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Cost-effectiveness of Trifluridine/tipiracil for Previously Treated Metastatic Colorectal Cancer in England and Wales

Ash Bullement,¹ Stuart Underhill,² Ronan Fougeray,³ Anthony James Hatswell^{1,4}

Abstract

A cost-effectiveness model predicting the outcomes of treatment with trifluridine/tipiracil based on the results of the randomised controlled trials conducted for regulatory agencies. The results demonstrate improved outcomes compared to standard care and improved outcomes and lower cost (dominance) compared to regorafenib.

Background: Treatment options at third-line and beyond for patients with late-line metastatic colorectal cancer (mCRC) are limited, and outcomes are poor with best supportive care (BSC). This study investigated the cost-effectiveness of trifluridine/tipiracil and regorafenib relative to BSC alone in patients with mCRC who have been previously treated with, or are not considered candidates for, standard chemotherapies. **Materials and Methods:** A partitioned survival model was constructed to assess the lifetime costs and benefits accrued by patients. Clinical data were derived from the pivotal phase III (Randomized, Double-Blind, Phase 3 Study of TAS-102 plus Best Supportive Care [BSC] versus Placebo plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapies [RECURSE]) and supporting phase II (J003-10040030) randomized controlled trial of trifluridine/tipiracil + BSC versus placebo + BSC, as well as the phase III Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy (CORRECT) randomized controlled trial of regorafenib, and were extrapolated to estimate lifetime outcomes. Costs were taken from published sources, and health effects sourced from previous mCRC studies. **Results:** Trifluridine/tipiracil was associated with a 0.27 incremental life year versus BSC alone, which corresponds to a 0.17 quality-adjusted life year gain. The incremental cost of treatment with trifluridine/tipiracil was £8,479, resulting in an incremental cost-effectiveness ratio of £51,194 per quality-adjusted life year gained. Trifluridine/tipiracil was shown to dominate regorafenib (improve outcomes with reduced costs). Sensitivity analyses showed principal areas of uncertainty were survival estimates and patient utility. **Conclusions:** The results show that trifluridine/tipiracil is more clinically and cost-effective than regorafenib, with clinical outcomes greatly exceeding those for patients treated with BSC alone. Based on the results of the analysis, trifluridine/tipiracil offers an important new treatment option for patients with mCRC maintaining good performance status at the end of life.

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Keywords: Cost-utility, Economic model, mCRC, NICE, TAS-102

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Introduction

Metastatic colorectal cancer (mCRC) is the second most common cause of cancer-related death in the United Kingdom (UK).^{1,2} Five-year survival rates for UK patients with mCRC are notably lower than those in many other countries, including Canada, Australia, Sweden, and Norway.³ Survival rates are particularly poor in late-line disease, that is, for patients who have progressed on available first- or second-line treatments, and expected survival with no active pharmacologic treatment is approximately 6 months. As such, this poor prognosis designates mCRC as an “end of life” disease (ie, patients are entering their final year of life).⁴⁻⁷

Cost-effectiveness of Trifluridine/tipiracil for mCRC

Trifluridine/tipiracil (Lonsurf, Servier) is a chemotherapy indicated for the treatment of adult patients with mCRC 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 which are only used in Kirsten rat sarcoma viral oncogene homolog wild-type patients.⁸ Clinical trial data from the primary analysis cut-off date (after the 571st death) of the placebo-controlled phase III Randomized, Double-Blind, Phase 3 Study of TAS-102 plus Best Supportive Care [BSC] versus Placebo plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapies (RECOURSE) study demonstrated an increase in median overall survival (OS) of 1.8 months (7.1 vs. 5.3 months) for trifluridine/tipiracil (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.58-0.81; $P < .001$).⁴

Follow-up data from RECOURSE provided additional information on the primary endpoint of OS, with the median survival gain extending to 2.0 months (7.2 vs. 5.2 months) for trifluridine/tipiracil (HR, 0.69; 95% CI, 0.59-0.81; $P < .0001$).⁹ Similar results were also observed in the phase II trial used for registration in Japan, with an increase in median OS of 2.4 months (9.0 vs. 6.6 months) for trifluridine/tipiracil (HR, 0.56; 95% CI, 0.39-0.81; $P = .0011$).⁵

Regorafenib (Stivarga, Bayer) is an oral multi-kinase inhibitor indicated for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including a fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, an anti-vascular endothelial growth factor therapy, and an anti-epidermal growth factor receptor therapy.¹⁰ Clinical trial data from the placebo-controlled phase III Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy (CORRECT) study demonstrated an increase in median OS of 1.4 months (6.4 vs. 5.0 months) for regorafenib (HR, 0.77; 95% CI, 0.64-0.94; $P = .0052$).¹¹

Trifluridine/tipiracil was recently approved for use through the UK National Health Service (NHS) following positive recommendation from the National Institute for Health and Care Excellence (NICE).¹² Prior to the introduction of trifluridine/tipiracil, NHS patients with late-line disease had no active treatment options available as regorafenib is not currently recommended for use in the UK, although it is available in many European countries.¹³⁻¹⁶

The objective of this study was to estimate the cost-effectiveness of trifluridine/tipiracil compared with other available treatment options for patients at this line (ie, best supportive care [BSC] and regorafenib) from a UK NHS perspective.

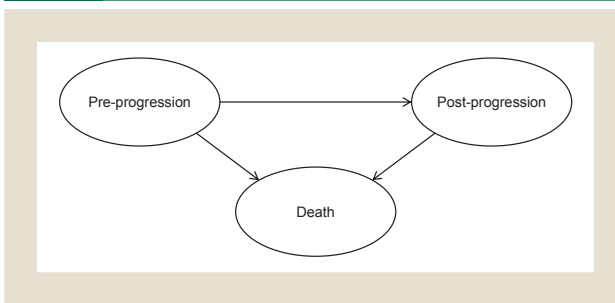
Materials and Methods

Model

A partitioned survival (also known as an “area under the curve”) cost-utility model was constructed in Microsoft Excel. A partitioned survival model calculates the proportion of patients by progression status (that is, those patients in pre- and post-progression) at a given time point based on survival curves, and uses these proportions to inform the benefits accrued and costs incurred over the time horizon of the model.

The model utilizes a standard 3-state structure of pre-progression survival, post-progression survival, and death. This structure was chosen based on its wide use in previous UK health technology

Figure 1 Model Schematic. Note: Arrows Represent Possible Transitions Through the Model Health States



appraisal submissions in cancer.¹⁷⁻¹⁹ The model structure is presented in Figure 1.

A 10-year time horizon was used in the model (ie, costs and outcomes for patients were considered up until 10 years after the initiation of treatment). This time horizon was assumed to reflect patient lifetime as the model predicted that, by this time, over 99% of patients had died in each treatment arm, and further extrapolation of model results was deemed unnecessary for decision-making.

Outcomes in the model were presented in the form of costs, life years (LYs), and quality-adjusted life years (QALYs). QALYs are a combined outcome to describe accrued treatment benefit that takes into account both the length of life (presented as LYs) and the health-related quality of life (HRQL), by adjusting the length of life according to derived HRQL.

Costs and QALYs were discounted at an annual rate of 3.5%, in line with NICE guidance.²⁰ Discounting is included within economic modeling based on the principle that, generally, people prefer to receive goods and services now rather than later (also known as ‘time preference’).²¹

Efficacy and Safety

Efficacy and safety data for trifluridine/tipiracil and BSC used in the model were derived from the pivotal phase III RECOURSE trial⁴ and the supporting Japanese phase II registration trial.⁵ Both trials were multicenter, double-blind, randomized (2:1), placebo-controlled studies on the efficacy and safety of trifluridine/tipiracil.^{4,5} Owing to similarities in the trial protocols, both were deemed appropriate for inclusion in the model. Following the publication of the phase III RECOURSE trial, follow-up data were made available for the efficacy outcomes of OS and progression-free survival (PFS), which was consequently used to inform the model as the follow-up data provided more complete information on both OS and PFS outcomes.⁹

Efficacy outcomes from the 2 trifluridine/tipiracil trials were pooled using 2 methods: naive pooling (ie, breaking randomization) and study-stratified pooling (ie, preserving randomization), both of which yielded similar outcomes compared with BSC. For OS, naive pooling yielded an HR of 0.67 (95% CI, 0.58-0.78; $P < .001$), and study-stratified pooling also yielded an HR of 0.67 (95% CI, 0.58-0.77; $P < .001$). For PFS, naive pooling yielded an HR of 0.46 (95% CI, 0.40-0.53; $P < .001$), and study-stratified pooling yielded an HR of 0.47 (95% CI, 0.40-0.54; $P < .001$). As both methods produced very similar results, naive pooling was deemed appropriate

and consequently used to inform the model (as this methodology reduced the complexity of the analysis).

Parametric survival curve fitting was subsequently performed on pooled OS and PFS data according to NICE guidance,²² as this allowed for outcomes to be modeled beyond the observed data (also referred to as extrapolation beyond the duration of the study). By the end of follow-up in both trials, the pooled data showed that 86.1% of patients had died, and 91.5% of patients had either progressed or died. Consequently, minimal extrapolation was required to establish estimates of long-term outcomes.

For patients treated with regorafenib, efficacy data from the placebo-controlled phase III CORRECT trial publication by Grothey et al were used to inform the model.¹¹ The HRs against placebo for the OS and PFS curves from both this trial and the phase III RECURSE trial were used to elicit an indirect comparison of trifluridine/tipiracil and regorafenib using the Bucher method.¹⁹

To account for toxicity, all common adverse events (AEs) recorded in the RECURSE study were included in the model, and were pooled with equivalent AE rates recorded in the phase II study.^{4,5} AEs were classified as common if they occurred in 10% or more of patients, and were seen in a higher proportion of patients receiving trifluridine/tipiracil compared with BSC.²³ The RECURSE study showed that trifluridine/tipiracil was associated with few serious AEs, and of these, neutropenia was the most frequently observed.²³

AE rates for regorafenib were sourced directly from the CORRECT study.¹¹ The CORRECT study showed that regorafenib was also associated with few serious AEs, with hand-foot skin reaction being the most frequently observed.

Naively comparing AE rates across studies relies on the assumption of direct comparability between the study populations, and the associated assessment of AEs within the studies. Given that the studies were performed under different conditions and in non-identical populations, the generalizability of the toxicity profiles across studies is questionable. The rapporteur from the Committee for Medicinal Products for Human Use (CHMP) stated that “Overall, the toxicity of trifluridine/tipiracil is considered manageable and is not considered worse than the safety profile of regorafenib.”²⁴ Therefore, results regarding the relative toxicity profiles of regorafenib and trifluridine/tipiracil should be interpreted with caution.

Treatment Cost and Posology

Trifluridine/tipiracil is available in a variety of pack sizes, ranging from a 20-pack of 15 mg tablets priced at £500.00, to a 60-pack of 20 mg tablets priced at £2000.00; equivalent to a cost per milligram of £1.67 (prices correct at time of print).²⁵ Treatment is administered 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.⁸

Trifluridine/tipiracil is dosed according to body surface area (BSA), as stated in the summary of product characteristics (SPC).⁸ The distribution of patient BSA was derived using patient-level data from the pooled clinical trials. The use of patient-level data accounts for patients receiving the range of doses of trifluridine/tipiracil specified in the SPC, as considering only the mean dose would introduce bias owing to the skewed distribution of BSA.

A log-normal curve was fitted to the distribution of patient BSA from the pooled data (to ensure consistency with the efficacy data),

based on previous work by Porter et al, who showed the log-normal distribution to be a good fit to BSA from Health Survey for England data.²⁶ The average BSA of the pooled population was 1.75 m², which is notably lower than the mean BSA reported by Porter et al for the UK general population (approximately 1.88 m²). The use of lower BSA for patients with late-line mCRC compared with the general population was validated by clinicians at both an advisory board meeting in January 2016 and at the NICE appraisal committee meeting for trifluridine/tipiracil,¹² as it would be expected that patients with late-line mCRC weigh less than the general population owing to disease-related weight loss.

Dosing adjustments for patients treated with trifluridine/tipiracil may be required based on individual safety and tolerability.⁸ A maximum of 3 dose reductions are permitted for patients treated with trifluridine/tipiracil, as indicated in the SPC. Therefore, within the model, the proportion of patients experiencing a dose reduction in each of the first 3 model cycles were allocated the next largest dose available, assuming that the proportion of dose reductions was linear across all BSA categories.

Regorafenib is available in an 84-pack of 40 mg tablets priced at £3744.00; equivalent to a cost per tablet of £44.57.²⁵ Treatment is administered on Days 1 to 21 of a 28-day treatment cycle as long as benefit is observed or until unacceptable toxicity occurs. In the model, regorafenib is dosed at 160 mg once daily, as per the SPC,¹⁰ with treatment assumed to continue until progression or death (in the absence of time on treatment data).

Health Outcomes

HRQL data were required for use in the model to ascertain the impact of treatment and progression status on patient utility. Utility values are numerical values that reflect an individual's preferences for different health outcomes, measured on an interval scale with 0 reflecting states of health equivalent to death and 1 reflecting perfect health.²⁷ These utility values are used to adjust LYs gained in order to produce the outcome of QALYs in the model.

Neither of the trifluridine/tipiracil studies directly considered the HRQL of patients; however, the CORRECT study of regorafenib included the EuroQol EQ-5D-3L index questionnaire and visual analog scale.¹¹ We used utilities derived from the index scale measure in our model in line with NICE guidance, which states that “the EQ-5D is the preferred measure of health-related quality of life in adults.”²⁰ EQ-5D-3L utilities from the CORRECT study were reported as 0.73 and 0.74 for patients who received regorafenib plus BSC and placebo plus BSC, respectively, at baseline, and 0.59 for both patient groups at the end of treatment. These utility values were used to directly inform patient HRQL in each of the model health states considered (as shown in Figure 1), by applying the baseline values for pre-progressive patients and the post-treatment values for patients in post-progressive disease (after which all patients discontinue treatment).

Utility values from the CORRECT study implied a small disutility (−0.01) for patients who have not yet progressed and are actively receiving treatment with regorafenib, which we applied in our model to account for the potential decrement in HRQL associated with receiving active treatment with either trifluridine/tipiracil or regorafenib (ie, HRQL decrements attributable to toxicity). A disutility attributable to active treatment was used owing to the lack

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of data available to inform AE-specific utility decrements (ie, reductions in health utility owing to the occurrence of AEs), and was assumed to be reasonable given the non-inferior safety profile of trifluridine/tipiracil compared with regorafenib.²⁴

Medical Resource Use (MRU)

MRU was estimated by clinical experts in the treatment of colorectal cancer because, given the lack of treatment options, data regarding resource use estimates for patients with late-line mCRC are scarcely reported. Initial estimates were based on the MRU for patients at earlier lines of therapy (taken from the previous manufacturers' submissions to NICE of cetuximab, bevacizumab, and panitumumab for the treatment of mCRC after first-line chemotherapy).⁷ These estimates were reviewed and updated by clinical experts to reflect the anticipated MRU of patients eligible for trifluridine/tipiracil and regorafenib (and also those who would receive BSC at this line of disease).

The cost of treating AEs was applied in the model as a lump sum upon initiation of treatment, and was calculated as £730.82, £103.50, and £349.51 for patients receiving trifluridine/tipiracil, BSC, and regorafenib, respectively. Costs were calculated based on NHS reference costs for specific AEs, taking into account the frequency of occurrence. Of note, the cost of treating AEs for patients receiving regorafenib was calculated at a lower cost compared with patients receiving trifluridine/tipiracil owing to the difference in treatment setting and associated costs for the different AEs experienced across treatment arms.

End of life care was associated with a cost taken from a cancer-specific study into the cost of end-of-life care by Round et al, and was applied as a lump sum upon death.²⁸ The study considered the cost of health, social, charity, and informal care for patients with lung, breast, colorectal, and prostate cancer at the end of life in England and Wales. From this study, the colorectal cancer-specific cost of health, social, and charity care, £6343, was used to inform our model; the cost of informal care (£2850) is not included in NICE calculations of the cost per QALY and was therefore omitted from our model.

All MRU estimates and their associated costs are presented in Table 1.

Validation

Throughout development, the model underwent a number of validation processes. A full technical review was performed by an independent economic expert who was involved in the NICE reviews of cetuximab and panitumumab for the treatment of first-line mCRC.²⁹ Following this, the model was subject to review from an advisory board of both health economic and clinical experts held in January, 2016. The model was also critiqued by an independent group as part of the NICE submission process (Kleijnen Systematic Reviews Ltd).³⁰

Results

Survival Analysis

Following NICE guidance on survival curve fitting to patient-level data, the statistical and visual goodness of fit were analyzed for potential candidate curves. From Akaike information criterion scores, a log-logistic curve stratified by treatment group was

Table 1 Medical Resource Use Estimates

Resource Use by Progression Status				
Resource	Pre-progression		Post-progression	Unit Cost
	T/T & Rego	BSC	All	
Oral chemotherapy day case ^a	1.00			£192
Medical oncologist		1.00		£171
GP home consultation			0.25	£97
Community nurse specialist visit			1.00	£44
Health home visitor	0.25	0.25	1.00	£44
District nurse			1.00	£44
GP surgery visit			1.00	£37
Other Resource Use				
Resource	T/T	Rego	BSC	All
Adverse event costs	£731	£350	£104	
End of life care				£6343

Abbreviations: BSC = best supportive care; GP = general practitioner; MRU = medical resource use; Rego = regorafenib; T/T = trifluridine/tipiracil.

^aPatients that experience a dose reduction incur the cost of an additional oral chemotherapy day case.

identified as the best fit for both OS and PFS, which also appeared to fit well visually. The 5-year OS for patients using this curve was 1.4% and 0.6% for trifluridine/tipiracil and BSC, respectively. These estimates were deemed acceptable by clinical experts on the advisory board.

HRs derived using the Bucher method of indirect comparison for trifluridine/tipiracil versus regorafenib were 0.88 (95% CI, 0.68-1.14) for OS and 0.98 (95% CI, 0.78-1.23) for PFS. These HRs were subsequently applied in the model to derive estimates for the relative efficacy of regorafenib versus both trifluridine/tipiracil and BSC.

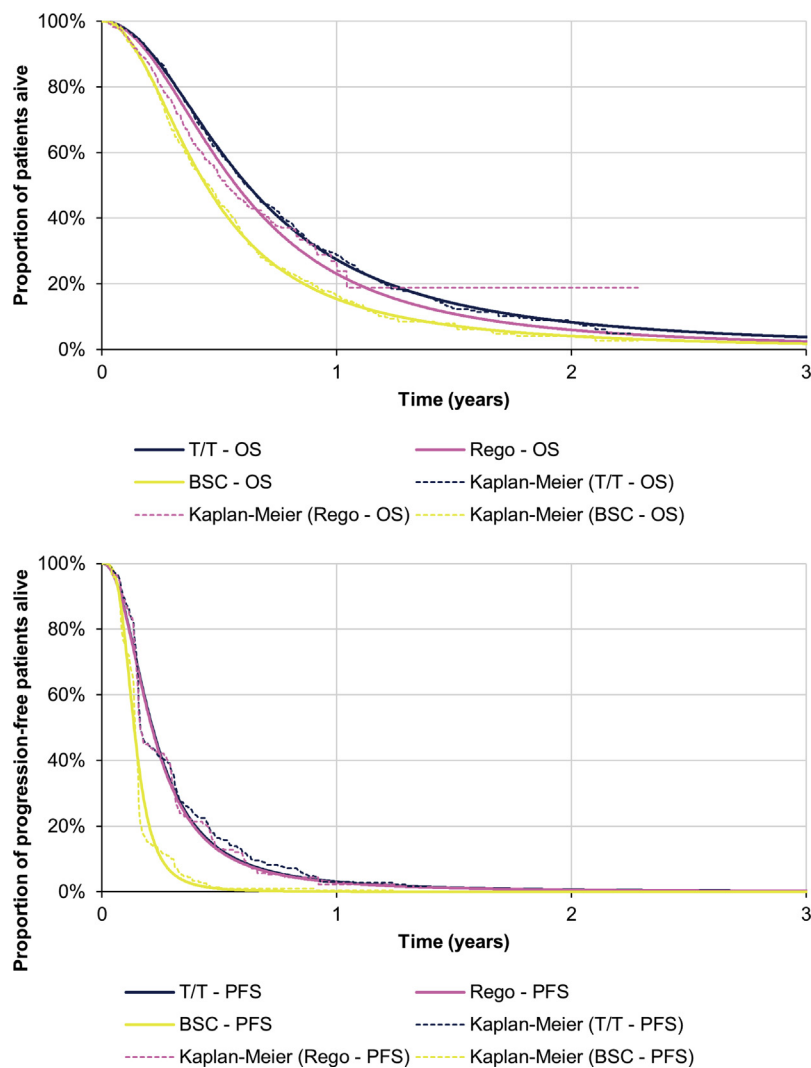
A plot of the resultant curves used for OS and PFS for all treatment options, along with the Kaplan-Meier curves from trial data is shown in Figure 2. The figure shows the expected OS and PFS for patients over time, with the curve fits providing extrapolation beyond the duration of the studies and the Kaplan-Meier curves showing the survival outcomes observed within the duration of the studies. A summary of the validation of clinical outcome results is presented in Table 2.

Model Outcomes

Model outcomes were costs, LYs, and QALYs for each treatment arm. From these, incremental costs and QALYs were used to produce the incremental cost-effectiveness ratio (also known as the cost per QALY gained), which is NICE's preferred measure of cost-effectiveness.³¹ Results presented in this paper are probabilistic, as these results capture the uncertainty attributable to individual model parameters. Mean values as well as percentiles from 5000 model runs are presented to demonstrate uncertainty in the calculated costs, QALYs, and LYs.

In addition, the results include the probability of the pharmaceutical interventions (trifluridine/tipiracil and regorafenib)

Figure 2 Efficacy Curves for All Treatments



Abbreviations: BSC = Best supportive care; OS = overall survival; PFS = progression-free survival; Rego = regorafenib; T/T = trifluridine/tipiracil.

providing a mean extension in survival of at least 3 months. This outcome was deemed of particular interest in the context of decision making, as fulfilment of this criterion qualifies the treatment for special consideration as for end-of-life drugs (the other criterion being that life expectancy is expected to be less than 24 months in the absence of treatment).³²

Base-case Results

BSC alone is associated with costs of £9499, 0.66 Lys, and 0.40 QALYs. Trifluridine/tipiracil is associated with costs of £17,978, 0.92 Lys, and 0.57 QALYs. Regorafenib is associated with costs of £24,112, 0.82 Lys, and 0.51 QALYs. Compared with BSC alone, trifluridine/tipiracil is associated with an LY gain (LYG) of 0.26, incremental QALY gain of 0.17, and incremental costs of £8479 per patient, resulting in an incremental cost-effectiveness ratio of £51,194 per QALY gained. Probabilistic analysis (accounting for

the uncertainty in estimates) indicates trifluridine/tipiracil is associated with a 61.0% probability of providing an extension in life beyond 3 months compared with BSC alone.

Compared with BSC alone, regorafenib is associated with a 0.16 LYG, incremental QALY gain of 0.11, and incremental costs of £14,613. Regorafenib is associated with a 22.5% probability of providing an extension in life beyond 3 months compared with BSC alone.

Compared with regorafenib, trifluridine/tipiracil is associated with a 0.10 LYG, incremental QALY gain of 0.06, and a cost saving of £6134, and therefore, trifluridine/tipiracil dominates regorafenib (ie, increased expected benefit for reduced expected cost). Results comparing regorafenib with either BSC or trifluridine/tipiracil were associated with considerably more uncertainty than the comparison between BSC and trifluridine, largely driven by the lack of head-to-head data available.

Full pairwise results are summarized in Table 3.

Cost-effectiveness of Trifluridine/tipiracil for mCRC

Table 2 Survival Analysis Summary Results (All Studies)

Outcome	Clinical Trial Result, mos			Model Result, mos		
	BSC ^a	T/T ^a	Rego ^b	BSC ^a	T/T ^a	Rego ^b
OS						
Median	5.4	7.3	6.4	5.3	7.5	6.9
RM	7.2	9.6	8.8	7.2	9.7	8.8
EM (Δ RM) ^c				7.9 (+7.0%)	11.1 (+10.1%)	9.8 (+8.8%)
PFS						
Median	1.7	1.9	1.9	1.7	2.6	2.6
RM	1.9	3.6	3.6	1.9	3.5	3.4
EM (Δ RM) ^c				1.9 (+0.1%)	3.7 (+5.7%)	3.7 (+8.8%)

Abbreviations: BSC = best supportive care; EM = extrapolated mean; OS = overall survival; PFS = progression-free survival; Rego = regorafenib; RM = restricted mean; T/T = trifluridine/tipiracil.

^aT/T and BSC data taken from the pooled RECOURSE and phase II studies.

^bRego data taken from the CORRECT study.

^cThis outcome demonstrates the additional survival gained by extrapolating data beyond the observed period of the clinical trials.

Sensitivity Analysis

Following the production of these headline model results, key areas of the model were explored via a sensitivity analysis, where aspects of the model were varied using alternative model settings. The results of the sensitivity analysis performed in the model are presented in Table 4.

The results demonstrate that the main areas of model uncertainty are attributable to the source of, and statistical fit to, efficacy data for trifluridine/tipiracil, the comparison of trifluridine/tipiracil to regorafenib, and patient HRQL. Of note, all sensitivity analysis scenarios produced for trifluridine/tipiracil versus regorafenib showed trifluridine/tipiracil to be dominant, even when regorafenib was assumed to have the same efficacy as trifluridine/tipiracil (owing to the higher cost of regorafenib).

Sensitivity analysis results shown in Table 4 also demonstrate that survival benefits observed for patients treated with trifluridine/

tipiracil versus BSC were consistent across pooled, phase III, and phase II analyses. Mean OS improvement in each analysis was calculated as 3.2, 3.0, and 4.4 months for the pooled, phase III, and phase II analyses, respectively. Mean PFS improvement was also reported similarly across each analysis, as 1.8, 1.5, and 2.1 months, respectively.

Conclusion

Compared with the BSC, trifluridine/tipiracil is associated with a mean improvement in OS of approximately 3.2 months. This relatively large benefit, with an over 60% chance of achieving a 3-month survival gain, along with the small number of UK patients with late-line mCRC, means that the end-of-life criteria set out by NICE are satisfied. Compared with regorafenib, trifluridine/tipiracil is associated with an improvement in OS of approximately 1.3 months, as well as an average cost saving of £6134 per patient.

Table 3 Base Case Model Results

Treatment	Total (95% Confidence Interval)		
	Costs	QALYs	LYs
BSC	£9499 (£3911-£15,245)	0.40 (0.36-0.45)	0.66 (0.59-0.74)
T/T	£17,978 (£12,385-£23,657)	0.57 (0.52-0.61)	0.92 (0.85-1.00)
Rego	£24,112 (£17,924-£30,432)	0.51 (0.40-0.65)	0.82 (0.63-1.08)
Comparison	Incremental (95% Confidence Interval)		
	Costs	QALYs	LYs
T/T vs. BSC	£8479 (£7959-£9011)	0.17 (0.11-0.22)	0.26 (0.16-0.37)
Rego vs. BSC	£14,613 (£12,027-£17,642)	0.11 (-0.01 to 0.26)	0.16 (-0.05 to 0.43)
Rego vs. T/T	£6134 (£3554-£9214)	-0.06 (-0.16 to 0.08)	-0.10 (-0.29 to 0.15)
Comparison	Mean Cost per QALY Gained	Probability of Intervention Providing a Survival Gain of at Least 3 Months	
T/T vs. BSC	£51,194		61.0%
Rego vs. BSC	£133,561		22.5%
Rego vs. T/T	T/T dominates		0.5%
T/T vs. Rego			7.6%

Abbreviations: BSC = best supportive care; LY = life year; QALY = quality-adjusted life year; Rego = regorafenib; T/T = trifluridine/tipiracil.

Table 4 Sensitivity Analysis Results

Scenario	BSC: Totals			T/T: Totals			Rego: Totals			Mean Cost per QALY Gained		
	Costs	QALYs	LYs	Costs	QALYs	LYs	Costs	QALYs	LYs	T/T vs. BSC	Rego vs. BSC	Rego vs. T/T
Base case	£9499	0.40	0.66	£17,978	0.57	0.92	£24,112	0.51	0.82	£51,194	£133,561	T/T dominates
Population												
RECOURSE	£9498	0.39	0.65	£17,934	0.55	0.89	£23,822	0.49	0.79	£55,230	£145,958	T/T dominates
Phase II	£9605	0.43	0.71	£18,179	0.66	1.07	£25,589	0.60	0.96	£36,509	£93,256	T/T dominates
Curve choice												
Generalised Gamma	£9862	0.41	0.63	£18,212	0.54	0.83	£24,399	0.49	0.76	£63,270	£176,427	T/T dominates
Log-normal	£9411	0.38	0.62	£17,893	0.55	0.89	£24,051	0.50	0.79	£51,376	£130,340	T/T dominates
Indirect comparison												
Equal efficacy ^a	£9499	0.40	0.66	£17,978	0.57	0.92	£24,446	0.57	0.92	£51,194	£90,247	T/T dominates
Utilities												
Cetuximab NICE STA ^b	£9499	0.43	0.66	£17,978	0.61	0.92	£24,112	0.54	0.82	£48,558	£131,286	T/T dominates
Dosing												
General population ^c	£9499	0.40	0.66	£18,487	0.57	0.92	£24,112	0.51	0.82	£54,263	£133,561	T/T dominates

Abbreviations: BSA = body surface area; BSC = best supportive care; LY = life year; mCRC = metastatic colorectal cancer; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; Rego = regorafenib; STA = single technology appraisal; T/T = trifluridine/tipiracil.

^aThis scenario uses the assumption of equal efficacy between T/T and Rego (ie, the same OS and PFS).

^bThis scenario uses utilities from the previous NICE STA of cetuximab for the first-line treatment of mCRC.²⁹

^cThis scenario uses a log-normal distribution for the UK general population BSA, as reported by Porter et al (2015).²⁶

Cost-effectiveness of Trifluridine/tipiracil for mCRC

The strengths of the analysis are the extent of the validation conducted owing to the model having been used in a decision-making context, and not having to rely on long-term extrapolation for clinical outcomes such as OS and PFS (as follow-up of the trifluridine/tipiracil clinical trials was sufficient to observe approximately 85% of deaths in the studies). The limitations of the analysis relate to the lack of directly measured HRQL data for patients in this line of disease, and assumptions made regarding the comparative efficacy of regorafenib. These limitations were explored thoroughly within the sensitivity analysis to determine the potential impact on model results, but uncertainty still remains as to the applicability of data.

In summary, the results of this analysis confirm current clinical opinion that trifluridine/tipiracil is an effective drug that provides benefits to UK NHS patients with late-line mCRC, who maintain good performance status and desire active treatment for their disease. When factoring in the discount scheme offered by Servier to the NHS, NICE considered trifluridine/tipiracil a cost-effective use of NHS resources, and recommended that it should be offered as a treatment option for patients with late-line mCRC.¹²

Clinical Practice Points

- Trifluridine/tipiracil presents an important treatment option for patients with late-line mCRC maintaining good performance status, providing an OS improvement of over 3 months compared with patients receiving BSC alone.
- When factoring in the discount scheme offered by Servier to the NHS, trifluridine/tipiracil offers a cost-effective treatment option versus BSC alone.
- Trifluridine/tipiracil dominates regorafenib with incremental LY and QALY gains of 0.10 and 0.06, respectively; and a cost saving of over £6000 per patient.

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References

1. Cancer Research UK (CRUK). Bowel cancer incidence by sex and UK region, Available at: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer#heading-Zero> 2012. Accessed: December 19, 2016.

2. Cancer Research UK (CRUK). Bowel cancer survival statistics, Available at: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/survival> 2012. Accessed: December 19, 2016.
3. Macmillan Cancer Support. The Rich Picture on People Living with Colorectal Cancer, Available at: <http://www.macmillan.org.uk/Documents/AboutUs/Research/Richpictures/Richpicture-Colorectalcancer.pdf> 2016. Accessed: December 19, 2016.
4. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 2015; 372:1909-19.
5. Yoshino T, Mizunuma N, Yamazaki K, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol* 2012; 13:993-1001.
6. Hoyle M, Peters J, Crathorne L, et al. Cost-effectiveness of cetuximab, cetuximab plus irinotecan, and panitumumab for third and further lines of treatment for KRAS wild-type patients with metastatic colorectal cancer. *Value Health* 2013; 16: 288-96.
7. National Institute for Health and Care Excellence (NICE). TA242: Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy, Available at: <https://www.nice.org.uk/guidance/ta242> 2012. Accessed: December 19, 2016.
8. European Medicines Agency (EMA). Trifluridine/tipiracil (Lonsurf) (Updated: 2015) Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003897/WC500206246.pdf 2015. Accessed: December 19, 2016.
9. Mayer RJ, Ohtsu A, Yoshino T. 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 RECURSE trial [abstract]. *J Clin Oncol* 2016; 34(suppl 4S), Abstract 634.
10. European Medicines Agency (EMA). Regorafenib (Stivarga), Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002573/WC500149164.pdf 2014. Accessed: December 19, 2016.
11. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; 381:303-12.
12. National Institute for Health and Care Excellence (NICE). Final appraisal determination: trifluridine-tipiracil hydrochloride for previously treated metastatic colorectal cancer, Available at: <https://www.nice.org.uk/guidance/GID-TA10023/documents/final-appraisal-determination-document> 2016. Accessed: December 19, 2016.
13. Health Service Executive (HSE) Ireland. New Cancer Drugs, Available at: <http://www.hse.ie/eng/services/list/5/cancer/profinfo/medoncd/cdmp/new.html> 2016. Accessed: December 19, 2016.
14. [Haute Autorité de Santé] (HAS) - Medical EaPHAD. Transparency committee opinion: STIVARGA 40 mg, film-coated tablet (Updated: 14 May 2014). Available at: http://www.has-sante.fr/portail/upload/docs/application/pdf/2015-01/stivarga_en_ct13240_prlabo.pdf 2014. Accessed: December 19, 2016.
15. [Ministero della Giustizia]. [Gazzetta Ufficiale della Repubblica Italiana, Anno 156° - Numero 180] (Updated: 5 August 2015). Available at: <http://www.gazzettaufficiale.it/home> 2015. Accessed: December 19, 2016.
16. [Agencia española de medicamentos y productos sanitarios]. [Informe de Posicionamiento Terapéutico de regorafenib (Stivarga) en cáncer colorrectal] (Updated: 4 March 2015). Available at: <https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-regorafenib-Stivarga.pdf> 2015. Accessed: December 19, 2016.
17. Pfizer Limited. Crizotinib for the second-line treatment of ALK positive non-small cell lung cancer: manufacturer's submission, Available at: <https://www.nice.org.uk/guidance/TA296/documents/lung-cancer-nonsmallcell-anaplastic-lymphoma-kinasefusion-gene-previously-treated-crizotinib-pfizer2> 2012. Accessed: December 19, 2016.
18. AstraZeneca Pharmaceuticals LP. Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy: Manufacturer's submission, Available at: <https://www.nice.org.uk/guidance/TA381/documents/ovarian-fallopian-tube-and-peritoneal-cancer-brca-1-or-2-mutated-relapsed-platinumsensitive-olaparib-maintenance-id735-committee-papers12> 2015. Accessed: December 19, 2016.
19. Merck Sharp & Dohme Ltd. Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab: Manufacturer's submission, Available at: <https://www.nice.org.uk/guidance/TA357/documents/melanoma-unresectable-metastatic-pembrolizumab-after-ipilimumab-id760-committee-papers2> 2015. Accessed: December 19, 2016.
20. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal, Available at: <https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf2007975843781> 2013. Accessed: December 19, 2016.
21. Cabinet Office. Discount rates and net present value, Available at: https://data.gov.uk/sib_knowledge_box/discount-rates-and-net-present-value 2014. Accessed: December 19, 2016.
22. Latimer N. NICE Decision Support Unit technical support document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data, Available at: <http://www.nicedsu.org.uk/NICE%20DSU%20TSD%20Survival%20analysis.updated%20March%202013.v2.pdf> 2013. Accessed: December 19, 2016.

23. Ohtsu A, Yoshino T, Wahba MM, et al. Phase 3 RECURSE trial of TAS102 versus placebo with best supportive care in patients with metastatic colorectal cancer: Geographic subgroups. *J Clin Oncol* 2015; 33(15 Supp):3564.
24. Taiho Pharmaceutical Company Ltd. Final response to CHMP's major objection: trifluridine (FTD) tipiracil hydrochloride (TPI). 28 August 2015 2015. Data on File.
25. Monthly Index of Medical Specialities (MIMS). Lonsurf - price and dosing regimen. Available at: <http://www.mims.co.uk/drugs/cancer/antineoplastics/lonsurf> 2016. Accessed: December 19, 2016.
26. Porter J, Latimer N, Lee D, Hatswell A. Vial sizes of pharmaceuticals for infusion – the potential for cost reductions and reduced wastage by optimising fill volumes. ISPOR 18th Annual European Congress. Milan, Italy. 7-11 November 2015 2015. Poster PRM29.
27. Tolley K. What are health utilities?, Available at: http://www.bandolier.org.uk/painres/download/What%20is%202009/What_are_health_util.pdf 2009. Accessed: December 19, 2016.
28. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. *Palliat Med* 2015; 29:899-907.
29. Peninsula Technology Assessment Group (PenTAG). Cetuximab (review of TA176) and panitumumab (partial review of TA240) for the first line treatment of metastatic colorectal cancer 2015, Available at: <http://www.nice.org.uk/guidance/GID-TAG470/documents/colorectal-cancer-metastatic-cetuximab-review-ta176-and-panitumumab-part-review-ta240-1st-line-id794-assessment-report2>. Accessed: December 19, 2016.
30. Wolff R, Ramaekers BLT, van Giessen A, et al. *Trifluridine in combination with tipiracil hydrochloride for previously treated metastatic colorectal cancer: a Single Technology Assessment*. York: Kleijnen Systematic Reviews Ltd; 2016. Available at: <https://www.nice.org.uk/guidance/GID-TA10023/documents/committee-papers>. Accessed: December 19, 2016.
31. Rawlins M, Barnett D, Stevens A. Pharmacoeconomics: NICE's approach to decision-making. *Br J Clin Pharmacol* 2010; 70:346-9.
32. National Institute for Health and Care Excellence (NICE). Appraising life-extending, end of life treatments. Available at: <https://www.nice.org.uk/guidance/gid-tag387/resources/appraising-life-extending-end-of-life-treatments-paper2> 2009. Accessed: December 19, 2016.