracil plus bevacizumab (n=246)	Trifluridine/tipiracil (n=246)
Primary outcome: overall survival		
Median follow-up	14.2 months	13.6 months
Number of deaths	148	183
Median overall survival	10.8 months	7.5 months
Hazard ratio (95% CI)	0.61 (0.49 to 0.77) p<0.001	
KM estimate survival probability at 6 months	77%	61%

Key secondary outcome: progression-free survival (investigator-assessed)		
Number of events	206	236
Median PFS	5.6 months	2.4 months
Hazard ratio (95% CI)	0.44 (0.36 to 0.54) p<0.001	
KM estimate progression-free survival at 6 months	43%	16%
Secondary outcome: best overall response		
Complete response	0	0.4%
Partial response	6.1%	0.8%
Stable disease	63%	41%
Non-CR/Non-PD	1.2%	1.2%
Progressive disease	25%	51%
Non-evaluable	4.5%	5.7%

Abbreviations: CI = confidence interval; CR = complete response; KM = Kaplan Meier; PD = progressive disease; PFS = progression-free survival.

2.2. Health-related quality of life outcomes

Quality of life was assessed using the patient-completed questionnaires European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EQ-5D-5L. For EORTC QLQ-C30 Global Health Status, there were no clinically meaningful changes (absolute or relative) detected in either treatment group from baseline. For EQ-5D-5L Visual Analogue Scale, there were no clinically relevant changes from baseline detected in either treatment group.[2]

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

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

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Network meta-analysis.
Population	Adult patients with metastatic CRC who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti EGFR agents.
Comparators	Best supportive care, trifluridine/tipiracil monotherapy, and regorafenib.
Studies included	The CONCUR[7] and CORRECT[8] studies: regorafenib 160 mg (licensed dosing) versus placebo. The RECOURSE[9], TERRA[10] and Yoshino 2012[11] studies: trifluridine/tripiracil 35 mg/m^2 monotherapy (licensed dosing) versus placebo. The Pfieffer[12] and SUNLIGHT[4] studies: trifluridine/tipiracil monotherapy 35 mg/m^2 versus trifluridine/tipiracil 35 mg/m^2 plus bevacizumab 5 mg/kg intravenously (licensed dosing).
Outcomes	Overall survival, progression-free survival, and safety, including the time to worsening of Eastern Cooperative Oncology Group performance status score from 0 or 1 to 2 or more (on a scale from 0 to 5, with higher scores indicating greater disability).

Results	**Trifluridine/tipiracil plus bevacizumab versus regorafenib (random effects model)** Trifluridine/tipiracil plus bevacizumab was superior to regorafenib for PFS, however credible intervals crossed 1 for overall survival suggesting no evidence of a difference; fixed effects model for OS however did demonstrate superiority of trifluridine/tipiracil plus bevacizumab. **Trifluridine/tipiracil plus bevacizumab versus tipiracil/trifluridine monotherapy (random effects model)** Trifluridine/tipiracil plus bevacizumab was superior to trifluridine/tipiracil monotherapy for PFS and OS. **Trifluridine/tipiracil plus bevacizumab versus placebo (best supportive care [BSC]) (random effects model)** Trifluridine/tipiracil plus bevacizumab was significantly superior to placebo (best supportive care) for PFS and OS.

Abbreviations: CrI = credible interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; VEGF = vascular endothelial growth factor.

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

3. Summary of Safety Evidence

In the SUNLIGHT study at data-cut 19 July 2022, the median duration of treatment in the trifluridine/tipiracil plus bevacizumab group was 5.0 months and in the trifluridine/tipiracil monotherapy group was 2.1 months. In the trifluridine/tipiracil plus bevacizumab group and trifluridine/tipiracil monotherapy group respectively, patients reporting a grade 3 or higher adverse events (AE) were 72% versus 70%, patients with a reported serious AE were 25% versus 31%, patients with a dose reduction of trifluridine/tipiracil due to treatment emergent AEs were 7.3% versus 8.1%, and patients discontinuing therapy due to an AE was 13% versus 13%. In the trifluridine/tipiracil plus bevacizumab group emergent AEs caused bevacizumab to be withdrawn in 15% of patients.[2, 4]

The most frequently reported treatment-related/emergent AEs of any grade with an incidence >15% in the trifluridine/tipiracil and bevacizumab group versus the trifluridine/tipiracil monotherapy group were: neutropenia (60% versus 48%), nausea (33% versus 21%), anaemia (24% versus 25%), asthenia (19% versus 14%), fatigue (16% versus 12%) diarrhoea (15% versus 15%), vomiting (17% versus 11%), thrombocytopenia (15% versus 8.9%).[2, 4]

The safety profile is consistent with what has previously been reported for trifluridine/tipiracil and bevacizumab respectively.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- SUNLIGHT was a well-conducted phase III study that compared trifluridine/tipiracil in combination with bevacizumab to the most relevant comparator in this setting, trifluridine/tipiracil monotherapy.
- The addition of bevacizumab to trifluridine/tipiracil was associated with a statistically significant benefit in overall survival (HR = 0.61 [95% CI: 0.49 to 0.77]; p<0.001). The improvement in median overall survival of 3.3 months between treatment groups can be considered clinically relevant for these patients where prognosis is generally poor. With 60% of

events (deaths) in the trifluridine plus tipiracil plus bevacizumab group and 74% in the trifluridine plus tipiracil group, overall survival data can be considered mature. Sensitivity analyses and subgroup analyses of overall survival were consistent with the primary analysis.[2]

- The key secondary outcome, investigator-assessed progression-free survival, was also significantly greater in the trifluridine/tipiracil plus bevacizumab group and is supportive of the primary analysis.[2]

4.2. Key uncertainties

- The study population of SUNLIGHT represents a fit group of patients in this setting, and it is less clear if the results could be extrapolated to less fit patients. Patients had ECOG performance status 0 or 1, had received all available standard treatment options for advanced CRC in the first and second line, and had no significant comorbidities, which may limit generalisability to Scottish clinical practice. The Scottish population may also differ from the study population in terms of the proportion of patients with prior exposure to anti-VEGF treatment; roughly 70% of the study population had prior exposure to anti-VEGF which is expected to be much lower in the Scottish population. However, this may mean that patients in Scotland may derive greater benefit from treatment with trifluridine/tipiracil in combination with bevacizumab.[2]
- SUNLIGHT was an open-label study, which may bias some outcomes such as investigator-assessed PFS, patient reported outcomes (HRQoL), and safety outcomes.[2]
- There is no direct evidence comparing trifluridine/tipiracil in combination with bevacizumab to regorafenib. The indirect treatment comparison (ITC) had the following limitations:
    - Heterogeneity was observed across included studies, including methodological heterogeneity (phase II versus phase III studies, double-blinded versus open-label studies) and clinical heterogeneity (variation in ethnicities, ECOG performance statuses, prior bevacizumab use, and number of prior treatments).
    - The assumption of proportional hazards may have been violated in the ITC. This potential issue has been explored with the submitting company and given the maturity of overall survival data throughout the network, it was concluded that the amount of bias present in the ITC is likely small.

  Despite these limitations, the results of the ITC seem reasonable.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that trifluridine/tipiracil in combination with bevacizumab fills an unmet need in this area and consider it to be a therapeutic advancement, namely due to the overall survival and progression-free survival benefits demonstrated in the SUNLIGHT study. They felt that this combination would be used instead of trifluridine/tipiracil monotherapy in practice.

4.4. Service implications

The introduction of trifluridine/tipiracil in combination with bevacizumab may increase burden on chemotherapy day units since the relevant comparators are oral medications and bevacizumab is administered intravenously. However, as an orphan equivalent medicine, patient numbers may be limited.

5. Patient and Clinician Engagement (PACE)

A PACE meeting with patient group representatives and clinical specialists 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 NHSScotland.

The key points expressed by the group were:

- A bowel cancer diagnosis is life-changing and can affect almost every aspect of daily life. This is even more acute for those diagnosed at the later stages of the disease, when it is harder to treat, and outcomes are poorer. CRC does not just affect older patients; younger patients are also being increasingly diagnosed. Patients experience numerous difficulties and challenges across the pathway, from getting an initial diagnosis to timely treatment and care. These challenges relate to the impact and reality of an advanced bowel cancer diagnosis, the difficulty and complexity in navigating treatment and care pathways and the impact treatment can have on quality of life. In addition to the symptoms caused by the cancer itself, patients undergoing treatments for advanced bowel cancer experience a range of side effects which significantly affect their quality of life – both physically and emotionally. Survival for advanced bowel cancer is poor, especially for patients in this setting who have received two prior anticancer treatment regimens. Metastatic CRC is incurable, and patients may only have months to live. Additionally, there is a significant mental toll that cannot be understated.
- Current treatment options approved for use in NHSScotland for advanced bowel cancer are extremely limited and are associated with limited efficacy (low response rates and poor survival benefit). Patients in this setting are often fit enough to receive further treatment, therefore there is a high unmet need.
- Trifluridine/tipiracil plus bevacizumab offers many potential benefits to patients. Evidence shows there is a benefit in terms of extending life as a result of this treatment. Additional months of life with loved ones can be of vital importance to patients' quality of life in being able to share precious moments and/or get their affairs in order. Trifluridine/tipiracil plus bevacizumab could also improve patients' quality of life if the cancer responds, giving them more energy and less symptoms from their cancer such as pain or shortness of breath. For patients who are in work or education, the significantly improved outcomes will allow people to remain in work or education longer. For those who have caring responsibilities, this treatment will allow them to carry these out better and for longer periods. Patients with metastatic CRC could be caring for their children or could be carers for older family members. The improved outcomes for patients on this new regimen will also lower their psychological distress. PACE clinicians noted that they have some experience of using trifluridine/tipiracil plus bevacizumab in this setting (approximately 70 patients), and that their observations in a real-world setting seem to reflect what was reported in the clinical study. Compared with the current standard treatment, the benefits were achieved without significantly increasing the number of adverse events.
- Patient's family and carers support the introduction of trifluridine/tipiracil plus bevacizumab to NHSScotland as it has the potential to extend the life of loved ones. It offers hope to family members and carers, and relief knowing that an effective treatment option is available. It may reduce the burden of care, meaning patient's carers and families will be able to maintain their other commitments for longer. The improved outcomes for patients on trifluridine/tipiracil plus bevacizumab may also lower the psychological distress for their families and carers.

- The combination of trifluridine/tipiracil plus bevacizumab will require two additional visits to the chemotherapy unit compared to trifluridine/tipiracil monotherapy in a 28-day cycle. However, PACE participants noted that in their experience patients will almost always prefer the most effective treatment and place less importance on the number of visits required for administration. There may be a group of patients in this setting who do not want treatment with IV bevacizumab, but patients really value having the choice to decide.

Additional Patient and Carer Involvement

We received a patient group submission from the Bowel Cancer UK, which is a registered charity. Bowel Cancer UK has received 2% pharmaceutical company funding in the past two years, including 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

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime time horizon defined as 15 years based on a starting age of approximately 62 years in the model (mean-average age of patients in SUNLIGHT study).A cycle length of one week was used.
Population	Adult patients with metastatic CRC who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.
Comparators	The comparators considered in the economic evaluation were trifluridine/tipiracil monotherapy, regorafenib, and BSC. BSC was assumed to consist of palliative care.
Model description	A *de novo* model was developed using a partitioned survival analysis framework. The model structure was comprised of three 'core' health states ('progression-free', 'post-progression, and 'death'). All patients start in the 'progression-free' health state and can transition to any of the other 'core' health states at any point in time. After experiencing disease progression, the only transition available to patients was to the 'death' health state.
Clinical data	The clinical evidence used to inform the economic evaluation differed by comparator. For the comparison versus trifluridine/tipiracil monotherapy, the key source of clinical evidence was the SUNLIGHT study. For the comparison versus regorafenib and BSC, the source was a combination of patient-level data from the SUNLIGHT study and aggregated data from the network meta-analysis (NMA) conducted by the company.
Extrapolation	The company's approach to extrapolating health outcomes to the economic evaluation time horizon differed by comparator. For the comparison versus trifluridine/tipiracil monotherapy, log-normal and log-logistic parametric models were independently fitted to PFS and OS data, while time-on-treatment (ToT) was extrapolated using a Weibull model for combination therapy and a generalised gamma model for monotherapy.

	For the comparisons versus regorafenib and BSC, PFS and OS were extrapolated by applying hazard ratios (HRs) from the company's NMA to the parametric models for combination therapy described above. ToT for regorafenib was assumed to be equal to PFS due to insufficient data to conduct a NMA.
Quality of life	Health benefits were measured in terms of both the quantity (life years) and quality of life (QoL), using the quality-adjusted life year (QALY). Health status was measured during the SUNLIGHT study using a generic HRQoL questionnaire called the EuroQoL-5-Dimension-5-Level (EQ-5D-5L) questionnaire. The data generated using this questionnaire were subsequently 'cross-walked' to EQ-5D-3L scores using an algorithm by Hernández-Alva et al and converted into preference-based single indices using a UK time trade-off (TTO) algorithm designed to represent the relative value of changes in these dimensions among the general population. The health effects accounted for in determining these included: changes in health state (e.g. transitioning from a progression-free form of disease to progressed disease), differences in HRQoL by treatment, age-related effects reported in the literature, and the impact of AE associated with treatment.
Costs and resource use	Medication-related costs accounted for in the economic evaluation included: acquisition costs for the intervention and comparators, subsequent treatments received by patients, and administration costs (non-oral therapies only). Other NHS costs accounted for in the economic evaluation included: general practitioner appointments, district nurse appointments, oral chemotherapy outpatient appointments, medical oncologist appointments, computed tomography scans, healthcare resource use associated with end of life care, among others.
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 discount was offered on the list price. The results presented do not take account of the PAS for trifluridine/tipiracil or the PAS for regorafenib and bevacizumab but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for regorafenib due to commercial confidentiality and competition law issues.

Abbreviations: AE= adverse event; EQ-5D-5l = EuroQoL-5-Dimension-5-Level; HRQoL: health-related quality of life; mCRC = metastatic colorectal cancer; NMA = network meta-analysis; OS = overall survival; PAS = patient access scheme; PASAG = patient access scheme assessment group; PFS = progression-free survival; QALY = quality-adjusted life year; QoL = quality of life; ToT = time-on-treatment; TTO = time trade-off.

6.2. Results

The base case economic results at list prices for all treatments are shown in Table 6.2.1.

Table 6.2.1: Base Case Results (List prices)

Trifluridine/tipiracil in combination with bevacizumab versus:	**ICER (£/QALY)**
Trifluridine/tipiracil monotherapy	59,596
BSC	64,028
Regorafenib	30,848

Abbreviations: ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years
Note: biosimilar pricing for bevacizumab has been used above.

6.3. Sensitivity analyses

The submitting company conducted a range of different types of sensitivity analyses which highlighted particular areas of uncertainty regarding economic results.

A selection of these results at list price for all treatments are included in **Table 6.3.1.**

Table 6.3.1: Sensitivity and Scenario Analysis Results (List price)

	Parameter	Base case	Scenario	ICER (£/QALY) versus comparator		
				Trifluridine/tipiracil monotherapy	BSC	Regorafenib
	Base case	-	-	59,596	64,028	30,848
1	Time horizon	15 years	10 years	60,572	65,224	31,534
2	Relative dose intensity	Include	Exclude	69,194	72,226	36,039
3	OS curve - intervention	Log-logistic	Generalised gamma	97,832	83,938	41,981
4			Weibull	120,791	92,288	46,767
5	HR versus BSC for OS extrapolation	Point estimate	Upper bound estimate	NA	88,803	NA
6			Lower bound estimate		54,183	
7	HR versus regorafenib for OS extrapolation	Point estimate	Upper bound estimate	NA	NA	430,233
8			Lower bound estimate			22,380
9	Treatment specific health state utility values from SUNLIGHT study	Include	Exclude	69,569	69,477	34,986
10	Data source for health state utility values	Health state utility values from SUNLIGHT study	Health state utility values from NICE TA 405 for trifluridine-tipiracil	72,571	72,788	36,665

Abbreviations: BSC = best supportive care; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; NICE= National Institute for Health and Care Excellence; N/A = not applicable; OS = overall survival; QALY = quality-adjusted life year; TA = technology appraisal

6.4. Key strengths

- A Phase 3, randomised-controlled study comparing trifluridine/tipiracil in combination with bevacizumab versus a comparator (trifluridine/tipiracil monotherapy) was conducted by the company. The availability of direct evidence such as this reduces the uncertainty associated with economic results compared to economic evaluations using mixed or indirect evidence.

- A range of different sources of health benefits (i.e. changes in health state, differences in HRQoL by treatment, age-related effects, and impact of AEs) were incorporated into the economic evaluation.
- HRQoL data in the form of EQ-5D questionnaire responses were available from the key direct evidence for trifluridine/tipiracil to inform health state utility values in the economic evaluation.

6.5. Key uncertainties

- There was no direct evidence comparing trifluridine/tipiracil in combination with bevacizumab versus the other comparators identified by the company (regorafenib and BSC). The company has therefore had to conduct a NMA to estimate relative efficacy versus these comparators, which may bias economic results due unobserved confounding variables; however, assessment of the company's NMA suggests that conclusions drawn from it appear reasonable. Feedback from SMC clinical experts confirmed that trifluridine/tipiracil monotherapy is the most relevant comparator.
- The company's analysis suggests a significant improvement in HRQoL associated with trifluridine/tipiracil in combination with bevacizumab regardless of health state; however, the underlying biological and clinical reasoning for this is associated with uncertainty. The impact on results of removing this treatment- specific improvement in HRQoL from the analysis can be seen in scenario 9.
- The health state utility values for the progressed disease state used in the company's analysis are significantly higher than those used in a prior NICE TA in a similar indication. Again, the company doesn't appear to provide any biological or clinical reasoning for this difference. The impact on the results of using health state utility values from a prior NICE TA can be seen in scenario 10.
- The company's preferred base case approach to extrapolating health outcomes appears broadly reasonable. However, results where the generalised gamma or Weibull model are used to extrapolate OS for trifluridine/tipiracil in combination with bevacizumab are provided to illustrate the impact on results of assuming poorer modelled outcomes for these patients (scenarios 3 and 4).

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

7. Conclusion

The Committee also considered the benefits of trifluridine/tipiracil in combination with bevacizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in life expectancy in the patient population targeted in the submission was satisfied. In addition, as trifluridine/tipiracil in combination with bevacizumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted trifluridine/tipiracil in combination with bevacizumab for use in NHSScotland.

8. Guidelines and Protocols

Metastatic colorectal cancer: European Society for Medical Oncology (ESMO) Clinical Practice Guideline for diagnosis, treatment and follow-up was published in 2023.[5]

Scottish Intercollegiate Guidelines Network (SIGN). SIGN 126: Diagnosis and management of colorectal cancer was published in 2011 and revised in 2016.[6]

9. Additional Information

9.1. Product availability date

02 November 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28-day cycle (£)
Trifluridine/tipiracil in combination with bevacizumab	**Trifluridine/tipiracil: 35 mg/m^2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle until disease progression or unacceptable toxicity** **Bevacizumab: 5 mg/kg of body weight given once every 2 weeks**	**Trifluridine/tipiracil: £2,000** **Bevacizumab: £1,620**

Costs from BNF online on 12 April 2024. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs calculated assuming a body surface area of 1.8 m^2 and a bodyweight of 70 kg. 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 180 patients eligible for treatment with trifluridine/tipiracil in combination with bevacizumab in each year. The estimated uptake rate was 75% in year 1 which remained stable to year 5. This resulted in 135 patients estimated to receive treatment in year 1 which remained at 135 patients in year 5.

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 or PAS associated with medicines used in a combination regimen.

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

References

1. Servier Laboratories Limited. Trifluridine/tipiracil film-coated tablets (Lonsurf). Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk Last updated 08 November 2023.
2. European Medicines Agency (EMA). European Public Assessment Report. Trifluridine/tipiracil (Lonsurf). EMA/CHMP/221594/2023. 22 June 2023. www.ema.europa.eu
3. Public Health Scotland (PHS). Cancer Statistics – Colorectal Cancer. https://www.publichealthscotland.scot/publications/scottish-atlas-of-healthcare-variation/scottish-atlas-of-healthcare-variation-6-december-2022/colorectal-cancer-dashboard/ Accessed 04 April 2024.
4. Prager GW, Taieb J, Fakih M, Ciardiello F, Van Cutsem E, Elez E, et al. Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer. The New England journal of medicine. 2023;388(18):1657-67. https://dx.doi.org/10.1056/NEJMoa2214963
5. Cervantes A, Adam R, Roselló S, Arnold D, Normanno N, Taïeb J, Seligmann J, De Baere T, Osterlund P, Yoshino T, Martinelli E. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology. 2023 Jan 1;34(1):10-32.
6. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 126: Diagnosis and management of colorectal cancer. December 2011 (revised August 2016) www.sign.ac.uk
7. Li J, Qin S, Xu R, Yau TCC, Ma B, Pan H, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology. 2015;16(6):619-29. 10.1016/S1470-2045(15)70156-7
8. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-12. 10.1016/s0140-6736(12)61900-x
9. Mayer RJ, Ohtsu A, Yoshino T, Falcone A, Garcia-Carbonero R, Tabernero J, et al. TAS-102 versus placebo plus best supportive care in patients with metastatic colorectal cancer refractory to standard therapies: Final survival results of the phase III RECOURSE trial. Journal of Clinical Oncology. 2016;34(4_suppl):634-. 10.1200/jco.2016.34.4_suppl.634.
10. Xu J, Kim TW, Shen L, Sriuranpong V, Pan H, Xu R, et al. Results of a Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of Trifluridine/Tipiracil (TAS-102) Monotherapy in Asian Patients With Previously Treated Metastatic Colorectal Cancer: The TERRA Study. J Clin Oncol. 2018;36(4):350-8. 10.1200/jco.2017.74.3245.
11. Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol. 2012;13(10):993-1001. 10.1016/s1470-2045(12)70345-5

12. Pfeiffer P, Yilmaz M, Möller S, Zitnjak D, Krogh M, Petersen LN, et al. TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open-label, randomised, phase 2 trial. Lancet Oncol. 2020;21(3):412-20. 10.1016/s1470-2045(19)30827-7

13. Roche Products Limited. Bevacizumab concentrate for solution for infusion (Avastin®). Summary of product characteristics. Electronic Medicines Compendium. www.medicines.org.uk Last updated 07 December 2022.

This assessment is based on data submitted by the applicant company up to and including 16 May 2024.

**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.