Single Technology Appraisal

Trifluridine with tipiracil hydrochloride for treating metastatic colorectal cancer after standard therapy [ID876]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Trifluridine with tipiracil hydrochloride for treating metastatic colorectal cancer after standard therapy [ID876]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Trifluridine in combination with tipiracil hydrochloride for previously treated metastatic colorectal cancer

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

- Trifluridine–tipiracil hydrochloride is indicated in adults with metastatic colorectal cancer who:
  - have been previously treated with available therapies including:
    - fluoropyrimidine-chemotherapies
    - oxaliplatin-based chemotherapies
    - irinotecan-based chemotherapies
    - anti-VEGF agents
    - and anti-EGFR agents, OR
  - are NOT considered candidates for these therapies.

The company intends that trifluridine–tipiracil hydrochloride is used in people who have no other treatment options in the third- or subsequent-line setting. Does this reflect the marketing authorisation? Does it reflect clinical practice in England?

Clinical effectiveness

- Trifluridine–tipiracil hydrochloride is indicated for metastatic colorectal cancer in adults who have been previously treated with, or are not considered candidates for, available therapies. The ERG noted that none of the patients in RECOURSE had been considered unsuitable for available therapies. Can one generalise the evidence from people who have been previously treated with available therapies to those who cannot take them?
- Are the results of RECOURSE generalisable to clinical practice considering that only 9 patients from the UK were included in the trial?
- Patients in RECOURSE had to have received bevacizumab; those with KRAS wild-type tumours also had to have received cetuximab or panitumumab. However, people in England cannot access bevacizumab, cetuximab or panitumumab for previously treated metastatic colorectal cancer because these drugs are neither recommended by NICE nor funded by the Cancer Drugs Fund. The company considered that there was no biological reason for the effect of trifluridine–tipiracil hydrochloride to differ in people who did not receive biological therapies. Are the results of the trial generalisable to people who did not receive bevacizumab?
- The company presented a meta-analysis based on a naïve pooling of data from Yoshino et al. and RECOURSE, and subsequently used these data in the model. The ERG noted that the definition of progression-free survival and the populations included differed slightly between the trials. In addition, the ERG could not fully assess whether the data were pooled appropriately because the company did not provide full information about the statistical methods it used. Is the analysis sufficiently robust?
- Is trifluridine–tipiracil hydrochloride considered innovative?

Cost effectiveness

- The company modelled progression-free survival and overall survival based on the pooled analysis of Yoshino et al. and RECOURSE. The ERG preferred using data from RECOURSE only. What is the best source to inform clinical effectiveness in the model?
- Is the modelling of overall survival plausible?
  - To extrapolate survival, is it more appropriate to choose a single model with a predictor for treatment group, or independent models for each treatment group?
- The ERG did not agree with the utility values that the company used in the model, preferring to use an alternative source. Which source is more appropriate?
- The ERG disagreed with the company's approach to the following, and explored alternative modelling, but these changes had only a small impact on the results. Which approach does the committee prefer in each instance?
  - Estimating the distribution of body surface area in the model.
  - Costing adverse events used in the model.
  - Costing post-progression treatment.
  - Modelling the delays in starting treatment with trifluridine–tipiracil hydrochloride or best supportive care.
- Does trifluridine–tipiracil hydrochloride meet the end-of-life criteria?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of trifluridine in combination with tipiracil hydrochloride within its marketing authorisation for treating metastatic colorectal cancer after standard therapy.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	Adults with metastatic colorectal	Same as final scope.	The company stated that trifluridine–tipiracil	Trifluridine–tipiracil hydrochloride is indicated for

	cancer whose disease has progressed after standard therapies or for whom standard therapies are unsuitable		hydrochloride would be used as a third- or subsequent-line treatment.	metastatic colorectal cancer in adults who have been previously treated with, or are not considered candidates for, available therapies. The ERG noted that none of the patients in RECOURSE were considered unsuitable for available therapies.
Int.	Fixed-dose combination of trifluridine and tipiracil hydrochloride	Same as final scope.	None.	None.
Com.	Best supportive care	Same as final scope.	None.	The ERG stated that the best supportive care provided in the clinical trials could vary across centres, and it might differ from that provided in England.
Out.	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	Same as final scope.	Health-related quality of life data were not collected in the clinical trials for trifluridine–tipiracil hydrochloride.	None.

2 The technology and the treatment pathway

2.1 Trifluridine–tipiracil hydrochloride (Lonsurf, Servier Laboratories) comprises of a nucleoside analogue (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil hydrochloride). The nucleoside analogue is incorporated into the DNA of tumour cells and inhibits tumour growth, whereas the thymidine phosphorylase inhibitor slows the breakdown of trifluridine to prolong its action.

2.2 Trifluridine–tipiracil hydrochloride is indicated for treating adults with metastatic colorectal cancer who have been previously treated with available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents. It is also indicated for people who cannot receive these therapies. Trifluridine–tipiracil hydrochloride is administered orally as a fixed-dose combination; the dose depends on body surface area. The recommended starting dose is 35 mg/m^2 twice daily on days 1–5 and 8–12 of each 28-day cycle. See summary of product characteristics for details on adverse reactions and contraindications.

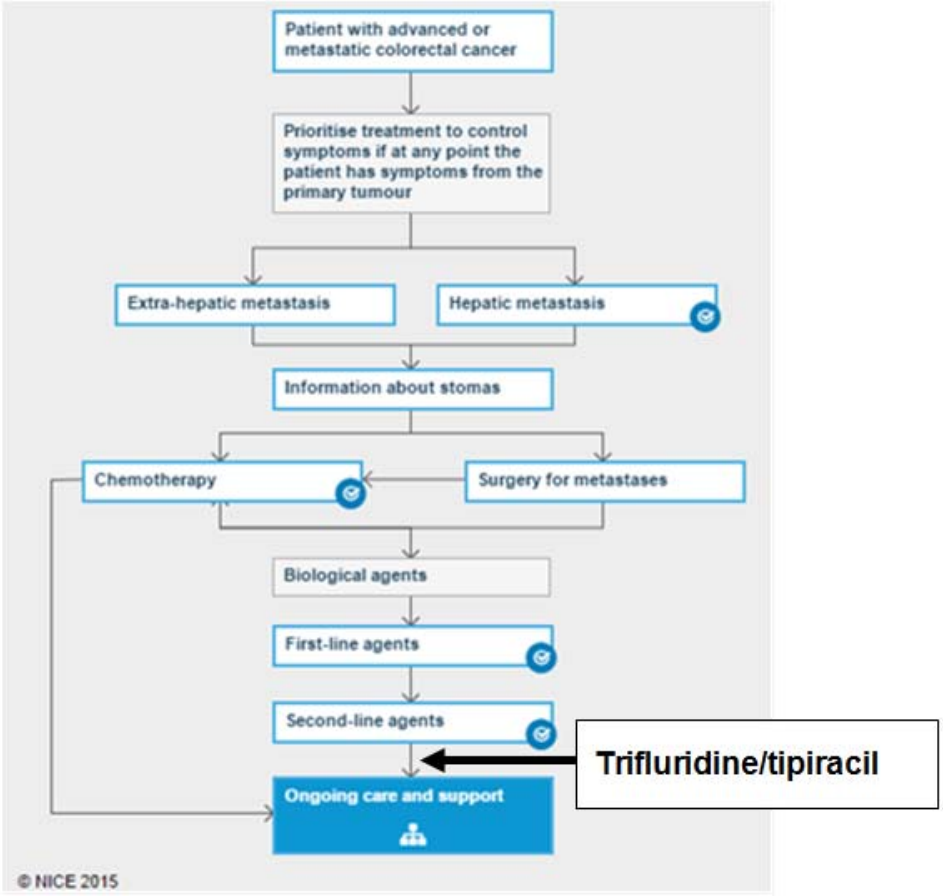
2.3 The list price of a 20-tablet pack of 15 mg and 20 mg trifluridine–tipiracil hydrochloride is £500 and £667 respectively. Each dose is available in 60-tablet packs at pro rata prices. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of trifluridine–tipiracil hydrochloride. The level of the discount is commercial in confidence. For a body surface area of 1.78 m^2 (reflecting patients in the RECOURSE trial), the average cost per patient per cycle is £1625 based on the discounted price including the patient access scheme. Assuming that patients receive 3.4 repeat courses of treatment (the average number in RECOURSE), the cost of trifluridine–tipiracil hydrochloride per patient, including the patient access scheme discount, is estimated to be £5525.

2.4 Treating metastatic colorectal cancer may involve a combination of surgery, chemotherapy, radiotherapy and supportive care. When possible, surgically removing the primary tumour and metastases may be considered. When offering chemotherapy to people with advanced and metastatic colorectal cancer, NICE's guideline on colorectal cancer: diagnosis and management recommends one of the following sequences of chemotherapy unless it is contraindicated:

- FOLFOX (folinic acid plus fluorouracil 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 fluorouracil plus irinotecan) as second-line treatment or
- XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment.

Chemotherapy may be combined with biological agents such as EGFR inhibitors (cetuximab or panitumumab) or VEGF inhibitors (bevacizumab). If standard therapies are ineffective, not tolerated or contraindicated, the condition is managed with supportive care. For a diagram of the treatment pathway including where trifluridine–tipiracil hydrochloride would fit, see Figure 1.

Figure 1 Proposed place of trifluridine–tipiracil hydrochloride in the treatment pathway for metastatic colorectal cancer



Source: Figure 5 of the company's submission.

3 Clinical-effectiveness evidence

Overview of the clinical trials

3.1 The company systematically reviewed the literature, and identified 2 clinical trials relevant to the decision problem: Yoshino et al. (2012), and RECOURSE. Both trials were double-blind, randomised, controlled trials comparing trifluridine–tipiracil hydrochloride with placebo. Yoshino et al. (n=172) was a phase II trial conducted in Japan only, whereas RECOURSE (n=800) was a phase III international trial, including 9 UK patients. All patients in both trials received best supportive care as background therapy.

3.2 The populations in Yoshino et al. and RECOURSE differed, but the treatments were the same. Both trials included adults with metastatic colorectal cancer who were treated with 2 or more regimens of standard chemotherapy, and were refractory to or could not tolerate fluoropyrimidine, irinotecan, and oxaliplatin. However, patients in RECOURSE had to have received bevacizumab; those with KRAS wild-type tumours had to have also received cetuximab or panitumumab. In both trials, patients were randomly assigned (2:1) to either trifluridine–tipiracil hydrochloride (35 mg/m^2 twice a day on the treatment days of the cycle) or placebo. Treatment continued until the tumour progressed, unacceptable toxicity occurred, or the patient withdrew their consent. The primary end point was overall survival. Progression-free survival was a secondary end point in both trials. Yoshino et al. recorded progression when the patient developed 'progressive disease'. In RECOURSE, this was when the investigators determined that the disease progressed radiologically. Neither trial collected data on health-related quality of life.

Clinical trial results

3.3 The results of Yoshino et al. and RECOURSE are presented in Table 2. The Kaplan–Meier curves for overall survival from both trials are presented in Figure 2. For the Kaplan–Meier curves for progression-free survival, see figures 14 (Yoshino et al.) and 17 (RECOURSE) of the company's submission. All the efficacy analyses are based on the intention-to-treat analyses (that is, all patients randomised at baseline). The company presented 2 analyses for overall survival from RECOURSE; the original analysis (after 71.8% of patients had died) and an updated analysis (after 89.0% of patients had died). The results presented here are from the updated analysis. The company stated that the survival benefit of trifluridine–tipiracil hydrochloride was consistent across subgroups, including KRAS status, time since diagnosis of first metastases, and geographic region.

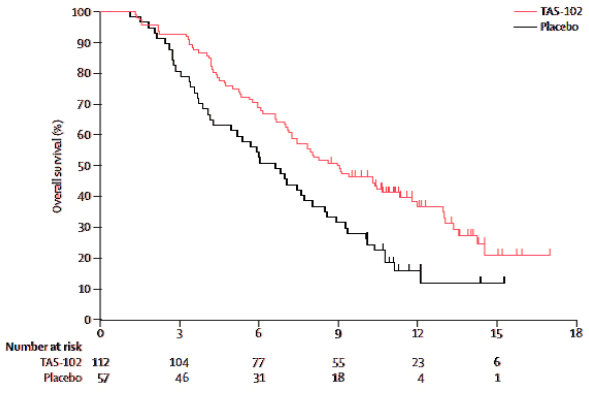
Table 2 Clinical trial outcomes

Outcome	Yoshino et al.		RECOURSE	
	Trifluridine–tipiracil hydrochloride (n=112)	Placebo (n=57)	Trifluridine–tipiracil hydrochloride (n=534)	Placebo (n=266)
Median follow-up (months)	11.3		NR[1]	
Overall survival				
Number of deaths (%)	75 (67.0)	48 (84.2)	463 (86.7)	249 (93.6)
Median (months)	9.0	6.6	7.2	5.2
Difference	2.4		2.0	
HR (95% CI)	0.56* (0.39 to 0.81)		0.69* (0.59 to 0.81)	
Progression-free survival[2]				
Number of progression events (%)	NR	NR	472 (88.4)	251 (94.4)
Median (months)	2.0	1.0	2.0	1.7
Difference	1.0		0.3	
HR (95% CI)	0.41* (0.28 to 0.59)		0.48* (0.41 to 0.57)	
*p<0.01 level (that is, the effect was statistically significant).				
[1]Median follow-up at the cut-off date for the primary analysis (almost 9 months earlier) was 8.29 months. [2]As assessed by the independent review committee.				
Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reported				

Source: Tables 22, 26 and 27 of the company's submission, and the RECOURCE trial publication (Mayer et al., 2015).

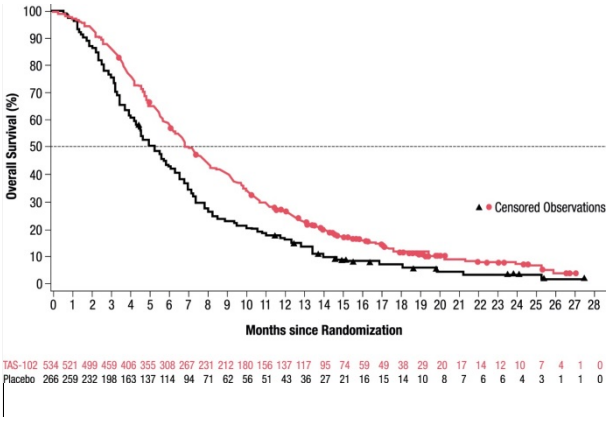
Figure 2 Kaplan–Meier curves for overall survival

Yoshino et al.



Source: Figure 13 of the company's submission.

RECOURSE (updated analysis)



Source: Figure 16 of the company's submission.

ERG comments

3.4 The ERG questioned how each trial defined best supportive care. The company clarified that there was no internationally accepted definition of best supportive care, but that all necessary support was provided to patients, except the therapies that were not permitted in the trial protocols. The ERG considered that best supportive care could vary between trial centres, and differ from that available in the UK.

3.5 The ERG noted that RECOURSE included only 9 patients (1.1%) from the UK. The company pointed out that in RECOURSE, the treatment effect did not differ across subgroups, including geographic region (that is, there was no statistically significant interaction between any potential prognostic factor and treatment). Furthermore, a pre-specified subgroup analysis of patients in RECOURSE from the US, EU or Japan showed consistent results with the overall population.

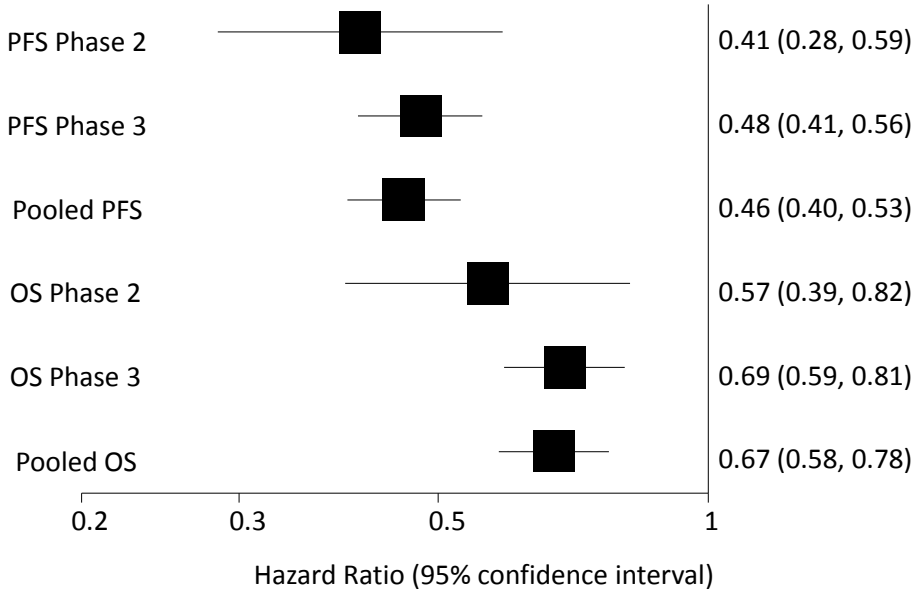
3.6 The ERG noted that patients in RECOURSE had to have received bevacizumab and, if their tumour was KRAS wild-type, cetuximab or panitumumab. However, people in England cannot access bevacizumab, cetuximab and panitumumab for previously treated metastatic colorectal cancer because these drugs are neither recommended by NICE nor funded by the Cancer Drugs Fund. The company did not consider this to affect the generalisability of the trial results because there was no biological reason for the effect of trifluridine–tipiracil hydrochloride to differ in people who did not receive biological therapies. It noted that 22% of patients in Yoshino et al. had not received bevacizumab. Among this group, the hazard ratio for overall survival was 0.37 (95% confidence interval [CI] 0.16 to 0.86) compared with 0.63 (95% CI 0.42 to 0.95) among those who had received bevacizumab, although statistically there was no interaction. This was in line with clinical advice to the company suggesting that the fewer the lines of therapy received, the less resistant to treatment the disease would be. In view of that, the ERG considered that the evidence presented for trifluridine–tipiracil hydrochloride might

underestimate the treatment effect in UK clinical practice where people will not have received bevacizumab.

Meta-analyses

3.7 The company did a meta-analysis, which pooled the individual patient-level data for overall survival and progression-free survival from Yoshino et al. and RECOURSE (using the updated analysis of overall survival from RECOURSE). Across both trials, 538/646 (83.3%) patients in the trifluridine–tipiracil hydrochloride group and 297/323 (92.0%) patients in the placebo group died (for the Kaplan–Meier curve, see Figure 25 of the company's submission). The respective patient numbers for progression were 563/646 (87.2%) and 300/323 (92.9%). Trifluridine–tipiracil hydrochloride led to statistically significant reductions in the risks of death and progression (Figure 3).

Figure 3 Forest plot for the meta-analysis of Yoshino et al. and RECOURSE



Source: Figure 27 of the company's submission.

ERG comments

3.8 The ERG stated that company did not provide full information about the statistical methods used in the meta-analysis, nor did it formally test for

heterogeneity between trials, although the definition of progression-free survival and the populations included differed slightly between the trials (see section 3.2). As a result, the ERG could not fully assess whether the data were pooled appropriately. Also, the company naively pooled the data from both trials, which breaks the randomisation in the trials. Nevertheless, Yoshino et al. and RECOURSE had similar designs and disease characteristics at baseline, and the pooled results appeared consistent with those from the individual trials. Because of this, the ERG considered that pooling data from these trials could be acceptable for assessing clinical effectiveness.

Adverse effects of treatment

3.9 Trifluridine–tipiracil hydrochloride was associated with a higher incidence of adverse events than placebo (Yoshino et al.: 96.5% compared with 70.2%; RECOURSE: 85.7% compared with 54.7%). Compared with placebo, the incidence of serious adverse events among patients who received trifluridine–tipiracil hydrochloride was higher in Yoshino et al. (18.6% compared with 8.8%), but lower in RECOURSE (29.6% compared with 33.6%). In Yoshino et al., 50% of patients taking trifluridine–tipiracil hydrochloride in the safety population (n=113) had neutropenia of grade 3 or 4, 28% had leukopenia, and 17% had anaemia. No patient who was treated with placebo (n=57) had grade 3 or worse neutropenia or leukopenia; 5% had grade 3 or worse anaemia. The most frequent adverse events associated with trifluridine–tipiracil hydrochloride in RECOURSE were also neutropenia and leukopenia, with 38% and 21% of patients respectively.

4 Cost-effectiveness evidence

4.1 To compare the cost effectiveness of trifluridine–tipiracil hydrochloride with best supportive care for previously treated metastatic colorectal cancer, the company developed a partitioned-survival (area-under-the-curve) model consisting of 3 states; pre-progression, post-progression,

and death (see figure 29 of the company's submission for the model diagram). Everyone entered the model in the pre-progression state, and remained in this state until their disease progressed, or until they died. People whose disease progressed could remain in the post-progression state or die. The model time horizon was 10 years (lifetime). The perspective of the analysis was that of the NHS. Costs and health effects were modelled over a 10-year time horizon, with an annual discount rate of 3.5% applied to both. The company used a daily cycle length.

Model details

4.2 People in the model who received trifluridine–tipiracil hydrochloride received it at the dosage recommended in the summary of product characteristics (see section 2.2). To estimate the distribution of body surface area for people in the model, the company grouped patients in RECOURSE into dosing groups based on their body surface area, and fitted the log-normal distribution to these data (see figure 33 of the company's submission for the distribution of body surface area). Because some people may reduce their recommended dose (that is, move down 1 dosing group), the company assumed in the model that 9.9% of people reduced their dose once, that 3.4% reduced it twice, and that 0.4% reduced it 3 times, based on the frequency at which patients reduced their dose in RECOURSE.

4.3 To model progression-free survival and overall survival, the company used the pooled data from Yoshino et al. and RECOURSE (as opposed to data from either trial) to make use of all available evidence. It then fitted different parametric distributions to the data, and chose the best fitting curve based on visual inspection of the fit to the data, the results of statistical tests, and the plausibility of long-term survival outcomes. For both end points, the company chose the log-logistic distribution, modelling each treatment (trifluridine–tipiracil hydrochloride or placebo) independently, in the base case. It considered modelling each treatment independently to be appropriate because the trials randomised patients in

a 2:1 ratio. Therefore, the model that includes a predictor for treatment group would have used more data for the trifluridine–tipiracil hydrochloride group than for the placebo group to estimate the corresponding survival curves. The company's modelling predicted that 8.34% of people who are treated with trifluridine–tipiracil hydrochloride would be alive 2 years after starting treatment compared with 4.11% of those who are treated with placebo, and that 1.37% and 0.63%, respectively, would be alive 5 years after starting treatment. The survival outcomes predicted by the model, compared with the trial results, are shown in Table 3.

Table 3 Comparison of the clinical trials and model results

Outcome		Clinical trials (pooled data)		Model	
		Trifluridine–tipiracil hydrochloride	Placebo	Trifluridine–tipiracil hydrochloride	Placebo
Overall survival	Median (months)	7.3	5.4	7.4	5.3
	Mean (months)	9.6[1]	7.2[1]	11.1	7.9
Progression-free survival	Median (months)	1.9	1.7	2.6	1.6
	Mean (months)	3.7[1]	1.9[1]	3.7	1.9

[1]Restricted mean estimates (that is, based on observed trial data, which exclude patients who are still alive or progression-free at the end of the trial follow-up).

Source: Table 74 of the company's submission.

4.4 Patients in Yoshino et al. and RECOURSE stopped treatment when they experienced disease or clinical progression or unacceptable toxicity, or withdrew their consent. However, the company could not model the time spent on treatment because neither trial reported this. Instead, it accounted for the delays in starting a treatment cycle by incorporating the average delay per cycle across all patients within each treatment arm (2.72 days for trifluridine–tipiracil hydrochloride and 1.40 days for best supportive care) into the modelled treatment cycle.

ERG comments

4.5 The ERG noted that trifluridine–tipiracil hydrochloride is indicated for metastatic colorectal cancer in adults who have been previously treated

with, or are not considered candidates for, available therapies. However, the modelling was based on patients in the trials, all of whom had been considered candidates for available therapies. It was unclear to the ERG how this influenced the outcomes of the model.

4.6 The ERG noted that, although the company modelled progression-free survival and overall survival based on the pooled analysis of Yoshino et al. and RECOURSE, to model the rates of adverse events, time on treatment, and dose reductions, it used only RECOURSE. The company subsequently presented its base-case analysis using pooled data for these parameters (see section 4.18).

4.7 The ERG stated that, in deciding whether to use a single model with a predictor for treatment group, or independent models for each treatment group to extrapolate survival, the company did not use the log-cumulative hazard plots to examine how the risks of disease progression and death change over time with each treatment. In response to a clarification request, the company provided these plots, based on which the ERG preferred using a single model with a predictor for treatment group (as opposed to the independent models for each treatment group used by the company). This was because the plots for both end points were reasonably parallel, suggesting that the proportional hazards assumption would hold.

4.8 The ERG considered that using the observed data on body surface area from RECOURSE was more reasonable to estimate drug costs than fitting the log-normal distribution to these data.

4.9 The ERG noted that how the company accounted for the delays in starting treatment led to a longer cycle length for trifluridine–tipiracil hydrochloride than best supportive care (30.72 days compared with 29.40 days respectively). Consequently, patients who were treated with best supportive care consumed more medical resources over the time horizon, which did not reflect clinical practice. The ERG considered that it would be

more appropriate to apply the cycle length for trifluridine–tipiracil hydrochloride to both treatment arms.

4.10 The ERG stated that the company incorrectly reported the rates of some adverse events that occurred in the placebo treatment arm of RECOURSE. It corrected these in exploratory analyses (see sections 4.22 and 4.23).

Health-related quality of life

4.11 Neither Yoshino et al. nor RECOURSE collected data on health-related quality of life. To estimate health-related quality of life in the model, the company averaged the utility values reported for the same health state in:

- the CORRECT trial, which evaluated regorafenib for previously treated metastatic colorectal cancer, and
- the company's submission for NICE's technology appraisal guidance on cetuximab for the first-line treatment of metastatic colorectal cancer (the company used the values for second- and third-line treatment in that submission for the pre-progression and post-progression states respectively).

The company considered that NICE's technology appraisal guidance on cetuximab reflects utility values at the higher end of the possible range because the utility value before progression was derived from patients receiving second-line treatment. It considered CORRECT to reflect utility values at the lower end of the range because regorafenib may be considered more toxic than trifluridine–tipiracil hydrochloride. The company applied utility values of 0.73 or 0.74 for people in the pre-progression state receiving trifluridine–tipiracil hydrochloride or best supportive care respectively, and 0.64 for people in the post-progression state. The company stated that there was not enough evidence to model the utility decrements associated with adverse events.

ERG comments

4.12 The ERG was concerned that the company used NICE's technology appraisal guidance on cetuximab for the first-line treatment of metastatic colorectal cancer to source utility values because the pre-progression utility value in that guidance was derived using the HUI3 instrument, which was not in line with the NICE reference case, and it was not ultimately used in the company's submission for that appraisal. Furthermore, the post-progression utility value was derived from people with KRAS wild-type metastatic colorectal cancer that was refractory to chemotherapy, and the ERG could not verify its original source. The ERG did not agree that regorafenib was more toxic than trifluridine–tipiracil hydrochloride because CORRECT reported similar utility values in the regorafenib and placebo groups. The ERG considered the utility values from CORRECT to be the most plausible for this appraisal because CORRECT provided EQ-5D utility values in a population similar to that in which trifluridine–tipiracil hydrochloride would be used.

4.13 The ERG did not agree with the company that it was not possible to model the utility decrements associated with adverse events. The ERG used utility decrements from the literature to model the grade 3 or above adverse events reported in RECOURSE.

Cost and healthcare resource use

4.14 The company estimated that the cost of trifluridine–tipiracil hydrochloride per treatment cycle (28 days), based on the patient access scheme price, ranged from £1625 (first cycle) to £1607 (fourth and subsequent cycle). It did not ascribe any acquisition costs to best supportive care. For both treatment arms, the company included costs for medical resource use (table 65 of the company's submission), adverse events (table 68 of the company's submission), end-of-life care, and post-progression treatment (table 69 of the company's submission). It based these on the assessment report for the draft NICE technology appraisal guidance on cetuximab and

panitumumab for previously untreated metastatic colorectal cancer, supplemented by data from the literature and clinical experts.

ERG comments

4.15 The ERG noted that the company assumed equal costs for treatment given after progression regardless of whether the patient had been treated with trifluridine–tipiracil hydrochloride or best supportive care. Alternately, the company also estimated post-progression costs after either treatment based on RECOURSE. Although these costs were similar (£1,549 and £1,487), the ERG preferred using the trial-based costs instead of assuming equal costs.

4.16 The ERG noted that the end-of-life costs used by the company included charity care costs, which are not relevant to the NHS or personal social services.

4.17 The ERG noted that the company did not cost some of the common adverse events reported in RECOURSE. Also, the company equated the cost of most adverse events to that of a general medicine outpatient visit, which the ERG considered unrealistic.

Company's base-case results and sensitivity analysis

4.18 The company’s base-case results, including the patient access scheme discount, are shown in Table 4.

Table 4 Company's base-case results (including the patient access scheme)

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYG	Costs (£)	QALYs	LYG	
BSC	10,286	0.42	0.66	–	–	–	–
Trifluridine–tipiracil hydrochloride	16,386	0.59	0.92	7,574	0.17	0.27	44,032

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Source: Table 73 of the company's submission.

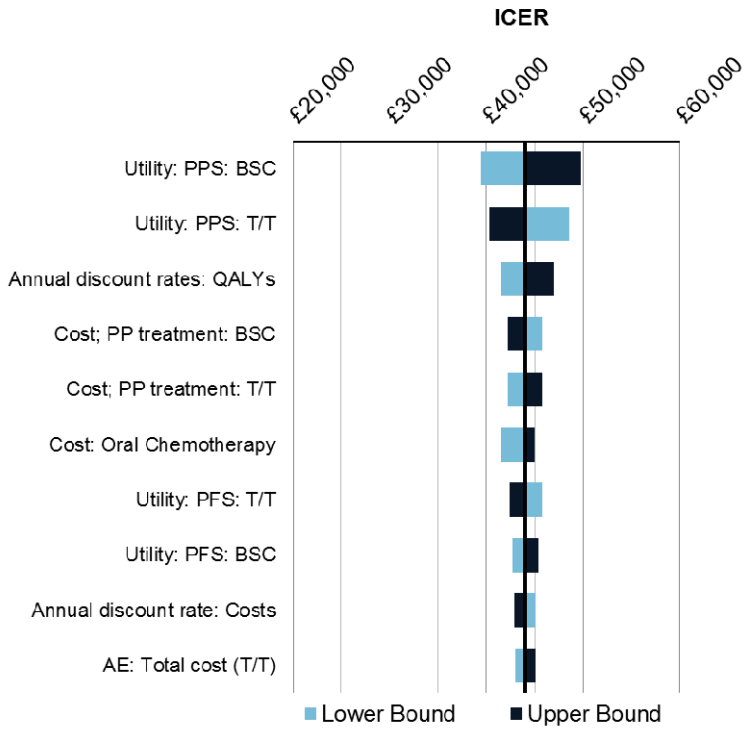
In response to a request for clarification from the ERG, the company updated its original model to include data pooled from Yoshino et al. and RECOURSE for the rates of adverse events, time on treatment, and dose reductions (see section 4.6). It incorporated the costs for adverse events that were previously missing (see section 4.17). The revised incremental cost-effectiveness ratio (ICER) for trifluridine–tipiracil hydrochloride compared with best supportive care was £42,674 per quality-adjusted life year (QALY) gained.

4.19 The company presented a probabilistic sensitivity analysis, varying parameter inputs simultaneously with values from a probability distribution. At the discounted price including the patient access scheme, trifluridine–tipiracil hydrochloride had 0% and 77% probability of being cost effective, compared with best supportive care, at maximum acceptable ICERs of £30,000 and £50,000 per QALY gained respectively. For the cost-effectiveness acceptability curve, see figure 40 of the company's submission. In response to a request for clarification from the ERG, the company provided the probabilistic ICER for trifluridine–tipiracil hydrochloride compared with best supportive care. This was £44,057 per QALY gained, including the patient access scheme discount.

4.20 The company presented one-way sensitivity analyses, varying parameter inputs one at a time. The 10 most influential parameters are presented in Figure 4. The key driver of cost effectiveness was the chosen utility

values, which the company attributed to few robust estimates of utility in this setting. This also impacted the certainty in the discount rate applied to QALYs (the third most influential parameter).

Figure 4 Tornado diagram for the company's one-way sensitivity analysis (including the patient access scheme)



Source: Figure 42 of the company's submission.

4.21 The company presented scenario analyses. The parameters influencing the results the most were the length of the time horizon selected, and the parametric distribution chosen to fit and extrapolate the survival outcomes (Table 5).

Table 5 Company's scenario analyses (including the patient access scheme)

Parameter	Base case	Scenario	ICER (£/QALY)
Base case			**44,032**
Time horizon	10 years	2 years	53,422
		4 years	47,113
		6 years	45,309
		8 years	44,488
Patient population	Pooled across Yoshino et al. and RECOURSE	RECOURSE	45,748
		Yoshino et al.	37,523
Dataset from RECOURSE informing OS	Updated	Original	45,279
Parametric distribution chosen to model OS and PFS	Stratified log-logistic	Generalised gamma	43,528
		Log-logistic	43,935
		Log-normal	46,260
		Stratified generalised gamma	47,460
		Stratified log-normal	44,460
Resource use	See section 4.14	Base-case costs increased by 20%	44,704
		Base-case costs decreased by 20%	42,647
Source of utility values	Average utility values across CORRECT and the company's submission for TA176[1]	The company's submission for TA176[1]	45,509
		BSC utility value from CORRECT assumed for all patients	44,702
Post-progression treatment costs	£1528 in both treatment arms	Trifluridine–tipiracil hydrochloride: £1549; BSC: £1487	44,385

[1] NICE's technology appraisal guidance on cetuximab for the first-line treatment of metastatic colorectal cancer.

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years

Source: Table 81 of the company's submission.

ERG exploratory analyses

4.22 Based on its review of the company's cost-effectiveness analysis, the ERG defined its own base case with the following modifications:

- Correcting the rates of some adverse events that occurred in the placebo treatment arm of RECOURSE with those reported in the trial publication (see section 4.10).
- Only including the end-of-life costs relevant to the NHS and personal social services (see section 4.15).
- Correcting an error in the cost of the medical oncologist outpatient consultation.
- Directly using the observed body surface area of patients in RECOURSE (see section 4.8).
- Using alternative costs for adverse events based on the NICE technology appraisal guidance on bortezomib for previously untreated mantle cell lymphoma (see section 4.17).
- Using treatment-specific post-progression costs (see section 4.15).
- Assuming equal delays in starting treatment with trifluridine–tipiracil hydrochloride or best supportive care (see section 4.9).
- Using the unstratified log-logistic distribution to model progression-free survival and overall survival (see section 4.7).
- Using utility values from CORRECT: 0.73 or 0.74 for people in the pre-progression state receiving trifluridine–tipiracil hydrochloride or best supportive care respectively, and 0.59 for people in the post-progression state (see section 4.12).

Because the ERG could not fully assess the appropriateness of the pooled analysis of Yoshino et al. and RECOURSE, or the potential bias resulting from naively pooling the data (see section 3.8), it preferred presenting results based on data from RECOURSE only alongside the results based on the pooled dataset (as per the company's base case).

4.23 The results of the ERG's base case are presented in Table 6.

Table 6 ERG's base-case results (including the patient access scheme)

Data source	Treatment	Total		Incremental		ICER (£/QALY)[1]
		Costs (£)	QALYs	Costs (£)	QALYs	
RECOURSE	BSC	9,605	0.40	–	–	–
	Trifluridine–tipiracil hydrochloride	17,167	0.54	7,562	0.14	52,695
Pooled analysis	BSC	9,584	0.407	–	–	–
	Trifluridine–tipiracil hydrochloride	17,197	0.561	7,613	0.15	49,392
[1]The company's base-case ICER was £44,032 per QALY gained.						
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years						

Source: Table 5.29 of the ERG report.

4.24 The ERG stated that the modifications with the largest impact on the company's base-case ICER were:

- Correcting the rates of some adverse events that occurred in the placebo treatment arm of RECOURSE with those reported in the trial publication.
- Sourcing the clinical data from RECOURSE (rather than the pooled analysis of Yoshino et al. and RECOURSE).
- Using utility values from CORRECT.

These modifications individually increased the company's base-case ICER of £44,032 per QALY gained to £45,335, £45,784 and £44,851 per QALY gained respectively.

4.25 The ERG presented a probabilistic sensitivity analysis for its own base case. Compared with best supportive care, the probability of trifluridine–tipiracil hydrochloride being cost effective at maximum acceptable ICERs of £30,000 and £50,000 per QALY gained were 0% and 37% respectively. The ERG presented one-way sensitivity analyses based on its base case that used clinical data only from RECOURSE. These showed little impact on the ICER, changing it by £150–2,044 per QALY gained.

Innovation

4.26 The company considered trifluridine–tipiracil hydrochloride to be innovative because:

- It is oral.
- It is the only available chemotherapy for third-line treatment of previously treated metastatic colorectal cancer.

5 End-of-life considerations

5.1 The data addressing the end-of-life criteria are presented in Table 7.

Table 7 End-of-life considerations (table 47 of the company's submission)

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• In NICE's technology appraisal guidance on cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy, the committee agreed that the criterion related to life expectancy was met. • A report by Hoyle et al. (2013) describing the cost-effectiveness analysis for cetuximab, cetuximab plus irinotecan, and panitumumab as third- and subsequent-line treatment in people with KRAS wild-type metastatic colorectal cancer reported a mean overall survival for best supportive care of 6.2 months. • The mean overall survival in the placebo arm of RECOURSE was 7.7 months. • The mean overall survival for best supportive care in the pooled analysis of RECOURSE and Yoshino et al. was 7.9 months.

<table>
<tr>
<td>There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment</td>
<td>The difference in mean overall survival between trifluridine–tipiracil hydrochloride and best supportive care in RECOURSE and the meta-analysis of RECOURSE and Yoshino et al. is shown in the table below.
<table>
<tr><th></th><th>RECOURSE</th><th>Pooled analysis</th></tr>
<tr><td>Trifluridine–tipiracil hydrochloride</td><td>10.7 months</td><td>11.1 months</td></tr>
<tr><td>Best supportive care</td><td>7.7 months</td><td>7.9 months</td></tr>
<tr><td>Difference</td><td>3.0 months</td><td>3.2 months</td></tr>
</table>
</td>
</tr>
</table>

5.2 In the ERG's base case, the difference in mean overall survival between trifluridine–tipiracil hydrochloride and best supportive care was 2.9 months (95% CI 1.8 to 4.0).

6 Equality issues

6.1 No potential equality were identified during the scoping process, or in the evidence submitted.

7 Authors

Ahmed Elsada

Technical Lead

Raisa Sidhu

Technical Adviser

with input from the Lead Team (Sanjeev Patel, Christopher O'Regan and Danielle Preedy).

Appendix A: The European public assessment report

The European public assessment report for trifluridine–tipiracil hydrochloride can be found here.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Trifluridine in combination with tipiracil hydrochloride for previously treated metastatic colorectal cancer

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of trifluridine in combination with tipiracil hydrochloride within its marketing authorisation for treating metastatic colorectal cancer after standard therapy.

Background

Colorectal cancer is a malignant tumour arising from the lining of the large intestine (colon and rectum). Metastatic colorectal cancer refers to disease that has spread beyond the large intestine and nearby lymph nodes. This type of cancer most often spreads first to the liver, but metastases may also occur in other parts of the body including the lungs, brain and bones.

In 2012, there were 34,322 people diagnosed with colorectal cancer[1] and 13,236 deaths[2] in England. About 20% to 25% of people with colorectal cancer have metastatic disease when first diagnosed[3,4], and approximately 50% of people who have surgery for early stage disease will eventually develop metastases[5].

Treatment of metastatic colorectal cancer may involve a combination of surgery, chemotherapy, radiotherapy and supportive care. When possible, surgical removal (resection) or destruction of the primary tumour and metastases may be considered.

Treatment for metastatic colorectal cancer aims to prolong survival, improve quality of life and/or make the primary tumour or metastases suitable for resection. Chemotherapy options include: folinic acid plus fluorouracil plus oxaliplatin (FOLFOX), folinic acid plus fluorouracil plus irinotecan (FOLFIRI), capecitabine plus oxaliplatin (XELOX), single-agent irinotecan, capecitabine or tegafur with uracil (in combination with folinic acid) (NICE clinical guideline 131). Chemotherapy may be combined with biological agents such as EGFR inhibitors (cetuximab or panitumumab) or VEGF inhibitors (bevacizumab). If standard therapies are unsuccessful, not tolerated or contraindicated, people are treated with supportive care to manage the symptoms and complications of the condition.

The technology

Trifluridine in combination with tipiracil hydrochloride (Lonsurf, Servier Laboratories) is an anti-cancer treatment comprising a nucleoside analogue and a thymidine phosphorylase inhibitor. The nucleoside analogue

(trifluridine) is incorporated into the DNA of tumour cells and inhibits tumour growth, whereas the thymidine phosphorylase inhibitor (tipiracil hydrochloride) slows the breakdown of trifluridine to prolong its action. It is administered orally as a fixed-dose combination.

Trifluridine in combination with tipiracil hydrochloride does not currently have a marketing authorisation in the UK. It has been studied in clinical trials, compared with placebo, for treating metastatic colorectal cancer in adults for whom 2 or more chemotherapy regimens have failed.

Intervention(s)	Fixed-dose combination of trifluridine and tipiracil hydrochloride
Population(s)	Adults with metastatic colorectal cancer whose disease has progressed after standard therapies or for whom standard therapies are unsuitable
Comparators	Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations	Related Technology Appraisals: 'Aflibercept in combination with irinotecan and

and NICE Pathways	fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy' (2014). NICE Technology Appraisal 307. Review date August 2016. 'Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of TA150 and part review of TA118)' (2012). NICE Technology Appraisal 242. Static list. 'Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer' (2010). NICE Technology Appraisal 212. Static list. 'Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer' (2007). Technology Appraisal 118. Guidance on static list. Partially reviewed as part of TA242. Terminated appraisals 'Regorafenib for metastatic colorectal cancer after treatment for metastatic disease' (terminated appraisal) (2015). NICE Technology Appraisal 334. 'Panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer' (terminated appraisal) (2011). NICE Technology Appraisal 240. Currently under review [ID794]. Proposed Appraisals 'Ramucirumab in combination with FOLFIRI for treating metastatic colorectal cancer after progression with bevacizumab, oxaliplatin and fluoropyrimidine'. Proposed NICE technology appraisal [ID867]. Publication date to be confirmed. Related Guidelines: 'The diagnosis and management of colorectal cancer' (2011, partially updated December 2014). NICE Guideline CG131. Review date February 2016. Related Quality Standards: 'Colorectal cancer (2012). Quality Standard 20. http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp Related NICE Pathways: 'Colorectal cancer' (2011). NICE Pathway. http://pathways.nice.org.uk/pathways/colorectal-cancer

Related National Policy	Department of Health, 2013, NHS Outcomes Framework 2014-2015. Domains 1, 2, 4 and 5. Department of Health, 2011, Improving outcomes: a strategy for cancer Department of Health, 2009, Cancer commissioning guidance Department of Health, 2007, Cancer reform strategy NHS England, 2014, Manual for prescribed specialised services 2013/14. Chapter 10. Public Health England, 2011, National Screening Committee policy on bowel cancer screening in adults.

References

1. Office for National Statistics (2012) '10 most common cancers in males and females'. Accessed December 2015.
2. Cancer Research UK (2014) 'Bowel cancer mortality statistics'. Accessed December 2015.
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5. Garden OJ, Rees M, Poston GJ et al. (2006) Guidelines for resection of colorectal cancer liver metastases. Gut 55 (Suppl III) iii1–iii8.

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Trifluridine in combination with tipiracil hydrochloride for previously treated metastatic colorectal cancer [ID876]

Final matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Servier Laboratories (trifluridine in combination with tipiracil hydrochloride) Patient/carer groups • Beating Bowel Cancer • Black Health Agency • Bowel Cancer Information • Bowel Cancer UK • Cancer Black Care • Cancer Equality • Cancer 52 • Colostomy Association • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • IA: Ileostomy and Internal Pouch Support Group • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Ostomy Lifestyle • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Cancer Physicians • Association of Surgeons of Great Britain and Ireland • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society (BPOS)	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Possible comparator companies None Relevant research groups • Bowel & Cancer Research • Cochrane Colorectal Cancer Group • CORE (Digestive Disorders Foundation) • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research Evidence Review Group • Kleijnen Systematic Reviews • National Institute for Health Research Health Technology Assessment Programme

Consultees	**Commentators (no right to submit or appeal)**
• British Society of Gastroenterology • Cancer Research UK • Pelican Cancer Foundation • Royal College of Anaesthetists • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal College of Surgeons • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS North Staffordshire CCG • NHS Richmond CCG • Welsh Government	<u>Associated Guideline Groups</u> • National Collaborating Centre for Cancer <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies;
Healthcare Improvement Scotland; the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines); other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

Evidence Review Group (ERG)

An independent academic group commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme) to assist the Appraisal Committee in reviewing the company evidence submission to the Institute.

[1]Non-company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Colorectal cancer (metastatic) - trifluridine with tipiracil hydrochloride, after standard therapy [ID876]

Company evidence submission

February 2016

File name	Version	Contains confidential information	Date
NICE STA Lonsurf_Final	**V1**	**Yes**	**26 February 2016**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

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Abbreviations

5-FU	5-fluorouracil
AE	Adverse event
AIC	Akaike Information Criterion
ARR	Absolute risk reduction
AUC	Area under the curve
BSA	Body surface area
BSC	Best supportive care
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee on Human Medicinal Products
CI	Confidence interval
CR	Complete response
CRC	Colorectal cancer
CrCl	Creatinine clearance
CT	Cytotoxic chemotherapy
DCR	Disease control rate
DMC	Data Monitoring Committee
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EQ-5D	EuroQol-five dimension
FOLFIRI	Folinic acid plus fluorouracil plus irinotecan
FOLFOX	Folinic acid plus fluorouracil plus oxaliplatin
GP	General practitioner
HR	Hazard ratio
HRQL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
IWRS	Interactive voice/web response system
LY	Life year
LYG	Life years gained
mCRC	Metastatic colorectal cancer
MRU	Medical resource use

NA	Not applicable
NE	Not estimable
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PP	Post progression
PPS	Post-progression survival
PR	Partial response
PS	Performance status
PSA	Probability sensitivity analysis
PSS(RU)	Personal Social Services (Research Unit)
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RGB	Regorafenib
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event.
SD	Stable disease
SE	Standard error
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
STA	Single technology appraisal
T/T	Trifluridine/tipiracil
TTF	Time to treatment failure
WT	Wild-type
VEGF	Vascular endothelial growth factor
WTP	Willingness to pay
XELOX	Capecitabine plus oxaliplatin

1 Executive summary

1.1 Statement of decision problem

This appraisal will consider adults with metastatic colorectal cancer (mCRC) whose disease has progressed after standard therapies or for whom standard therapies are unsuitable. At this stage of the disease, life expectancy is approximately 6 months[1-4], and there are currently no recommended therapeutic options for patients in England.[1, 5, 6]

If approved, trifluridine/tipiracil offers a therapeutic option for patients who are refractory or cannot tolerate 5-fluorouracil (5-FU), oxaliplatin and irinotecan-based regimens, but who are well enough and motivated to receive further treatment.[7]

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with metastatic colorectal cancer whose disease has progressed after standard therapies or for whom standard therapies are unsuitable	Final scope	
Intervention	Fixed dose combination of trifluridine and tipiracil hydrochloride	Final scope	
Comparator (s)	Best supportive care		
Outcomes	• overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.	• overall survival • progression-free survival • response rates • adverse effects of treatment	Trifluridine/tipiracil was in-licensed by Servier Laboratories Ltd from Taiho Pharmaceutical. Health-related quality of life data were not collected in the Phase III clinical trial
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	Final Scope. The economic analysis will be presented as reported in the final scope (December 2015) and in accordance with the NICE guide to the methods of technology appraisal (2013).	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	Costs will be considered from an NHS and Personal Social Services perspective.		
Subgroups to be considered	None specified		
Special considerations including issues related to equity or equality	No special considerations, including issues related to equity or equality have been identified.		

1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Trifluridine/tipiracil (Lonsurf)
Marketing authorisation/CE mark status	CHMP positive opinion expected late February 2016 Estimated marketing authorisation – May 2016
Indications and any restriction(s) as described in the summary of product characteristics	Trifluridine/tipiracil is indicated for the treatment of adult patients with metastatic colorectal cancer 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.
Method of administration and dosage	Oral

1.3 Summary of clinical and cost effectiveness

mCRC is the second cause of cancer-related deaths in the UK, equating to a death every half hour.[8, 9] Whilst cancer survival rates in England are improving overall, more can be done to increase survival for people with mCRC[10], which is approximately 6 months in patients relevant to the decision problem.[1-5]

Trifluridine/tipiracil is an effective new drug that provides benefits to patients who have failed on available therapy. The Phase III RECOURSE trial results showed a clinically meaningful increase in median overall survival (OS) of 2 months: 7.2 vs 5.2 for trifluridine/tipiracil and placebo, respectively (HR 0.69; 95% CI 0.59-0.81; p <0.0001).[11] In the Phase II trial used for registration in Japan the increase in median OS was 2.4 months: 9.0 vs 6.6 for trifluridine/tipiracil and placebo, respectively (HR 0·56; 95% CI 0·39-0·81; p = 0·0011).[3] The survival benefits of trifluridine/tipiracil are consistent for all subgroups; there is no population that should not benefit.[12] Placebo represents current clinical practice, which is best supportive care (BSC); at this stage of the disease, other than palliation, there are no NICE-recommended options.

All patients in both trials had received or were intolerant to NICE-approved first- and second-line therapies. Some patients in the Phase II trial had not received biological therapies; these data show that efficacy of trifluridine/tipiracil is maintained in patients who have received all NICE-recommended chemotherapy, but who have not necessarily received agents currently funded by the Cancer Drugs Fund. In addition more than 90% of patients had disease refractory to fluoropyrimidines when last exposed, validating preclinical data and indicating that the mechanism of action of trifluridine/tipiracil is different from other chemotherapies.[12]

Expert opinion is that the side effects are as expected for chemotherapy; and that the more problematic side effects from a clinical management perspective are rare (hand-foot syndrome, cardiac toxicity, stomatitis).[4] This manageable safety profile is demonstrated by the low levels of discontinuation due to adverse events of trifluridine/tipiracil versus placebo in both trials, 4% vs 2% respectively.[2, 3]

An economic model was constructed comparing trifluridine/tipiracil versus BSC based on progression-free, post-progression and death health states. Clinical data were taken from pooled placebo-controlled trials, and costs from the National Health Service (NHS) and published sources where available. The results show that trifluridine/tipiracil extends OS by a mean of 3.2 months compared to placebo (11.1 vs 7.9) using the pooled data, and a mean of 3.0 months (10.7 vs 7.7) from RECOURSE alone. This leads to a gain of 0.17 quality-adjusted life years (QALYs), at an incremental cost of [redacted] – an incremental cost-effectiveness ratio (ICER) of [redacted]. The model is most sensitive to assumptions regarding utilities.

To allow NICE to approve this product for the eligible population (approximately 2,600), who have no available treatment options and a prognosis of approximately 6 months, Servier has set a reasonable list price, and proposed a patient access scheme (PAS) of a [redacted]% confidential reduction to this, reducing the ICER to £44,032.

Table 3: Base-case results without patient access scheme

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER (£) incremental (QALYs)
BSC	[redacted]	0.42	0.66				
T/T	[redacted]	0.59	[redacted]	[redacted]	0.17	0.27	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; T/T, trifluridine/tipiracil.

Table 4: Base-case results with patient access scheme ([redacted]%)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER (£) incremental (QALYs)
BSC	10,286	0.42	0.66				
T/T	16,386	0.59	0.92	7,574	0.17	0.27	44,032

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; T/T, trifluridine/tipiracil.

2 The technology

2.1 Description of the technology

2.1.1 Brand name

Lonsurf

2.1.2 UK approved name

Trifluridine/tipiracil

2.1.3 Therapeutic class

Antineoplastic agents, antimetabolites

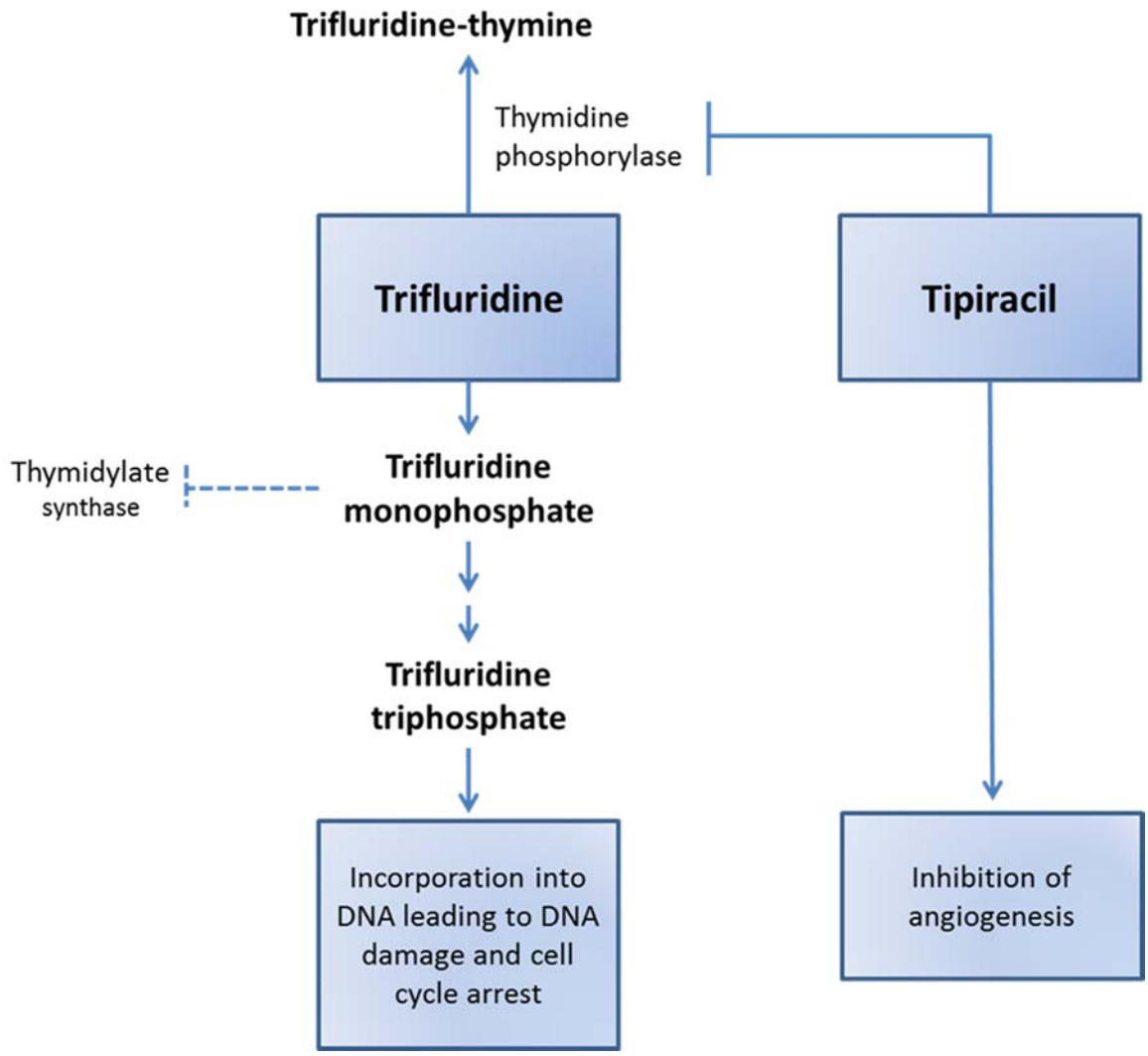
2.1.4 Mechanism of action

Trifluridine/tipiracil is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and a thymidine phosphorylase (TPase) inhibitor, tipiracil hydrochloride, at a molar ratio 1:0.5 (weight ratio, 1:0.471). Following uptake into cancer cells, trifluridine, is phosphorylated by thymidine kinase, further metabolised in cells to a deoxyribonucleic acid DNA substrate, and incorporated directly into DNA, thereby interfering with DNA function to prevent cell proliferation. However, trifluridine is rapidly degraded by TPase and readily metabolised by a first-pass effect following oral administration, hence the inclusion of the TPase inhibitor, tipiracil hydrochloride.[7] The mechanism of action is shown in Figure 1.

Trifluridine is known to inhibit the cell cycle via at least two mechanisms. The monophosphorylated form can bind and inhibit thymidylate synthase (TS).[13] This binding does not require folates and is reversible. The triphosphorylated form is incorporated into DNA.[13] Once trifluridine triphosphate is incorporated into DNA, it leads to abnormal DNA synthesis and inhibition of cell division. The two mechanisms of action are dependent on the mode of trifluridine delivery and exposure time. While continuous infusion of trifluridine results in significant TS inhibition, interrupted pulsed dosing, which is utilised in the clinical trials, results in greater DNA incorporation and disruption of DNA synthesis.[14]

Tipiracil is an essential component of trifluridine/tipiracil, and it has two different functions. It enhances the bioavailability of trifluridine by inhibiting TPase and possesses antiangiogenic properties. Tipiracil has demonstrated anti-tumour activity in a number of preclinical models both as a single agent and in combination with trifluridine.[15, 16]

Figure 1: Mechanism of action of trifluridine/tipiracil

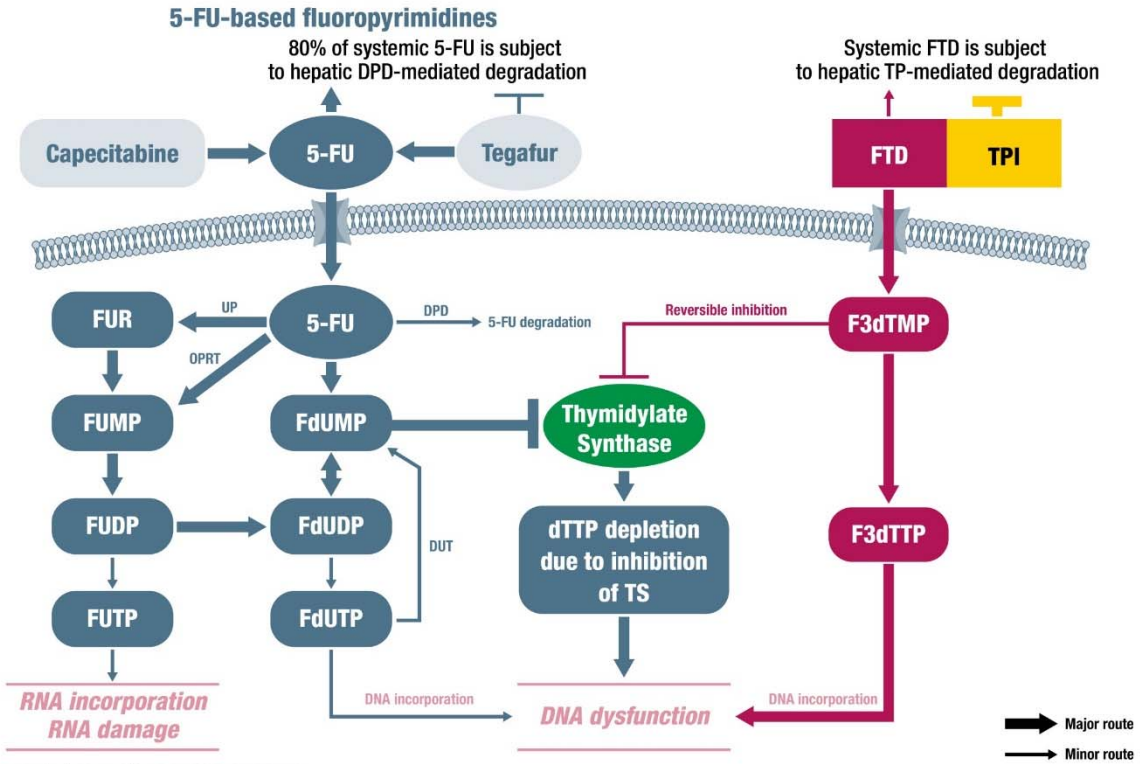


Source: Uboha N & Hochster HS Future Oncology 10.2217/fon.15.276 published online.[17]

In nonclinical studies, trifluridine/tipiracil hydrochloride demonstrated anti-tumour activity against both 5-Fluorouracil (5-FU) sensitive and resistant colorectal cancer cell lines.[7] The cytotoxic activity of trifluridine/tipiracil hydrochloride against several human tumour xenografts correlated highly with the amount of trifluridine incorporated into DNA, suggesting this as the primary mechanism of action.

Trifluridine/tipiracil has a distinct mechanism of action compared with other fluorinated antimetabolites, which accounts for the activity of this compound against tumours that are resistant to 5-FU and similar drugs (Figure 2).[18] The extensive incorporation of trifluridine into DNA, compared to the primary mechanism of action of 5-FU, which involves inhibition of TS and incorporation of 5-FU metabolites into RNA, explains the activity of trifluridine in 5-FU resistant tumours.

Figure 2: Mechanism of action trifluridine/tipiracil: Comparison with 5-FU-based fluoropyrimidines



Key: 5-FU: 5-fluorouracil; DPD: dihydropyrimidine dehydrogenase; dTTP: thymidine triphosphate; F3dTMP: trifluoromethyl deoxuridine 5'-monophosphate: F3dTTP: trifluoromethyl deoxyuridine 5'-triphosphate; FdUDP: fluorodeoxyuridine diphosphate; FdUMP: fluorodeoxyuridine monophosphate; FdUTP: fluorodeoxyuridine triphosphate; FTD: trifluorothymidine (trifluridine); FUDP: fluorouridine diphosphate; FUMP: fluorouridine monophosphate; FUTP: fluorouridine triphosphate; TK: thymidine kinase; TP thymidine phosphorylase; TPI: tipiracil hydrochloride; TS: thymidylate synthase; OPRT: orotate phosphoribosyltransferase; FUR: fluorouridine; UP: uridine phosphorylase; DUT: deoxyuridine pyrophosphatase.
Notes: Figure adapted from H Lenz et.al. Cancer treatment Review. 2015;41:777-783[18]

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 Regulatory status

Trifluridine/tipiracil is currently proceeding through the EU centralised procedure. A positive Committee for Medicinal Products for Human Use (CHMP) opinion is expected in late February 2016, with marketing authorisation in May 2016.

2.2.2 Anticipated licence

Trifluridine/tipiracil is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF (vascular endothelial growth factor) agents and anti-EGFR (epidermal growth factor receptor) agents.

2.2.3 Anticipated contra-indications or restrictions

Contraindications

Hypersensitivity to the active substances (trifluridine or tipiracil hydrochloride) or to any of the excipients.

Special warnings and precautions for use

Bone marrow suppression

Trifluridine/tipiracil caused an increase in the incidence of myelosuppression including anaemia, neutropenia, leucopenia, and thrombocytopenia. Complete blood cell counts must be obtained prior to initiation of therapy and as needed to monitor toxicity, and at a minimum, prior to each treatment cycle.

Treatment must not be started if the absolute neutrophil count is $<1.5 \times 10^9$/L, if the platelet counts are $<75 \times 10^9$/L, or if the patient has a Grade 3 or 4 non-haematological toxicity.

Serious infections have been reported following treatment with trifluridine/tipiracil. Given that the majority were reported in the context of bone marrow suppression, the patient's condition should be monitored closely, and appropriate measures, such as

antimicrobial agents and granulocyte-colony stimulating factor (G-CSF), should be administered as clinically indicated. In the RECOURSE study, 9.4% of patients in the trifluridine/tipiracil group received G-CSF mainly for therapeutic use.

Gastrointestinal toxicity

Trifluridine/tipiracil caused an increase in the incidence of gastrointestinal toxicities including nausea, vomiting and diarrhoea. Patients with these symptoms and other gastrointestinal toxicities should be carefully monitored, and anti-emetic, anti-diarrhoeal and other measures, such as fluid/electrolyte replacement therapy, should be administered as clinically indicated. Dose modifications (delay and/or reduction) should be applied as necessary.

Renal impairment

Trifluridine/tipiracil is not recommended for use in patients with severe renal impairment or end-stage renal disease (creatinine clearance [CrCl] <30 mL/min or requiring dialysis, respectively), as trifluridine/tipiracil has not been studied in these patients. Patients with moderate renal impairment (CrCl 30 to 59 mL/min) had a higher incidence (defined as a difference of ≥5%) of Grade ≥3 adverse events (AEs), serious AEs, and dose delays and reductions compared to the patients with normal (CrCl ≥90 mL/min) or mild renal impairment (CrCl 60 to 89 mL/min). In addition, a higher exposure of trifluridine/tipiracil was observed in patients with moderate renal impairment, compared to patients with normal renal function or mild renal impairment. Patients with moderate renal impairment should be more frequently monitored for haematological toxicities.

Hepatic impairment

Trifluridine/tipiracil is not recommended for use in patients with moderate or severe hepatic impairment (National Cancer Institute Criteria Group C and D) as trifluridine/tipiracil has not been studied in these patients.

Lactose intolerance

Trifluridine/tipiracil contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

2.2.4 Summary of main issues discussed by the regulatory authorities

Trifluridine/tipiracil is currently proceeding through the final stages of the regulatory process with a CHMP positive opinion expected in late February 2016. Therefore, a draft EPAR is currently not available to include within the submission. Servier have provided the "Summary of CHMP's Day 120 Clinical Major Objection", which includes the CHMP response in Appendix 1 (Note: Trifluridine/tipiracil is referred to as TAS-102 throughout this document).[19] This document is briefly summarised below:

The major objection received from the CHMP at Day 120 was as follows: "The limited benefit of trifluridine/tipiracil in terms of OS needs to be critically weighed against the low response rate and observed/expected drug-related toxicity. In terms of response, the effect in a substantial number of patients is related to stabilisation of the disease only and, in light of the safety profile, this raises the question whether the indication should be restricted to a clearly defined sub-population of patients identified as having a greater degree of benefit. Additional data on microsatellite instability status and other tumour characteristics may be needed for this purpose. Eligibility for treatment also needs to be addressed within the context of alternative therapies, in particular regorafenib. These issues should be discussed further before the benefit-risk of trifluridine/tipiracil for the currently claimed broad indication can be considered positive."

In response to this objection, the CHMP were provided with the following:

1. Risk benefit evaluation
2. Consideration of sub-populations
3. Comparison to regorafenib
4. Conclusion

Based on the provided evidence, the Rapporteur concluded the following:

"No specific biomarker predictive for response to trifluridine/tipiracil has been identified in RECOURSE. Therefore, no specific subgroup of patients with mCRC seems to benefit most from treatment with trifluridine/tipiracil in the proposed indication. Overall, the toxicity of trifluridine/tipiracil is considered manageable and is not considered worse than the safety profile of regorafenib. The benefit-risk of trifluridine/tipiracil for the proposed indication is considered positive. The issue is resolved."

At Day 180, the CHMP endorsed the Rapporteur's conclusion: the CHMP considers positive the overall benefit-risk of trifluridine/tipiracil (Lonsurf) for the proposed indication and did not raise any major objection on clinical aspects.

2.2.5 Estimated UK availability

It is estimated that trifluridine/tipiracil will be available in the UK from July 2016.

2.2.6 Regulatory approval outside the UK

Trifluridine/tipiracil is licensed in Japan and the US; details are provided in Table 5. Up to 21 December 2015 over 12,000 patients have received trifluridine/tipiracil (10,562 in Japan, 1,859 in the US).[20]

Table 5: Regulatory approval outside the UK

Country	Marketing authorisation
Japan	Treatment of patients with unresectable advanced or recurrent colorectal cancer[21]
US	Treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if *RAS* wild-type, an anti EGFR therapy.[22]
Key: EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.	

2.2.7 Other UK Health Technology Assessments

Trifluridine/tipiracil will be assessed by the Scottish Medicines Consortium (SMC). Servier plan to provide a submission to the SMC within 3 months of receiving the marketing authorisation for the product. Guidance should be available in Scotland between November 2016 and January 2017, depending on the date of the evidence submission.

2.3 Administration and costs of the technology

2.3.1 Costs of technology being appraised

Costs of trifluridine/tipiracil are set out in Table 6 and Table 7.

Table 6: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Tablet	SmPC[7]
Acquisition cost (excluding VAT)*	See Table 7 below	List price
Method of administration	Oral	SmPC
Doses	Dosing is based on BSA. Refer to the SmPC	SmPC
Dosing frequency	The recommended starting dose of trifluridine/tipiracil in adults is 35mg/m^2; this dose is administered orally twice daily for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest (1 treatment cycle). This treatment cycle is repeated every 4 weeks. Refer to the SmPC for further information	SmPC
Average length of a course of treatment	28 days	SmPC
Average cost of a course of treatment	The average BSA in the RECOURSE trial was 1.78m^2. The average cost per patient per cycle at this BSA is [redacted] based on the UK list price, with an associated PAS price of £1,625.	RECOURSE[2]
Anticipated average interval between courses of treatments	0 days	SmPC
Anticipated number of repeat courses of treatments	The average number of cycles in RECOURSE was 3.4	RECOURSE
Dose adjustments	Dosing adjustments may be required based on individual safety and tolerability. In the event of haematological and/or non-haematological toxicities patients should follow the dose interruption, resumption and reduction criteria stated in the SmPC	SmPC
Anticipated care setting	Secondary care	

Key: BSA, body surface area; SmPC, summary of product characteristics.
Note: Cycle length in the economic model is reflective of trial data.

Table 7: Trifluridine/tipiracil pack sizes and costs

Dose	Pack sizes	Cost*
15mg	20	£500
	60	£1,500
20mg	20	£667
	60	£2,000
Note: *The average cost per patient per cycle is [redacted] (based on list price) or £1,625 (based on PAS price) using an average BSA of 1.78m^2.		

[redacted]

2.4 Changes in service provision and management

2.4.1 Service provision

Trifluridine/tipiracil is an oral therapy; as such, treatment is not associated with any staff or infrastructure requirements. Patients will be managed and treated in secondary care either in a chemotherapy day case or outpatient setting.

Complete blood cell counts must be obtained prior to initiation of therapy and prior to each treatment cycle as they are needed to monitor toxicity. There are no companion diagnostic requirements (e.g. genetic or protein testing).

2.4.2 Resource use

The SmPC states that "trifluridine/tipiracil should be prescribed by physicians experienced in the administration of anticancer therapy"[7]; therefore, it is anticipated that prescribing will be undertaken in secondary care.

2.5 Innovation

There are currently no options in the NHS for patients with mCRC who have already received NICE-recommended therapy and are well enough and motivated to take further lines of therapy.[6] At this time, patients may receive capecitabine or chemotherapy re-challenge. However, there is no evidence to support this approach, and as patients are already refractory to prior regimens, it is unknown how effective this strategy would be.[4, 23] Trifluridine/tipiracil has a different mode of action to 5-FU (Section 2.1.4) and has proven efficacy in heavily pre-treated patients, including those with tumours refractory to 5-FU-based regimens.[2, 3, 18]

Trifluridine/tipiracil is an oral therapy, which is a route of administration that is likely to be beneficial for patients at this line of treatment and stage of their disease.[4]

3 Health condition and position of the technology in the treatment pathway

3.1 Description of the health problem

3.1.1 Aetiology and pathology of metastatic colorectal cancer

Colorectal cancer (CRC) includes cancerous growths in the colon (colon cancer) and rectum (rectal cancer). Most colorectal cancers arise from adenomatous polyps. These neoplasms are usually benign, but some develop into cancer over time. The occurrence of CRC is strongly related to age, with 83% of cases arising in people who are 60 years or older.[24]

Metastatic colorectal cancer (mCRC) refers to disease that has spread beyond the large intestine and nearby lymph nodes.[24] This type of cancer most often spreads first to the liver, but metastases may also occur in other parts of the body including the lungs, brain and bones.[24]

The pathology of the tumour is usually determined by analysis of tissue taken from a biopsy or surgery. The extent to which the cancer has spread is described as its stage.[25] Staging is essential in determining the choice of treatment and in assessing prognosis. More than one system is used for the staging of cancer. CRC stage can be described using the modified Dukes staging system, which is based on postoperative findings – a pathological staging based on resection of the tumour and measuring the depth of invasion through the mucosa and bowel wall. Alternatively, the TNM staging system, which is based on the depth of tumour invasion (T), nodal involvement (N), and metastatic spread (M) assessed pre-operatively by radiological examination, is more precise (Table 8).[25]

This appraisal focusses on mCRC that is classified as Stage IV or Modified Dukes Stage D.

Table 8: Staging of colorectal cancer

Staging group	TNM staging and sites involved	Modified Dukes stage
Stage 0	Carcinoma in situ (Tis, N0, M0)	
Stage I	No nodal involvement, no distant metastases Tumour invades submucosa (T1, N0, M0) Tumour invades muscularis propria (T2, N0, M0)	A
Stage II	No nodal involvement, no distant metastases Tumour invades muscularis propria into pericolorectal tissues (T3, N0, M0) Tumour penetrates surface of visceral peritoneum or directly invades or is adherent to other organs or structures (T4a/b, N0, M0)	B
Stage III	Nodal involvement, no distant metastases (Any T, Any N, M0)	C
Stage IV	Distant metastases (Any T, Any N, M1a/M1b)	D

Key: T0, no evidence of tumour, Tis, tumour in situ (abnormal cells present but may spread to neighbouring tissue, sometimes referred to as pre-invasive cancer); T1, T2, T3, T4, stage of cancer; N0, no regional lymph node involvement; M0, no distant metastases; M1 distant metastases is present.
Source: National Institute for Health and Care Excellence.[25]

Effect of genetic status

Normal cell behaviour is controlled by a complex network of signalling pathways which ensures that cells proliferate only when they are required to.[26] Cancer occurs when normal growth regulation breaks down, sometimes because of defects within these signalling mechanisms.[26] The rat sarcoma (*RAS*) genes, e.g. *KRAS*, play an important role in the EGFR signalling pathway. *KRAS* mutations are generally thought to be a negative predictive marker for the treatment effect of an anti-EGFR monoclonal antibody. As the mechanism of action of trifluridine/tipiracil involves direct incorporation of trifluridine into DNA, *KRAS* should not directly affect the activity of trifluridine/tipiracil. This is supported by the data analysis from the Phase II and RECOURSE trials, which demonstrate efficacy in *KRAS* wild-type and *KRAS* mutant tumours; these are discussed in detail in Sections 4.7 and 4.8.[2, 3]

3.1.2 Epidemiology of mCRC

Incidence of mCRC in England

In terms of incidence, CRC is the fourth most common cancer in the UK behind breast, lung and prostate cancer, accounting for 12% of all new cases.[8]

Table 9 summarises the number of new cases and incidence rates for mCRC in England. At diagnosis, 26% of patients present with metastatic disease.[27] In addition, approximately 55% of patients initially diagnosed with colorectal cancer Stage II, or III who receive initial treatment will ultimately progress to metastatic disease – which was the estimate used in TA242.[5] Therefore, the estimated annual number of new patients with mCRC in England is approximately 19,600. As annual mortality rates for mCRC are high (Section 3.4.1) and increase as the number of lines of therapy increases, it is assumed that the numbers of patients year on year with mCRC remains constant.

The number of patients relevant to this appraisal are presented in Section 3.4.2 and Section 6.

Table 9: Estimate of the annual number of patients with metastatic colorectal cancer in England

Details	%	Population
Number of new patients with CRC in England[8]		34,322
Stage I (assume cured following surgical resection)[27]	18%	6,095
Stage II[27]	27%	9,254
Stage III[27]	29%	9,905
New cases diagnosed as metastatic (Stage IV)[27]	**26%**	**9,069**
Patients with Stage II or Stage III that progress to metastatic disease[5]	**55%**	**10,537**
Total number of people with new metastatic disease each year		**19,606**
Key: CRC, colorectal cancer.		

3.2 Impact of colorectal cancer on patients, carers and society

CRC is a significant cause of morbidity and mortality. Psychological distress is common in patients with CRC, with depression and anxiety being particularly common; this is exacerbated further for patients who have had a stoma following surgery for their condition.[28]

The NICE clinical guidance on supportive and palliative care (CSG 4) advises those who develop and deliver cancer services for adults with cancer on what is needed to ensure that patients, and their families and carers, are well informed, cared for and supported.[29]

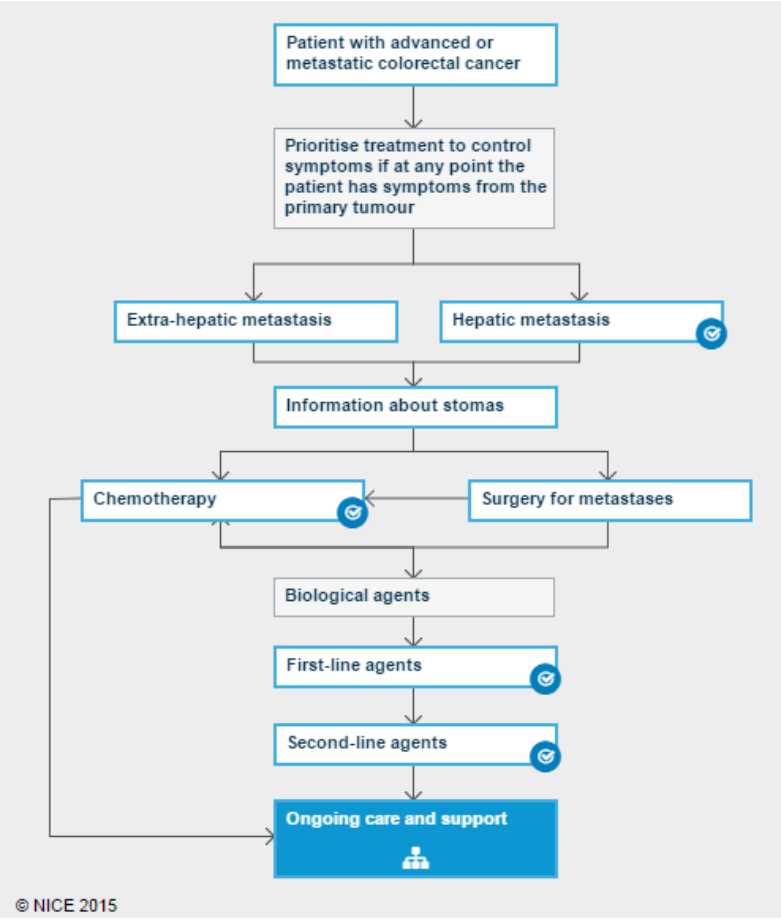
When treating people with mCRC, the main aims of treatment are to relieve symptoms and to improve health-related quality of life (HRQL) and survival.[24]

3.3 NICE clinical pathway for mCRC

Figure 3 shows the NICE clinical pathway for mCRC.[25]

NICE guidance is available on the diagnosis, management, and first- and second-line therapeutic treatments for mCRC. Table 10 provides details of therapeutic agents currently recommended by NICE for the management of mCRC, and Table 11 provides the therapies currently funded by the Cancer Drugs Fund (CDF).

Figure 3: NICE clinical pathway for patients with metastatic colorectal cancer



Key: NICE, National Institute for Health and Care Excellence.
Source: NICE, 2015.[25]

Table 10: NICE-recommended therapy for first- and second-line treatment of metastatic colorectal cancer

Regimen	Recommendation	Source
FOLFOX	As first-line treatment then single agent irinotecan as second-line treatment	NICE CG131[24]
FOLFOX	As first-line treatment then FOLFIRI as second-line treatment	
XELOX (capecitabine plus oxaliplatin)	As first-line treatment then FOLFIRI as second-line treatment	
Cetuximab*	Cetuximab in combination with FOLFOX, within its licensed indication, is recommended for the first-line treatment of mCRC only when specific criteria are met	NICE TA176[30]
Cetuximab*	Cetuximab in combination with FOLFIRI, within its licensed indication, is recommended for the first-line treatment of mCRC only when specific criteria are met	
Raltitrexed	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	NICE CG131[24]
Capecitabine or tegafur with uracil	First-line treatment of mCRC	NICE TA61[31]

Key: FOLFIRI, folinic acid plus fluorouracil plus irinotecan; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; mCRC, metastatic colorectal cancer; NICE, National Institute for Health and Care Excellence; XELOX, capecitabine plus oxaliplatin.

Note:* An update of TA176 is currently ongoing - ID794. Following the second appraisal committee meeting on 6 January, no preliminary recommendations have been made.

Table 11: Cancer Drugs Fund recommendations for first- or second-line treatment of metastatic colorectal cancer

Cetuximab	The first-line treatment of mCRC where all the following criteria are met: 1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy 2. mCRC 3. First-line indication 4. Patients with wild-type *RAS* 5. Given in combination with irinotecan- or oxaliplatin-based combination chemotherapy 6. Cetuximab given as a 2-weekly regimen at a dose of 500mg/m^2 7. a) Not eligible for NICE TA176[30] approved indications OR b) Eligible for treatment under TA176 and no progression after receiving the approved 16 weeks treatment with cetuximab but unsuitable for surgery and meeting criteria 1-6 8. No previous treatment with cetuximab or panitumumab (unless meeting condition 7b) Note: No treatment breaks of more than 4 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or in the case of intercurrent co-morbidities) Note: If excessive toxicity with irinotecan or oxaliplatin, cetuximab can be continued with a fluoropyrimidine alone until disease progression only.
Panitumumab	The first-line treatment of mCRC where all the following criteria are met: 1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy 2. mCRC 3. First-line indication 4. Patients with wild-type *RAS* 5. Given in combination with irinotecan- or oxaliplatin-based combination chemotherapy 6. No previous treatment with cetuximab or panitumumab Note: No treatment breaks of more than 4 weeks beyond the expected cycle length are allowed (to allow any toxicity of current therapy to settle or in the case of intercurrent co-morbidities) Note: If excessive toxicity with irinotecan or oxaliplatin, panitumumab can be continued with a fluoropyrimidine alone until disease progression only.
Key: CDF, Cancer Drugs Fund; mCRC, metastatic colorectal cancer. **Source:** Adapted from National Cancer Drugs Fund List Ver6.0, November 2015.[32]	

3.3.1 Therapeutic options for patients with mCRC at third line or beyond

The aim of treatment at third line for mCRC is to prolong life, improve symptoms and maintain quality of life.

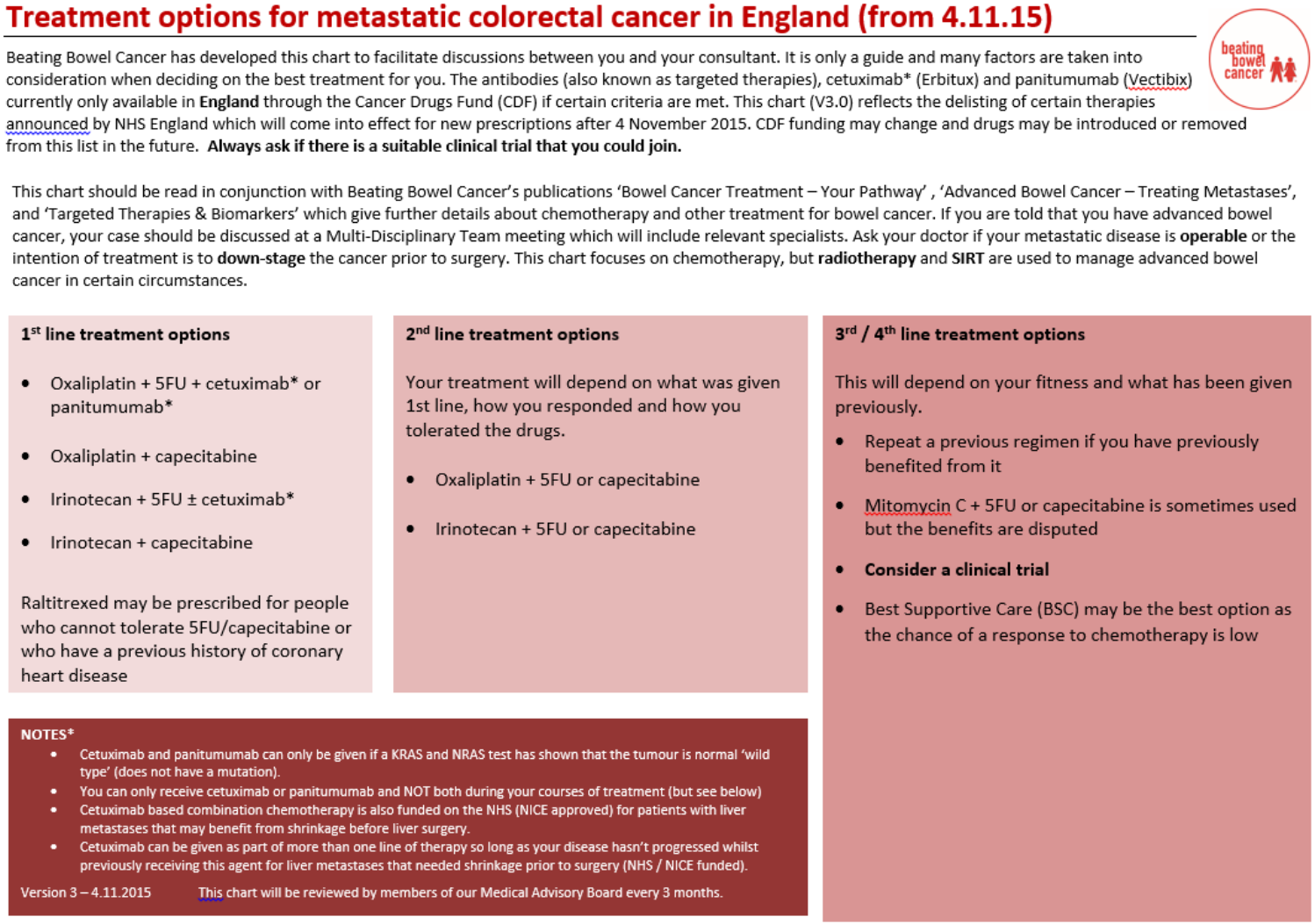
NICE recommendations for the treatment of mCRC at third line and beyond are presented in Table 12. Bevacizumab, cetuximab and panitumumab are not recommended by NICE at third line or beyond (NICE TA242) and were removed from the CDF-approved list on 4 November 2015.[32] As a result, there are currently no recommended therapeutic options for patients who have failed second-line treatment. These patients would receive best supportive care, described as on-going care and support in the NICE pathway.[24] Regorafenib is not recommended by NICE due to a non-submission.[33] Regorafenib is licensed for patients with mCRC who have been previously treated with, or not considered candidates for, available therapies, and therefore, it is only available in England for treatment of mCRC via private insurance.[34]

Table 12: NICE recommendations for the treatment of metastatic colorectal cancer at third line and beyond

Regimen	Recommendation	Source
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 (review of technology appraisal 150 and part review of technology appraisal guidance 118)	1.1 **Cetuximab** monotherapy or combination chemotherapy is **not recommended** for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy. 1.2 **Bevacizumab** in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy is **not recommended** for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy. 1.3 **Panitumumab** monotherapy is **not recommended** for the treatment of people with metastatic colorectal cancer that has progressed after first-line chemotherapy.	NICE TA242[5]
Regorafenib	NICE is unable to make a recommendation about the use of regorafenib for mCRC after treatment for metastatic disease because no evidence submission was received from Bayer for the technology	NICE TA334[33]

Beating Bowel Cancer has developed a chart to facilitate discussion between patients and clinicians following the changes to the CDF in November 2015 (Figure 4).[23] This details potential third and fourth line options for patients with mCRC; however, these options are not approved by NICE.

Figure 4: Beating Bowel Cancer treatment options for metastatic colorectal cancer



Treatment options for metastatic colorectal cancer in England (from 4.11.15)

Beating Bowel Cancer has developed this chart to facilitate discussions between you and your consultant. It is only a guide and many factors are taken into consideration when deciding on the best treatment for you. The antibodies (also known as targeted therapies), cetuximab* (Erbitux) and panitumumab (Vectibix) currently only available in **England** through the Cancer Drugs Fund (CDF) if certain criteria are met. This chart (V3.0) reflects the delisting of certain therapies announced by NHS England which will come into effect for new prescriptions after 4 November 2015. CDF funding may change and drugs may be introduced or removed from this list in the future. **Always ask if there is a suitable clinical trial that you could join.**

This chart should be read in conjunction with Beating Bowel Cancer's publications 'Bowel Cancer Treatment – Your Pathway' , 'Advanced Bowel Cancer – Treating Metastases', and 'Targeted Therapies & Biomarkers' which give further details about chemotherapy and other treatment for bowel cancer. If you are told that you have advanced bowel cancer, your case should be discussed at a Multi-Disciplinary Team meeting which will include relevant specialists. Ask your doctor if your metastatic disease is **operable** or the intention of treatment is to **down-stage** the cancer prior to surgery. This chart focuses on chemotherapy, but **radiotherapy** and **SIRT** are used to manage advanced bowel cancer in certain circumstances.

1st line treatment options

- Oxaliplatin + 5FU + cetuximab* or panitumumab*
- Oxaliplatin + capecitabine
- Irinotecan + 5FU ± cetuximab*
- Irinotecan + capecitabine

Raltitrexed may be prescribed for people who cannot tolerate 5FU/capecitabine or who have a previous history of coronary heart disease

2nd line treatment options

Your treatment will depend on what was given 1st line, how you responded and how you tolerated the drugs.

- Oxaliplatin + 5FU or capecitabine
- Irinotecan + 5FU or capecitabine

3rd / 4th line treatment options

This will depend on your fitness and what has been given previously.

- Repeat a previous regimen if you have previously benefited from it
- Mitomycin C + 5FU or capecitabine is sometimes used but the benefits are disputed
- **Consider a clinical trial**
- Best Supportive Care (BSC) may be the best option as the chance of a response to chemotherapy is low

NOTES*

- Cetuximab and panitumumab can only be given if a KRAS and NRAS test has shown that the tumour is normal 'wild type' (does not have a mutation).
- You can only receive cetuximab or panitumumab and NOT both during your courses of treatment (but see below)
- Cetuximab based combination chemotherapy is also funded on the NHS (NICE approved) for patients with liver metastases that may benefit from shrinkage before liver surgery.
- Cetuximab can be given as part of more than one line of therapy so long as your disease hasn't progressed whilst previously receiving this agent for liver metastases that needed shrinkage prior to surgery (NHS / NICE funded).

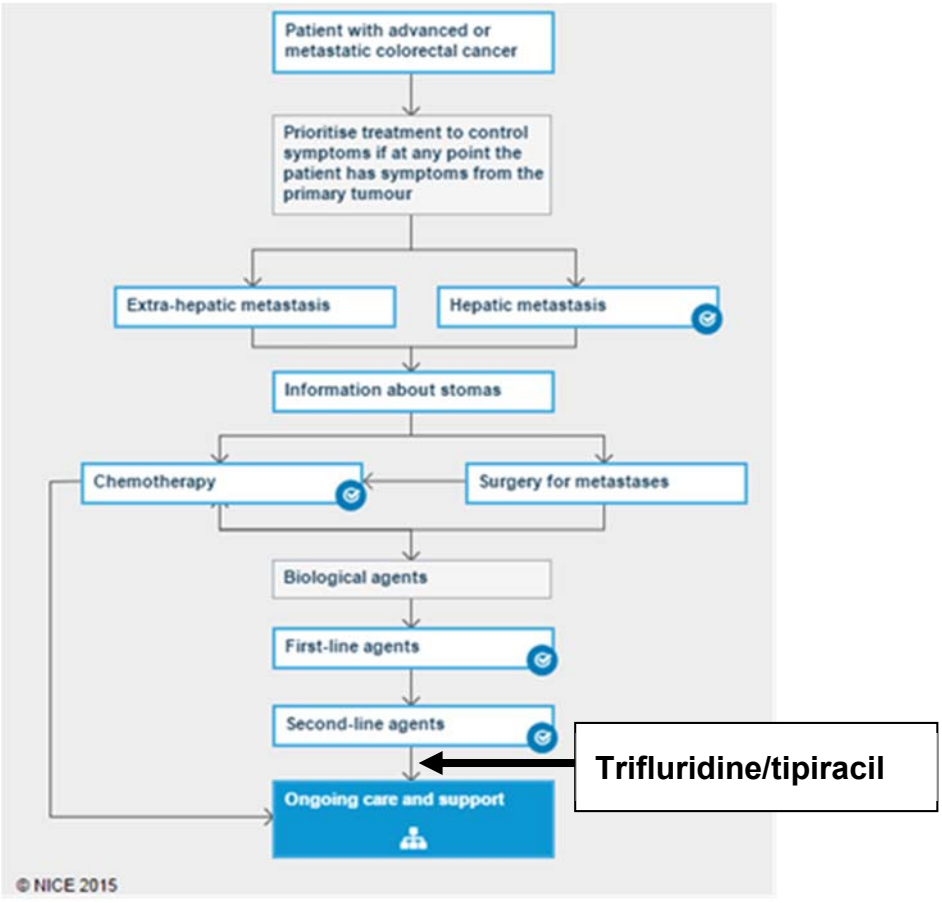
Version 3 – 4.11.2015 This chart will be reviewed by members of our Medical Advisory Board every 3 months.

Source: Beating Bowel Cancer.[23]

Discussions with clinical experts have indicated that patients at this stage of disease who are well enough and who wish to continue active treatment may receive capecitabine, chemotherapy re-challenge; however, there is no evidence base for the use of these options in this line of treatment.[4] Patients at this line of treatment would have progressed on 5-FU-based regimens and are generally considered "refractory" or intolerant to prior therapies. Therefore, the use of such options is unlikely to provide treatment benefit. Alternatively, these patients could be considered for clinical trials or regorafenib (if patients have private insurance). Clinical experts at the recent advisory board highlighted that trifluridine/tipiracil would be a preferred option to regorafenib based on tolerability.[4]

Trifluridine/tipiracil provides a therapeutic option for patients with tumours that have progressed following second-line treatment and who are well enough and motivated to receive further therapeutic intervention – Figure 5 shows where trifluridine/tipiracil would fit into the current treatment algorithm.

Figure 5: Proposed place of trifluridine/tipiracil in the treatment pathway for patients with metastatic colorectal cancer



Key: NICE, National Institute for Health and Care Excellence.
Source: NICE colorectal cancer pathway.[6]

3.4 Life expectancy and estimated patient numbers

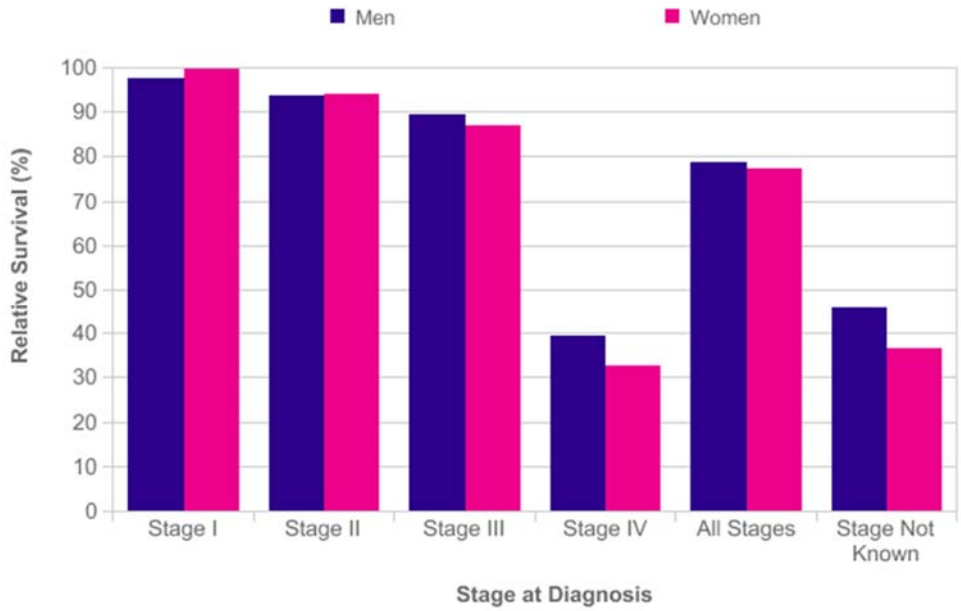
3.4.1 Mortality

Survival for bowel cancer is related to the stage of the disease at diagnosis. The 1-year and 5-year mortality rates for mCRC (Stage IV) are significantly higher than for patients diagnosed at earlier stages of the disease.[9]

Trifluridine/tipiracil is licensed for patients who have already received standard recommended treatment for mCRC, and are therefore likely to be receiving therapy at third line or later. At this stage of the disease, life expectancy is approximately 6 months.[1-4]

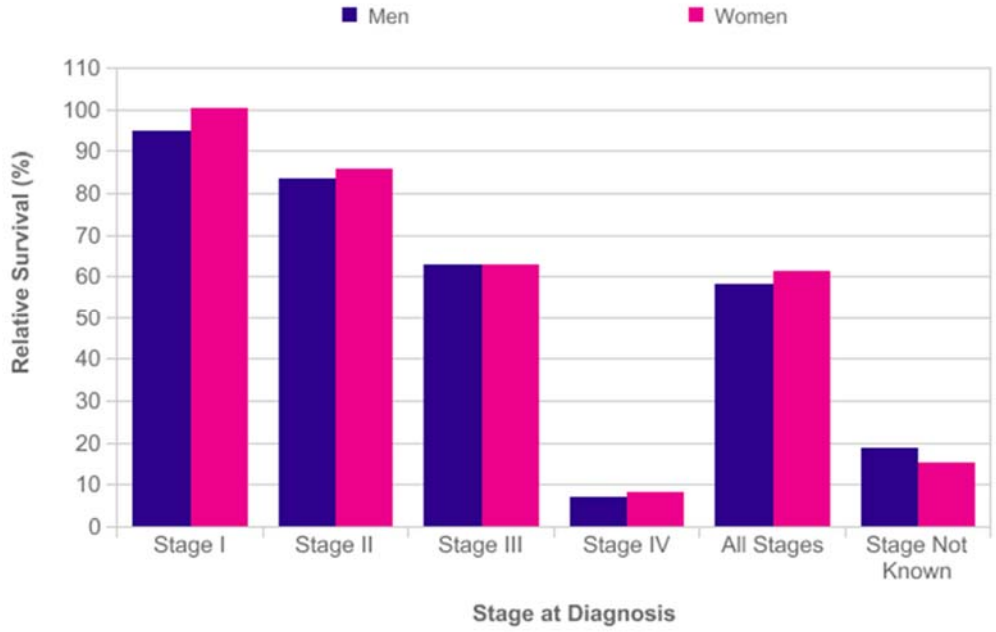
One-year relative survival for bowel cancer is highest for patients presenting at Stage I, with 98% of men and 100% of women surviving their disease for at least 1 year among patients diagnosed during 2006-2010 in the former Anglia Cancer Network (Figure 6).[9] One-year survival is lowest for those diagnosed with Stage IV disease (40% for men and 33% for women). In addition, the survival of patients with mCRC decreases with each line of therapy. Five-year survival for patients with mCRC is 7% and 8% for men and women, respectively (Figure 7).[9]

Figure 6: One-year relative survival (%) by stage, adults aged 15-99, former Anglia Cancer Network*



Note: *These data are independent of the line of treatment.
Source: Cancer Research UK: Bowel cancer survival statistics.[9]

Figure 7: Five-year relative survival (%) by stage, adults aged 15-99, former Anglia Cancer Network*



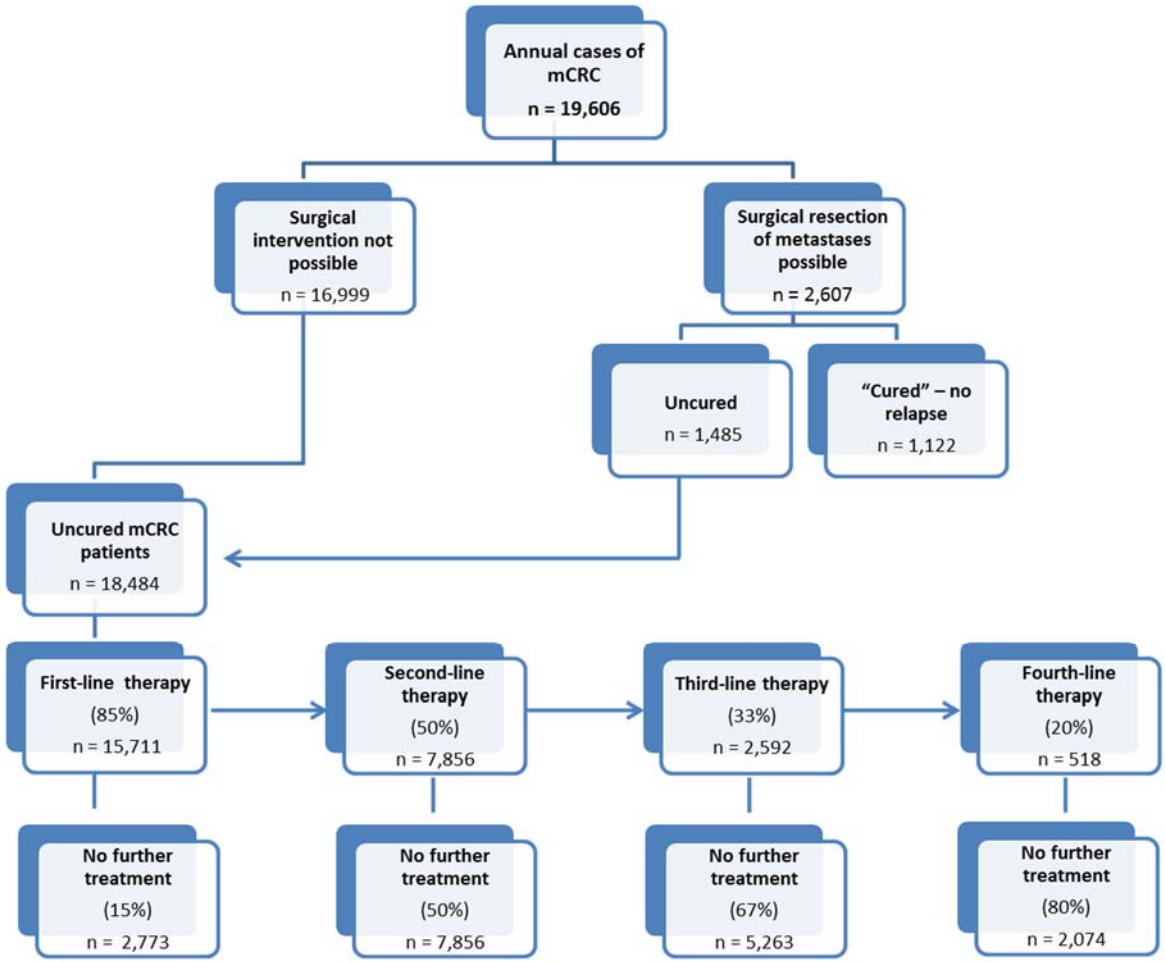
Note: *These data are independent of the line of treatment.
Source: Cancer Research UK: Bowel cancer survival statistics.[9]

3.4.2 Estimate of the number of mCRC patients at each line of therapy

Figure 8 sets out the estimated numbers of patients with mCRC at each line of treatment. The figures have been adapted from Hind et al.[35], following personal communication with a number of medical and clinical oncologists who have provided their expert opinion. Patients who are in the “no further treatment” group will have either died, be unsuitable for further treatment or have opted to stop therapy.

Following diagnosis of mCRC, approximately 13% (n = 2,607) of patients will have tumours that are suitable for surgical resection either immediately or following down-staging with chemotherapy.[35] For those patients viable for surgical intervention, approximately 43% (n = 1,122) will have no further relapse and have an effective cure.[35] Those mCRC patients not eligible for surgical intervention (n = 16,999) or who have relapsed following surgery (n = 1,485) have limited therapy options. These include therapeutic intervention, palliation, clinical trials or best supportive care (i.e. no further active treatment for their condition).

Figure 8: Estimate of the number of patients with metastatic colorectal cancer by treatment option



Key: mCRC, metastatic colorectal cancer.
Source: Adapted from Hind et al. following expert opinion from medical and clinical oncologists.[35]

Trifluridine/tipiracil would fit into the treatment pathway at third line or beyond. It is estimated that at this stage there would be approximately 2,600 patients who may be eligible for and are motivated to receive further treatment. A significant percentage of these patients may opt to go into clinical trials – particularly if they are being treated in a tertiary centre. Other patients may receive therapy not recommended by NICE at this line of treatment, such as capecitabine or chemotherapy re-challenge. The remainder of patients would be eligible for treatment with trifluridine/tipiracil.

3.5 Relevant NICE guidance, pathways or commissioning guides

As detailed in Section 3.3.1, there is no relevant guidance or recommendations in England for patients who have progressed beyond second-line therapy and who may be appropriate for and motivated to receive further therapeutic intervention (i.e. patients who may be appropriate to receive trifluridine/tipiracil).

3.6 Other clinical guidelines

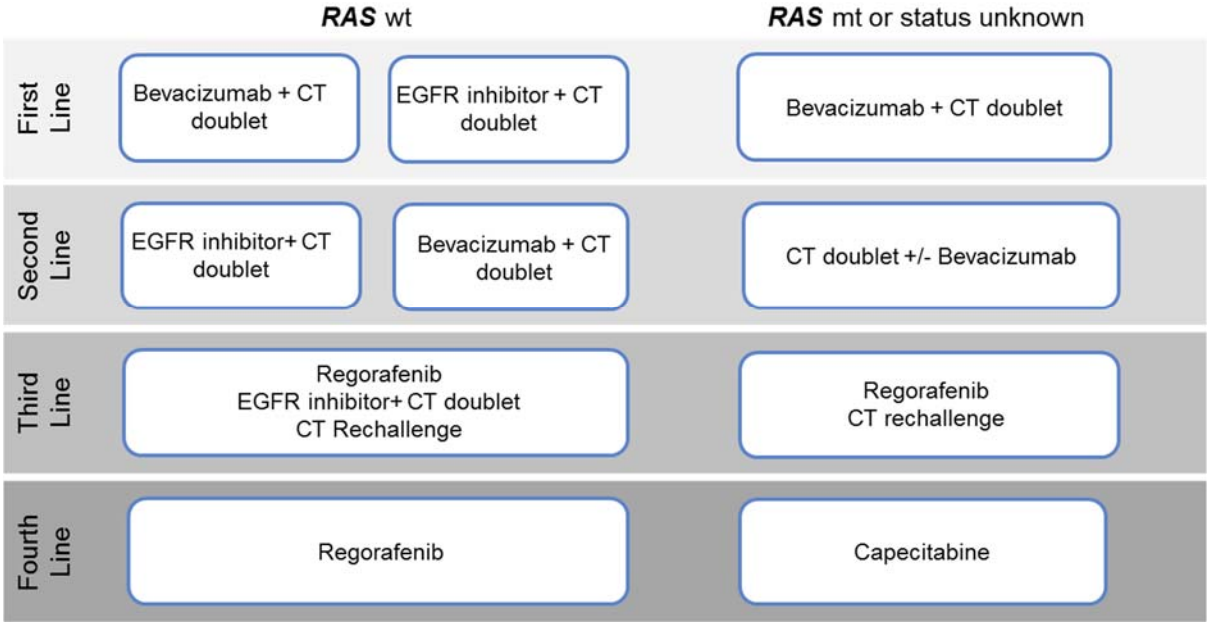
3.6.1 National Comprehensive Cancer Network (NCCN)

Trifluridine/tipiracil is included as an option in the latest version of the NCCN guidelines for colon cancer. The regimen of trifluridine/tipiracil was added as a subsequent therapy option (additional option to regorafenib in all cases) for patients with disease progression after oxaliplatin- and irinotecan-based chemotherapy. The continuum of care – Chemotherapy for advanced or metastatic disease is provided in Appendix 2.[36]

3.6.2 European Society of Clinical Oncology (ESMO) Clinical Practice Guidelines for mCRC

ESMO published their clinical practice guidelines for mCRC in 2014.[37] Figure 9 provides an overview of the current treatment recommendations. Trifluridine/tipiracil has been included in the ESMO pocket guidelines for lower gastrointestinal cancer 2015 as a potential option at third and further lines.[38]

Figure 9: Strategic scenarios in the continuum of care of metastatic colorectal cancer



Key: CT, cytotoxic chemotherapy; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; mt, mutation-positive; wt, wild-type.
Note: Cetuximab or panitumumab are EGFR inhibitors.
Source: Adapted from Van Cutsem, 2014.[37]

3.7 Issues relating to current practice

The key issues relating to current clinical practice in mCRC within the timelines of this technology appraisal are as follows:

1. On-going NICE Technology appraisal (ID794): Colorectal cancer (metastatic) – Cetuximab (review 176) and panitumumab (part review TA240) (first line)

   The following statement was published on the NICE website on 1 February 2016. “Following the second Appraisal Committee meeting on 6 January the Committee has not made any preliminary recommendations. The Committee felt that it did not have all the evidence and analyses necessary to make clinically meaningful recommendations, and we are considering what further analyses may be needed. We will therefore not issue an ACD or FAD at this point. We will provide an update once subsequent timelines are confirmed.”

   The outcome is unlikely to affect the appraisal for trifluridine/tipiracil, which is licensed for a later line of treatment.

2. CDF: A new operating framework for the CDF is due to be operational from April 2016. It is unclear how this will affect the therapies currently approved for mCRC.

3.8 Equality issues

No special considerations, including issues related to equity or equality have been identified.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

A systematic review was conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of trifluridine/tipiracil compared with best supportive care (BSC) for patients with advanced/metastatic colorectal cancer receiving treatment at the third line or beyond.

4.1.1 Search strategy

The following electronic databases were searched on the 26 October 2015: Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, EMBASE (Ovid), and the Cochrane library (Ovid), consisting of the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, the NHS Economic Evaluation Database (NHS EED), the Database of Abstracts of Reviews of Effects (DARE), and HTA.

Electronic searches were supplemented by hand searching reference lists of included publications and conference proceedings. Any relevant abstracts identified through the electronic database search or supplementary hand searching were checked for available associated posters.

Full details of the search are provided in Appendix 3.

4.1.2 Study selection

Studies identified by the electronic searches were initially assessed based on title and abstract. Papers not meeting the inclusion criteria were excluded, and allocated a “reason code” to document the rationale for exclusion. Papers included after this stage were then assessed based on the full text; further papers were excluded, yielding the final data set for inclusion. The final included data set consisted of clinical studies examining trifluridine/tipiracil versus BSC.

Inclusion and exclusion selection criteria are shown in Table 13.

Database searches and hand searching were conducted to identify studies investigating a broader range of comparators for trifluridine/tipiracil than specified in the NICE scope (BSC only). The additional interventions of interest included all

currently available treatments that have been used in this indication: regorafenib, aflibercept, capecitabine, raltitrexed, cetuximab, panitumumab, and bevacizumab. Data from these publications may be required to support future HTA submissions in other territories. Screening of titles and abstracts was performed according to the wider global criteria. Studies that were not considered relevant to support the current submission were then excluded upon full publication review according to the criteria shown in Table 13.

Table 13: Eligibility criteria used in search strategy

	Inclusion criteria	Exclusion criteria	Comments
Population	Adult patients with advanced/ mCRC receiving treatment at third line or beyond	Patients receiving treatment at first or second line	According to NICE scope
Interventions	Trifluridine/tipiracil	-	According to NICE scope
Comparators	BSC	-	Searches were conducted to identify studies investigating all currently available comparators for trifluridine/tipiracil (to support HTA submissions in other territories); however, comparators considered relevant for the current STA were restricted to BSC according to the NICE scope[†]
Outcomes	Efficacy: Overall survival 1-year survival rate Progression-free survival Time to progression Response rates (complete response, partial response, stable disease) Objective response rate Disease control rate Safety: All-grade AEs of interest Grade 3 or 4 AEs of interest HRQL	-	-

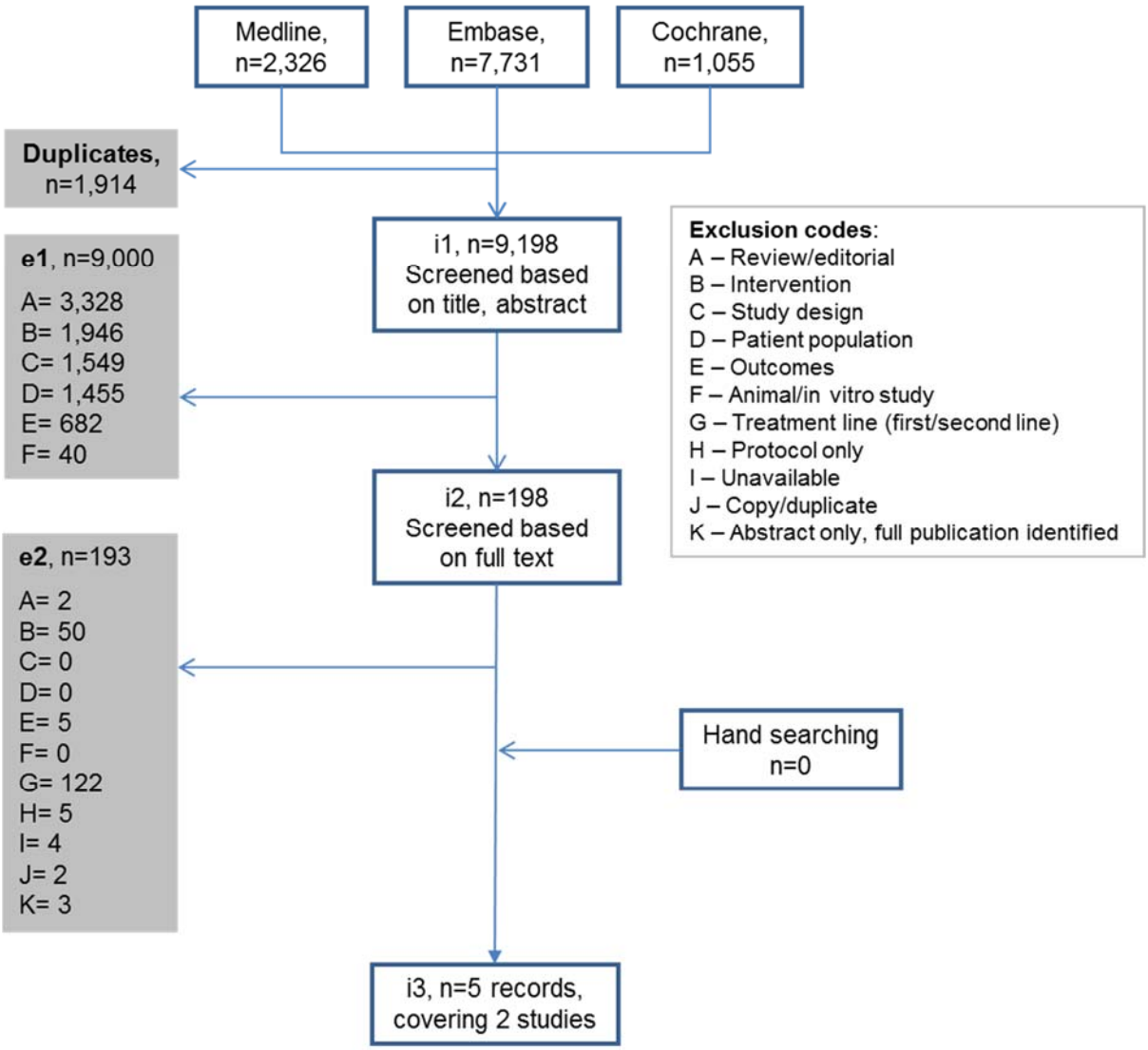
	Inclusion criteria	Exclusion criteria	Comments
Study design	RCTs with no restriction on phase or blinding	Non-randomised, observational studies	-
Language restrictions	No restriction	-	-

Keys: AE, adverse event; BSC, best supportive care; mCRC, metastatic colorectal cancer; HRQL, health-related quality of life; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial, STA, single technology assessment.
Notes: † Screening of publications by title and abstract was performed to include all currently available treatments; any studies that were not relevant according to the NICE scope were then excluded upon full publication review.

In total, 11,112 papers were identified through the electronic searches. Upon the removal of duplicate papers, 9,198 titles and abstracts were reviewed. Following assessment and exclusion of studies based on title, abstract and full text, two unique studies were included in the final data set.[2, 3] Five records were identified in total, but three were linked abstracts reporting subgroup analyses from the included studies.[39-41] Both included studies examined trifluridine/tipiracil versus placebo/BSC.

No additional studies were identified via hand searching. The systematic review schematic is shown in Figure 10, and a full list of excluded studies is provided in Appendix 3.

Figure 10: Schematic for the systematic review of clinical evidence



4.2 List of relevant randomised controlled trials

The systematic review of clinical evidence identified two unique RCTs of trifluridine/tipiracil versus BSC in the population of interest to this submission (Table 13).[2, 3] In addition, three linked abstracts were identified.[39-41]

The Phase II study was the primary licensing study for trifluridine/tipiracil in Japan. It involved 172 refractory mCRC patients who had previously been treated with, or were not candidates for available therapies (Fluoropyrimidine, oxaliplatin and irinotecan).[3] The pivotal study for trifluridine/tipiracil is the RECOURSE trial, which studied 800 end-stage mCRC patients. These patients were all refractory or intolerant to all available therapies.[2] The results of these studies have allowed for a

successful marketing authorisation application in Japan and the US and are the basis for the application within the EU. The choice of comparator within both studies, BSC, demonstrates the need for an effective third-line treatment; currently, there are no NICE-recommended options for patients when their disease reaches this stage.

Table 14: List of relevant randomised controlled trials

Trial no. (acronym)	Not reported (Phase II RCT, no acronym)	NCT01607957 (RECOURSE)
Population	Adult patients aged ≥20 years with histologically or cytologically confirmed unresectable metastatic colorectal adenocarcinoma with a previous treatment history of ≥2 regimens of standard chemotherapy	Adult patients aged ≥18 years with biopsy-documented adenocarcinoma of the colon or rectum who had received ≥2 prior regimens of standard chemotherapy
Intervention	Trifluridine/ tipiracil + BSC	Trifluridine/ tipiracil + BSC
Comparator	Placebo + BSC	Placebo + BSC
Primary study ref(s)	Yoshino 2012[3]	Mayer 2015[2]
Refs identified but not used further	Abstract reporting sub-analyses: Nishina 2012[39]	Abstracts reporting sub-analyses: Ohtsu 2015[40] Van Cutsem 2015[41]
Is study excluded from further discussion? If yes, state rationale	No	No
Key: BSC, best supportive care; RCT, randomised controlled trial.		

4.3 Summary of methodology of the relevant randomised controlled trials

The table below describes both studies. The study populations and study design are very similar to each other and are directly relevant to this decision problem.

Table 15: Methodology of the relevant randomised controlled trials

	Phase II	RECOURSE
Location	Japan	Worldwide (Japan, United States, Europe, Australia)
Trial Design	Multi-centre, double blind, randomised (in a 2:1 ratio), placebo controlled trial	Multi-centre, double blind, randomised (in a 2:1 ratio), placebo controlled trial
Eligibility criteria for participants	≥20 years old Histologically or cytologically confirmed unresectable metastatic colorectal adenocarcinoma Previous treatment with ≥2 regimens of standard chemotherapy (details in Table 17) Refractory or intolerant to a fluoropyrimidine, irinotecan, oxaliplatin Measurable lesions as per the RECIST ECOG PS of between 0 and 2 Adequate bone marrow, hepatic and renal function within 7 days of enrolment	≥18 years old Biopsy documented adenocarcinoma of the colon or rectum Received ≥2 prior regimens of standard chemotherapies, which could have included • adjuvant chemotherapy if a tumour had recurred within 6 months after the last administration of this therapy • tumour progression within 3 months after the last administration of chemotherapy • clinically significant AEs from standard chemotherapies that precluded the re-administration of those therapies Patients were also required to have received chemotherapy with each of the following agents (details in Table 18): • fluoropyrimidine • oxaliplatin • irinotecan • bevacizumab • cetuximab or panitumumab if *KRAS* wild-type ECOG PS of between 0 and 1 Adequate bone marrow, hepatic and renal function within 7 days of enrolment
Setting and locations where the data were collected	Secondary care oncology, gastroenterology or general medicine outpatient departments within Japan	Secondary care oncology, gastroenterology or general medicine outpatient departments within Japan, Europe, Australia and the United States

	Phase II	RECOURSE
Trial drugs	35mg/m^2 trifluridine/tipiracil taken orally after morning and evening meals 2 tablet doses were used in order to achieve the correct dose Trifluridine/tipiracil was taken in a 28-day cycle; a 2-week cycle of 5 days of treatment followed by a 2-day rest period and then a 14-day rest period Placebo was matched to trifluridine/tipiracil tablets for taste, colour and size In patients who had AEs, the dose could be reduced by 10mg/day as judged necessary Treatment continued until tumour progression, unacceptable toxic effects, or withdrawal of consent Patients were not allowed to cross-over between groups after progression or toxic effects Except in cases when deemed necessary from the perspective of safety or ethics, such as the treatment of an AE, other anti-cancer drugs or other investigational drugs were not to be used concomitantly.	35mg/m^2 trifluridine/tipiracil taken orally after morning and evening meals 2 tablet doses were used in order to achieve the correct dose Trifluridine/tipiracil was taken in a 28-day cycle; a 2-week cycle of 5 days of treatment followed by a 2-day rest period and then a 14-day rest period Placebo was matched to trifluridine/tipiracil tablets for taste, colour and size Protocol allowed for a maximum of three reductions in dose in decrements of 5mg/m^2 Treatment continued until tumour progression, unacceptable toxic effects, or withdrawal of consent Patients were not allowed to cross-over between groups after progression or toxic effects Other than BSC, permitted concomitant medications and therapies and study medication, patients were not permitted to receive any other medications and therapies, including other anticancer therapies, such as chemotherapy, immunotherapy, biological response modifiers or endocrine therapy, during the study treatment period. Palliative radiotherapy was not permitted while the patient was receiving study treatment. If used concomitantly with study medication, antiviral drugs that are human thymidine kinase substrates (e.g. stavudine, zidovudine, telbivudine) were to be used with caution because such drugs may theoretically compete with the effector of trifluridine/tipiracil, i.e. trifluridine, for activation via thymidine kinases.

	Phase II	RECOURSE
	The following medication(s)/therapies were allowed to be given concomitantly under the following guidelines: *Haematological Support* Haematological support was to be administered as medically indicated (e.g. blood transfusions, granulocyte colony stimulating factors [G-CSF; filgrastim]) according to the institutional site standards *Management of nausea/vomiting* For extreme nausea and vomiting that made continuation of the drug impossible, appropriate measures, including an antiemetic drug or fluid replacement were allowed *Management of fatigue* For extreme fatigue that made continuation of the drug impossible, appropriate measures, including treatment interruption were allowed	The following medication(s)/therapies were allowed to be given concomitantly under the following guidelines: *Haematological Support* Haematological support was to be administered as medically indicated (e.g. blood transfusions, granulocyte colony stimulating factors [G-CSF; filgrastim]) according to the institutional site standards *Management of nausea/vomiting* Antiemetic agents were to be administered as clinically indicated *Management of Diarrhoea* Patients were to be provided with loperamide or other standard anti-diarrhoeal therapy for use at first sign of diarrhoea; fluid and electrolyte balance was to be monitored, with appropriate interventions as clinically indicated. Prophylactic treatment for diarrhoea was to be administered as clinically indicated
Primary Outcomes	*Overall survival (OS)* Time between randomisation and death from any cause or the date of last follow-up	*Overall survival (OS)* Time (in months) between randomisation and death from any cause
Secondary Outcomes	*Progression-free survival (PFS*) Defined as the time (in months) from randomisation to the date that the patient's condition reached progressive disease (PD). If the patient died before reaching PD, the date of death was considered the date PD was reached. For patients that had not reached PD at the point that analysis was performed, and for patients in which the date that PD was reached was unknown, PFS time was censored at the date of the patient's final assessment prior to data cut-off. The randomisation date was used for cases in which lesion evaluation had not been performed after randomisation, and the initiation	*Progression-free survival (PFS)* Defined as the time (in months) from the date of randomisation until the date of the investigator-assessed radiological disease progression or death due to any cause. Patients who were alive with no radiological disease progression as of the analysis cut-off date were censored at the date of the last tumour assessment. Patients who received non-study cancer treatment before disease progression, or patients with clinical but not radiological evidence of progression, were censored at the date of the last radiological evaluable

	date of other (post-treatment) anti-cancer therapy was used when other anti-cancer therapy was initiated before the patient reached PD. *Time to treatment failure (TTF)* Defined as the period up to the date that PD was confirmed, the date that the study was discontinued, or the date of death if it occurred prior to the date of discontinuation of the study, whichever came sooner. *Response rate* Based on Response Evaluation Criteria in Solid Tumours (RECIST), the tumour shrinkage effect was evaluated and the response rate was calculated. The response rate was the percentage of patients in which the best overall response was determined to be complete response (CR) or partial response (PR) in each treatment group. The determination of the antitumor effect was to be performed in accordance with RECIST Ver. 1.0. At the independent image assessment site (CRO), determination of antitumor effect was made in accordance with RECIST Ver. 1.0 as well as RECIST Ver. 1.1 as a reference	tumour assessment before the non-study cancer treatment was initiated. *Time to treatment failure (TTF)* Defined as the time (in months) from the date of randomisation until the date of radiological disease progression, permanent discontinuation of study treatment, or death due to any cause. Patients who were still on study treatment as of the analysis cut-off date were censored at the last date the patient was known to be on treatment. Censoring for TTF was also applied in those patients who were given non-study cancer treatment, with censoring at the time the patient began the non-study cancer treatment. *Overall response rate (ORR)* Based on investigator review of radiological images and following RECIST criteria (version 1.1, 2009). ORR was defined as the proportion of patients with objective evidence of CR or PR with no confirmatory scan required. The primary assessment of ORR was for the ITT population, restricted to patients with measurable disease (at least 1 target lesion) at baseline. At the analysis stage, the best overall response was assigned for each patient as the best response recorded from all responses recorded from the start of treatment through the treatment period (excludes assessments during follow-up). If applicable, responses recorded after radiological disease progression or after initiation of non-study anti-tumour therapy were excluded. A best response assignment of SD required that SD be maintained for at least 6 weeks from the start of treatment.

	Phase II	RECOURSE
	Disease control rate (DCR) This was defined as the percentage of patients in which there was no clear worsening of the clinical condition for six weeks or more after the start of administration out of the patients in which the best overall response was determined to be CR, PR, or SD	*Disease control rate (DCR)* Disease control rate was defined as the proportion of patients with a best overall response of CR, PR, or SD
	Duration of response The date when CR or PR criteria were first met to the date where PD was first noted	*Duration of Response* Defined as the time from the first documentation of response (CR or PR) to the first documentation of objective tumour progression or to death due to any cause
	Efficacy of trifluridine/tipiracil in patients with or without KRAS mutations Measurement for codon 12 and 13 mutations of the *KRAS* gene in tumour tissue and effect of trifluridine/tipiracil with respect to the existence of a *KRAS* mutation	*Subgroup analysis by KRAS status on OS and PFS*
	Adverse event profile and tolerability Assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).	*Safety and tolerability* Standard safety monitoring and grading were performed using National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03. The evaluation of safety was based on the incidence, severity, and causality of AEs and SAEs and other safety assessments including physical examination, vital signs, ECOG performance status, 12-lead ECG, and clinical laboratory evaluations.
Pre-planned subgroups	Sex Male / Female Age <65yrs / ≥65 yrs. PS 0 / 1-2 Primary Site Colon / rectum Number of metastatic groups 1 / 2 / 3 / ≥4	**Stratification Groups** *KRAS* mutation status Time since diagnosis Geographical location **Pre-planned subgroups** Sex Male / Female Age <65yrs / ≥65 yrs.

	Phase II	RECOURSE
	Liver metastasis Lung metastasis Lymph node metastasis Peritoneum metastasis Previous treatment Previous surgery Adjuvant chemotherapy Palliative chemotherapy Bevacizumab Cetuximab *KRAS* mutation status	PS 0 / 1 Primary Site Colon / rectum Geographic region Japan / Rest of World Number of metastatic sites Number of prior regimens
Key: AE, adverse event; BSC, best supportive care; CR, complete response; DCR, disease control rate; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; ORR, overall response rate; PFS, progression-free survival; PR, partial response; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse events; SD, stable disease; TTF, time to treatment failure. **Source:** Phase II CSR.[42] RECOURSE CSR.[12]		

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1 Phase II

A sample size of 162 patients with a one-sided significance level of 10% was necessary to verify superiority in overall survival (OS) with a power of 80%, with an expected HR of 0.67. Median OS was anticipated to be 9.0 months in the trifluridine/tipiracil group and 6.0 months in the placebo group. A clinically relevant HR was estimated as 0.70. Patients continued to receive the study treatment (with group assignments remaining concealed) until the primary analysis of OS was done. The efficacy analysis was done in the intention-to-treat (ITT) population, and the safety analyses in the per-protocol population, when the number of deaths in the trial reached 121. The Kaplan-Meier method was used to estimate survival distribution. A stratified log-rank test was used and adjusted by the allocation factor, for comparisons between the two groups, and a Cox proportional hazards model to estimate HRs, the two-tailed 80% CIs corresponding to the significance level, and 95% CIs.

Additionally, interaction tests were performed to assess the treatment effects by the allocation factor as well as baseline characteristics, including *KRAS* mutational status. In the absence of death confirmation, or for patients alive as of the OS cut-off date, survival time was censored at the date of last study follow-up, or the final confirmation date on which survival was confirmed before follow-up became impossible (see Table 16).

Table 16: Demonstration of how censoring was handled in the Phase II trial

Adoption/rejection of event	Contents	Date
Event	Dead	Day of death
Censor	Alive	Day of confirmation of survival
	Whether the patient is alive or dead cannot be confirmed	Day of final confirmation of survival
Source: Phase II CSR.[42]		

Progression-free survival (PFS) and time to treatment failure were compared using the log-rank test. Objective response, disease control, and toxic effects were examined using the Fisher's exact test. Interaction tests for PFS and disease control to assess the differences between treatment effects by the allocation factor were performed as well as baseline characteristics, including *KRAS* mutational status. Relative dose intensity was calculated as the ratio of the actual dose taken to the planned dose. Two-sided p-values were used for the reporting of results.

In case of missing data; the results obtained prior to the day of final evaluation immediately before the missing test was used to establish the data for any required endpoints.

4.4.2 Phase III – RECOURSE

The study was designed to have 90% power to detect a HR for death of 0.75 (a 25% reduction in risk) in the trifluridine/tipiracil group compared with the placebo group, with a one-sided type I error rate of 0.025. Given the treatment assignment ratio of 2:1 (trifluridine/tipiracil: placebo), it was calculated that 800 patients had to be enrolled in the study, and at least 571 events (deaths) would be required for the primary analysis. OS (the primary endpoint) and radiologically confirmed PFS were analysed in the ITT population with the use of a two-sided, stratified log-rank test,

with the HR and two-sided 95% confidence intervals based on a stratified Cox model and the associated Kaplan-Meier survival estimates. The primary analysis of OS includes follow-up data (including death events) obtained up to the date of the 571st death observed in the study. Patients having a documented survival status (alive or dead) after this date were censored at the cut-off date, but are they included in an updated analysis, which is used in the economic analysis.

The median survival times were determined from the Kaplan-Meier curves. Rates of objective response and disease control were compared with the use of Fisher's exact test in the subgroup of the ITT population that had measurable disease at baseline. AEs and laboratory abnormalities were summarised for all patients who received at least one dose of study drug. Time to worsening of Eastern Cooperative Oncology Group (ECOG) performance status (PS) was analysed with the same methods used to assess OS. All subgroup analyses, as well as the time to worsening ECOG PS, were prespecified in the protocol or statistical analysis plan, and finalised before the data were unblinded. Multivariate Cox regression analysis was performed to examine the effect of all prespecified factors (prognostic and predictive) on the OS effect of trifluridine/tipiracil.

Regarding the secondary endpoints and censoring; patients who were alive with no radiological disease progression as of the analysis cut-off date were censored at the date of the last tumour assessment. Patients who received non-study cancer treatment before disease progression, or patients with clinical but not radiological evidence of progression, were censored at the date of the last radiological evaluable tumour assessment before the non-study cancer treatment was initiated.

Efficacy analysis and interim analyses

No interim analyses were planned or performed. As such, no alpha spending was taken into consideration for sample size calculation, and the primary analysis was performed at the one-sided 2.5% significance level. Comparisons for all secondary endpoints were made at the two-sided 0.05 significance level. Since PFS was the only key secondary efficacy endpoint for regulatory registration purposes, no further multiplicity adjustments were made. If analysis of OS demonstrated significance at the one-sided 0.025 level, PFS was to be tested at the one-sided 0.025 level.

Table 17: Summary of statistical analyses in the randomised controlled trials

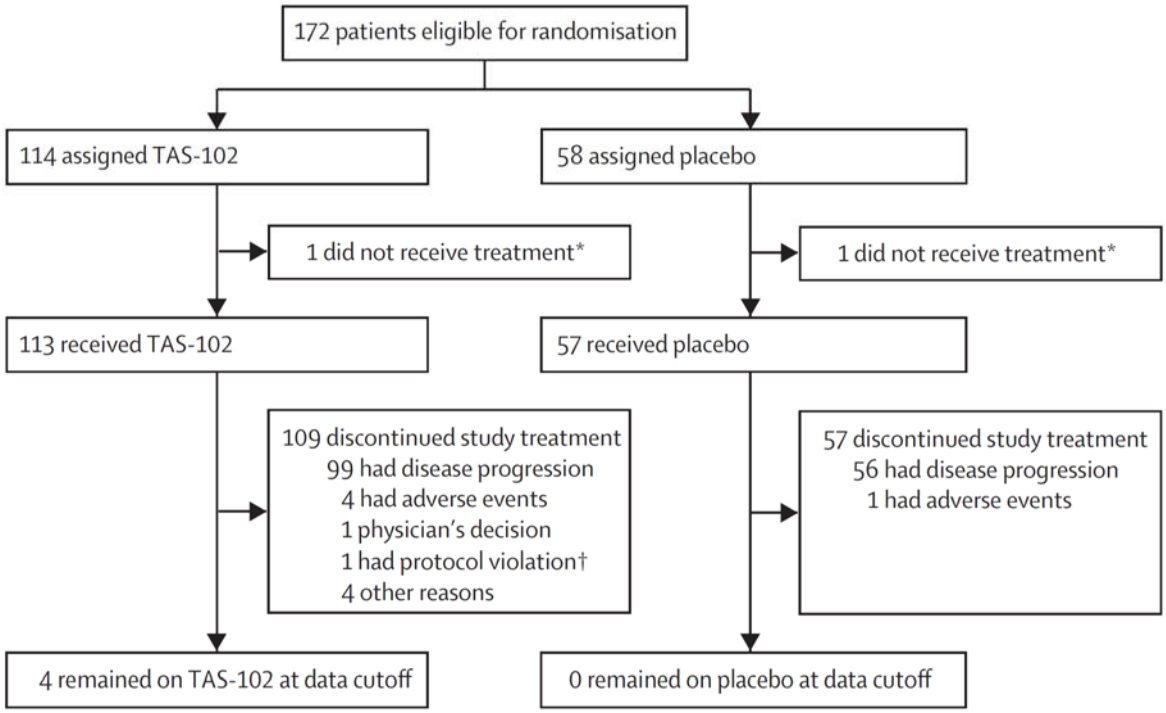
	Phase II[42]	RECOURSE[12]
Hypothesis	Trifluridine/tipiracil improves OS compared to placebo in patients with unresectable mCRC who have already received conventional chemotherapy with a fluoropyrimidine, irinotecan and oxaliplatin	Trifluridine/tipiracil improves OS compared to placebo in patients with mCRC whose cancer has been refractory to anti-tumour therapy or who had clinically significant adverse events that precluded the re-administration of those therapies
Study power	The study was designed to have an 80% power to verify superiority in OS with an expected HR of 0.67 using a one-sided significance level of 10%. Median OS was expected to be 9.0 months in the trifluridine/tipiracil group and 6.0 months in the placebo group. A clinical relevant HR was judged to be around 0.70.	The study was designed to have a 90% power to detect a HR for death of 0.75 (a 25% reduction in risk) for trifluridine/tipiracil compared with placebo, with a one-sided type I error rate of 0.025.
Sample size	162 patients were required with at least 121 deaths for the primary endpoint.	800 patients were required with at least 571 events (deaths) for the primary endpoint
Statistical Analysis	See Section 4.5 In the primary analysis, the HR of each covariate is estimated by the Cox proportional hazard model, with the treatment group and PS included in the model. The pharmacogenomics analysis is conducted by using Cox proportional hazard model with the covariates of *KRAS* gene mutation and nucleic-acid metabolising enzyme.	See Section 4.5 No interim analyses for efficacy or futility were planned or performed during this study. During the course of the study, an independent DMC periodically assessed the safety data. The primary efficacy endpoint of OS was analysed using the Cox proportional hazards model, including treatment and the 3 randomisation strata as factors in the model. This model was extended to include additional potential prognostic factors including baseline characteristics.
Key: DMC, Data Monitoring Committee; HR, hazard ratio; mCRC, metastatic colorectal cancer; OS, overall survival; PS, performance status.		

4.5 Participant flow in the relevant randomised controlled trials

4.5.1 Phase II

In total, 172 patients were eligible for randomisation and were randomised in a 2:1 fashion for active: placebo. During the study, no patients crossed over between groups (Figure 11).[3]

Figure 11: Patient flow in the Phase II trial



Notes: TAS-102 is trifluridine/tipiracil. *One patient was randomly allocated to TAS-102 did not receive treatment because of aggravation of a rash related to previous chemotherapy and one patient allocated to placebo did not receive treatment because of occurrence of pulmonary thromboembolism; these patients were excluded from the efficacy and safety populations. †One patient received TAS-102 but was concomitantly taking a prohibited treatment, so was excluded from the efficacy population, but included in the safety population

Source: Phase II CSR.[42]

One patient was randomly allocated to trifluridine/tipiracil and did not receive treatment because of aggravation of a rash related to previous chemotherapy, one patient allocated to placebo did not receive treatment because of the occurrence of pulmonary thromboembolism; these patients were excluded from the efficacy and safety populations. One patient received trifluridine/tipiracil but was concomitantly taking a prohibited treatment, and was therefore excluded from the efficacy population but was included in the safety population.

Overall, the two groups were relatively well balanced, although there were some differences in certain subgroups (Table 18). Given that there was no evidence of treatment heterogeneity during analysis of the trial results, it is unlikely that these minor imbalances impacted on the study results.

Table 18: Characteristics of participants in the Phase II trial

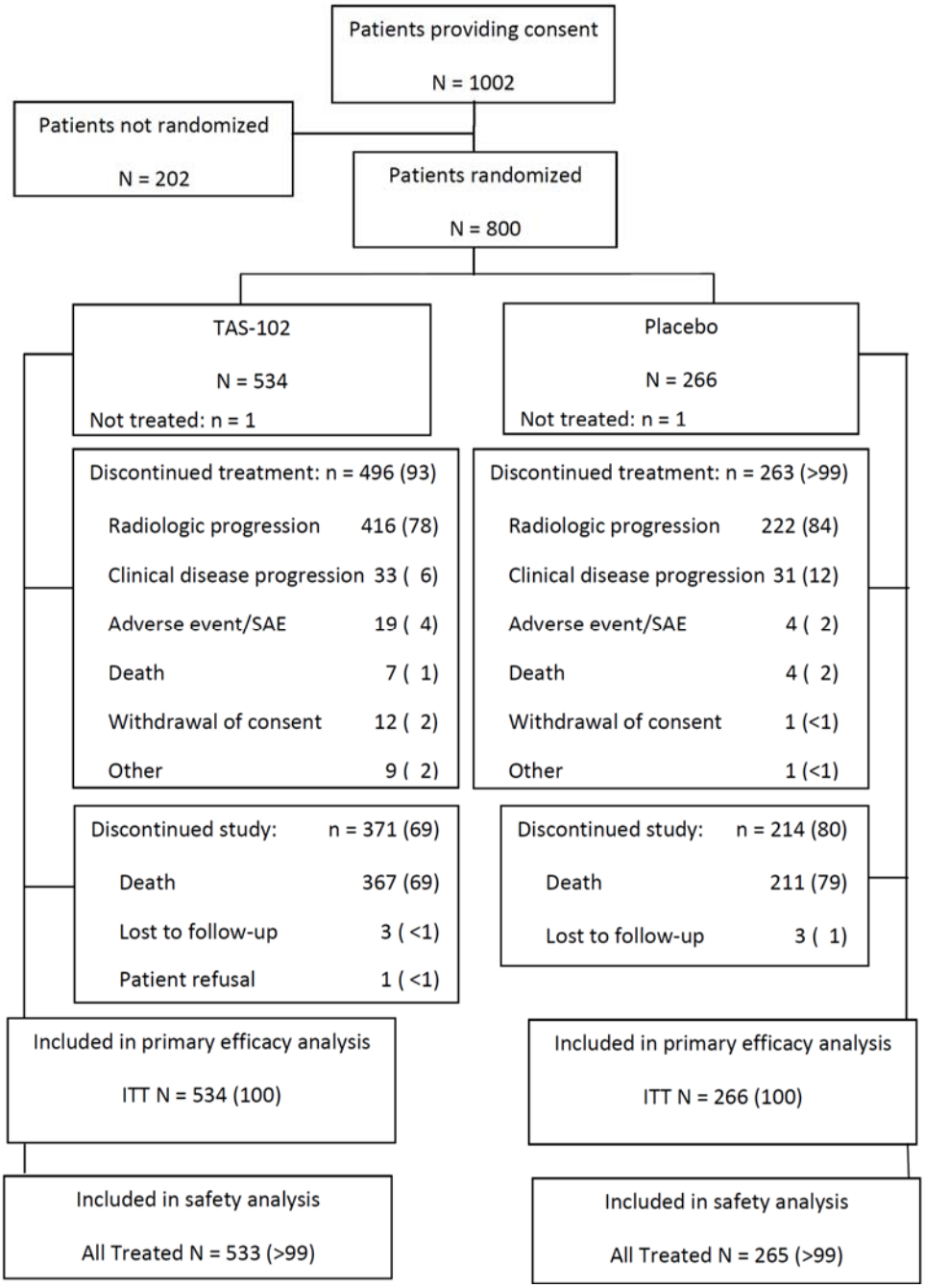
	Trifluridine/tipiracil N = 114	**Placebo N = 58**
Men	64 (57%)	28 (49%)
Women	48 (43%)	29 (51%)
Age (years)	63 (28 – 80)	62 (39 – 79)
ECOG		
0	72 (64%)	35 (61%)
1	37 (33%)	21 (37%)
2	3 (3%)	1 (2%)
Diagnosis		
Colon	63 (56%)	36 (63%)
Rectal	49 (44%)	21 (37%)
Number of metastatic sites		
1	25 (22%)	11 (19%)
2	43 (38%)	20 (35%)
3	27 (24%)	12 (21%)
4	17 (15%)	14 (25%)
Metastatic organ		
Liver	65 (58%)	38 (67%)
Lung	87 (78%)	44 (77%)
Lymph	48 (43%)	23 (40%)
Peritoneum	11 (10%)	17 (30%)

	Trifluridine/tipiracil N = 114	Placebo N = 58
Previous treatment and reason		
Surgical history	103 (92%)	50 (88%)
Adjuvant chemo	54 (48%)	15 (26%)
Number of palliative chemotherapies		
2	17 (15%)	13 (23%)
≥3	95 (85%)	44 (77%)
Fluoropyrimidine-based treatment	112 (100%)	57 (100%)
Refractory	109 (97%)	55 (96%)
Intolerant	3 (3%)	2 (4%)
Oxaliplatin-based treatment	112 (100%)	57 (100%)
Refractory	95 (85%)	45 (79%)
Intolerant	17 (15%)	12 (21%)
Irinotecan-based treatment	112 (100%)	57 (100%)
Refractory	106 (95%)	56 (98%)
Intolerant	6 (5%)	1 (2%)
Bevacizumab	87 (78%)	47 (82%)
Cetuximab	71 (63%)	36 (63%)
KRAS mutational status		
Wild-type	54 (55%)	24 (48%)
Mutation-positive	45 (45%)	26 (52%)

Key: ECOG, Eastern Cooperative Oncology Group.
Source: Phase II CSR.[42]

4.5.2 Phase III – RECOURSE

Figure 12: Patient flow in RECOURSE



Key: ITT, intention-to-treat; SAE, serious adverse event.[12]
Note: TAS-102 is trifluridine/tipiracil.
Source: RECOURSE CSR[12]

As shown in Figure 12, a total of 1,002 patients provided signed, informed consent for participation in the study. Of these, 202 (20%) did not meet eligibility criteria and were not randomised (i.e. screening failures). Of the 800 patients randomised (534, trifluridine/tipiracil; 266, placebo), two patients (one trifluridine/tipiracil; one placebo) did not receive study medication and only 6 patients were lost to follow-up (3 patients in each group).[2]

Overall, the two groups were well balanced, with little difference between the groups, as shown in Table 19. It is important to note that whether patients had received 2 prior lines of treatment or more, all patients had received all chemotherapies as specified in the inclusion criteria for each trial.

As shown in Table 20, 61.6% of patients in the ITT population had received a fluoropyrimidine-containing regimen as their last regimen prior to randomisation in the RECOURSE trial, and 93.1% of those patients were refractory to fluoropyrimidine.

Table 19: Characteristics of participants in RECOURSE

			Trifluridine/ tipiracil (N = 534)	**Placebo (N = 266)**
Age, median (range)			63.0 (27-82)	63.0 (27-82)
Gender, n (%)	Male		326 (61.0)	165 (62.0)
	Female		208 (39.0)	101 (38.0)
Race, n (%)	White		306 (57.3)	155 (58.3)
	Asian		184 (34.5)	94 (35.3)
	Black		4 (0.7)	5 (1.9)
Geographic region, %		Japan	33.3	33.1
		Europe	50.7	49.6
		US	12.0	13.2
		Australia	3.9	4.1
ECOG PS, n (%)		0	301 (56.4)	147 (55.3)
		1	233 (43.6)	119 (44.7)
Primary site, n (%)		Colon	338 (63.3)	161 (60.5)
		Rectum	196 (36.7)	105 (39.5)
KRAS mutational status, %		Wild-type	262 (49.1)	131 (49.2)
		Mutation-positive	272 (50.9)	135 (50.8)
Time since diagnosis of metastasis, n (%)				
		<18 months	111 (20.8)	55 (20.7)

		Trifluridine/ tipiracil (N = 534)	Placebo (N = 266)
	≥18 months	423 (79.2)	211 (79.3)
Number of prior regimens, n (%)[a]	2	95 (17.8)	45 (16.9)
	3	119 (22.3)	54 (20.3)
	≥4	320 (59.9)	167 (62.8)
All prior systemic cancer therapeutic agents, %			
Fluoropyrimidine		100	100
Irinotecan		100	100
Oxaliplatin		100	100
Bevacizumab		100	99.6
Anti-EGFR (if wild-type *KRAS*)		99.6	99.3
Regorafenib		17.0	19.9

Key: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PS, performance status.

Note: [a] Includes neoadjuvant, adjuvant, metastatic

Source: RECOURSE CSR.[12]

Table 20: Response to last fluoropyrimidine regimen prior to randomisation (ITT population)

Treatment	Number (%) of Patients	
	Trifluridine/tipiracil (N = 534)	Placebo (N = 266)
Fluoropyrimidine[a, b]		
Refractory last time fluoropyrimidine was part of the regimen	497 (93.1)	240 (90.2)
Intolerant last time fluoropyrimidine was part of the regimen	29 (5.4)	23 (8.6)
Violation	8 (1.5)	3 (1.1)
Last prior regimen contained fluoropyrimidine	329 (61.6)	156 (58.6)
Refractory to fluoropyrimidine	311 (94.5)	144 (92.3)
Intolerant to fluoropyrimidine	13 (4.0)	11 (7.1)
Violation	5 (1.5)	1 (0.6)

Key: ITT, intention-to-treat.

Notes: Refractory = Regimens with radiologic progression ≤93 days from the last dose of the last component of the regimen for regimens intended to treat metastatic disease (or of missing intent); and with radiologic progression ≤186 days for adjuvant/neo-adjuvant regimens.

Intolerant = Agents reported as discontinued due to toxicity or that could not be re-administered for medical reasons

Violation = Does not meet the criteria for either “intolerant” or “refractory”

[a] Includes neoadjuvant, adjuvant, and metastatic regimens.

[b] Fluoropyrimidines include fluorouracil, capecitabine, doxifluridine, S-1, tegafur/uracil

Source: RECOURSE CSR.[12]

4.6 Quality assessment of the relevant randomised controlled trials

In heavily pre-treated mCRC patients, there is a lack of available therapies and a demonstrable need for new treatments. Both trials examined a very specific and well defined population in a robust manner with a comprehensive and systematic approach to patient allocation and control of confounding factors.

The Phase II study was performed in a solely Japanese population, the study execution was of a high quality, and the patient population well defined. This study was the primary registration study for trifluridine/tipiracil in Japan and resulted in a marketing authorisation (Section 2.2.6). RECOURSE was an international, multi-centre Phase III trial with a similar study question and aim but a more diverse ethnic background than the Phase II study. As RECOURSE included Japanese patients, it was possible to observe whether all patients responded to trifluridine/tipiracil in a similar manner; as would be expected from the known pharmacology of the compound. In patients treated with trifluridine/tipiracil, outcomes and response for pre-specified regional subgroups were similar, with non-significant tests for interaction.[12, 40] Hence, it is possible to generalise the results of both studies to Western populations.

Due to recent funding changes within England, there is currently no means of obtaining bevacizumab, cetuximab or panitumumab (third or fourth line) within the NHS, apart from if a patient is included in a clinical trial or has private medical insurance. Whilst many trial patients had previously received bevacizumab, cetuximab or panitumumab, it may not be possible for future English mCRC patients to do so. There is no biological reason why trifluridine/tipiracil should not work in patients who have not received these therapies. Indeed within the Phase II study approximately 80% of patients had received bevacizumab and 60%, cetuximab; meaning that not all patients had received a biological therapy, despite this the results were consistent with the RECOURSE study. Expert clinical opinion considers that patient populations who are not as highly pre-treated as the population in RECOURSE would respond better because their tumours are less resistant to treatment.[4] Figure 19 (Phase II OS subgroup analysis) supports this comment: it seems patients who have not received bevacizumab or cetuximab do better, although statistically there is no interaction.

Therefore, the results of both trials are generalisable and applicable to patients within England.

Table 21: Quality assessment results for both parallel group randomised controlled trials

	Phase II[42]	RECOURSE[12]
Was the randomisation carried out appropriately?	**Yes** Following confirmation of eligibility as a subject for randomisation, on the basis of probability theory minimising methods, patients were assigned by the registration centre to the two treatment groups (trifluridine/tipiracil group and placebo group) at a ratio of 2:1. So as to ensure balance between the therapy groups, subjects were to be stratified at the time of randomisation according to the following stratification factors: • Performance Status: 0 vs 1/2 At the registration centre, on the basis of a random assignment table, a drug number including the appropriate drug that was distributed to each implementing medical institution was assigned. The drug number was recorded in the raw data of each patient. The assignment was a dynamic allocation and thus caution was taken that the drug numbers were conferred randomly. Note that in cases in which the investigational drug of a drug number assigned to a patient was not used, other patients were not to use it, including the same patient in a later study period. For details of the random assignment and drug number assignment, the "Registration manual" was referred to. Rationale for setting of allocation adjustment factors; 'PS (0, 1/2)' is a general prognosis factor in cancer clinical trials and it was established considering the difference in efficacy and safety evaluations due to differences in the patient's condition.	**Yes** Once patient confirmation of eligibility and the criteria for randomisation had been met, patients were centrally randomised in a 2:1 ratio to trifluridine/tipiracil or placebo via an IWRS based on a dynamic allocation method (biased coin). The IWRS assigned kit numbers corresponding to the patient's treatment assignment and informed the study site user of the kit number that had been assigned to the patient for the dispensing of study drug. If a patient was mistakenly given a kit(s) of study medication that was not the kit assigned by the IWRS, resulting in the patient being initiated in the alternate arm from which they were assigned at randomisation, the patient continued to receive this treatment for the rest of the study. Study medication administration was to begin within 3 days following randomisation.

	Phase II[42]	RECOURSE[12]
Was the concealment of treatment allocation adequate?	**Yes** This study was blinded for all the concerned parties of implementing medical institutions (such as patients, investigator or sub-investigators, and study research staff) as well as the sponsor. The investigator or a sub-investigator was to prescribe to the patient an investigational drug of the investigational drug number assigned by the registration centres. In cases where information was necessary on the treatment group to which a patient was assigned in order to manage symptoms of the patient during an emergency resulting from, for example, a serious adverse event during the course of the study, the investigator was to contact a specific management service. Unblinding of the study was to be made after the events specified in the "Statistical analysis implementation period" were reached. The investigational drug assignment manager was to confirm that closing out of all applicable cases was completed by the sponsor. In addition, prior to the unblinding, the investigational drug assignment manager was to confirm the sealed status of the collected investigational drug and confirm that the keycode for emergency unblinding was appropriately stored and managed.	**Yes** This was a double-blind study. Trifluridine/tipiracil tablets of each strength, 15-mg or 20-mg, and the corresponding placebo tablets, 15-mg and 20-mg, were identical in appearance and were packaged in identical containers. During the conduct of the study, the treatment assignment was unknown to all patients, investigators, and ancillary study personnel at each study site. During the conduct of the study, assigned treatment was unknown to the study team at Taiho Oncology, Inc. and Taiho Pharmaceutical Co., Ltd. except for pre-specified personnel involved in pharmacovigilance reporting activities and clinical trial material management. Among the CROs who assisted in the conduct of the study, treatment assignment was unknown except for personnel involved in drug labelling and distribution. Unblinding of the study treatment by the investigator was not to occur unless needed to manage a patient's medical condition. In an emergency, when specific knowledge of the patient's treatment assignment was needed to manage a patient's medical condition, the investigator could unblind the patient by calling the IWRS to obtain the patient's treatment assignment. If unblinding occurred, the investigator was not to disclose the unblinding information.
Were the groups similar at the outset of the study in terms of prognostic factors?	**No** There were some slight differences in some of the subgroups; namely sex, metastatic site, number of prior chemotherapy regimens and *KRAS* status.	**Yes** The groups were balanced in terms of *KRAS* status, time since diagnosis of 1st metastasis, region, *BRAF* status, age, race, gender, primary tumour site, ECOG score, number of prior regimens, and number of metastatic sites.

	Phase II[42]	RECOURSE[12]
Were the care providers, participants and outcome assessors blind to the treatment allocation?	**Yes** See above regarding concealment of treatment allocation	**Yes** See above regarding concealment of treatment allocation
Were there any expected imbalances in drop-outs between groups?	**No** Please see patient disposition	**No** Please see patient disposition
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No**	**No**
Did the analysis include an intention to treat analysis?	**Yes**	**Yes**
Key: ECOG, Eastern Cooperative Oncology Group; IWRS, interactive voice/web response system.		

4.7 Clinical effectiveness results of the relevant randomised controlled trials

4.7.1 Phase II results

The Phase II trial was a randomised (2:1), double-blind, placebo-controlled study of patients with chemotherapy-refractory advanced colorectal cancer who had failed two or more chemotherapeutic regimens which included fluoropyrimidine, irinotecan, and oxaliplatin.[3, 42]

Primary endpoint: Overall survival

A total of 172 patients were enrolled; the study drug was administered to 170 patients, and two patients discontinued before treatment with study drug. One patient was not eligible after treatment as the patient was co-prescribed a contraindicated concomitant medication; therefore, the intention-to-treat population for the efficacy endpoints comprised 169 patients (112, trifluridine/tipiracil; 57, placebo).

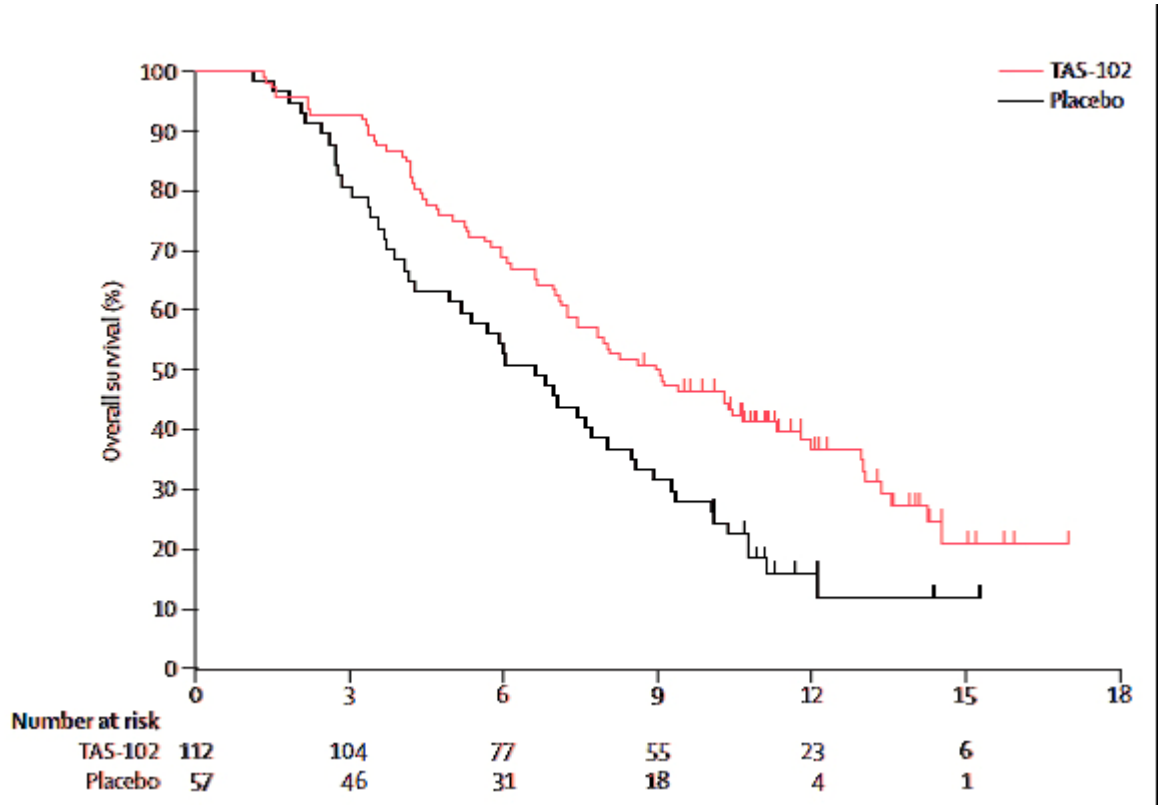
Table 22 shows the number of patients who died or were censored in the trifluridine/tipiracil and placebo groups, respectively. The percentage of deaths was 67.0% in the trifluridine/tipiracil group, compared to 84.2% in the placebo group.

Table 22: Deaths and censored patients in the Phase II trial (ITT population)

		Trifluridine/tipiracil (N = 112)		Placebo (N = 57)	
		n	%	n	%
Died		75	(67.0)	48	(84.2)
	Death by primary disease	73	(97.3)	48	(100.0)
	Death by other disease	0	(0.0)	0	(0.0)
	Other	2	(2.7)	0	(0.0)
	Unknown	0	(0.0)	0	(0.0)
Censored		37	(33.0)	9	(15.8)
	Survival	37	(100.0)	9	(100.0)
	Lost to follow-up	0	(0.0)	0	(0.0)
Source: Phase II CSR.[42]					

The median OS was 9.0 months in the trifluridine/tipiracil group and 6.6 months in the placebo group (HR 0.56; 95% CI 0.39 to 0.81; p = 0.0011 one-sided), see Figure 13.

Figure 13: Kaplan-Meier curves of overall survival in the Phase II trial (ITT population)



Key: TAS-102, trifluridine/tipiracil.
Source: Yoshino et al. 2012.[3]

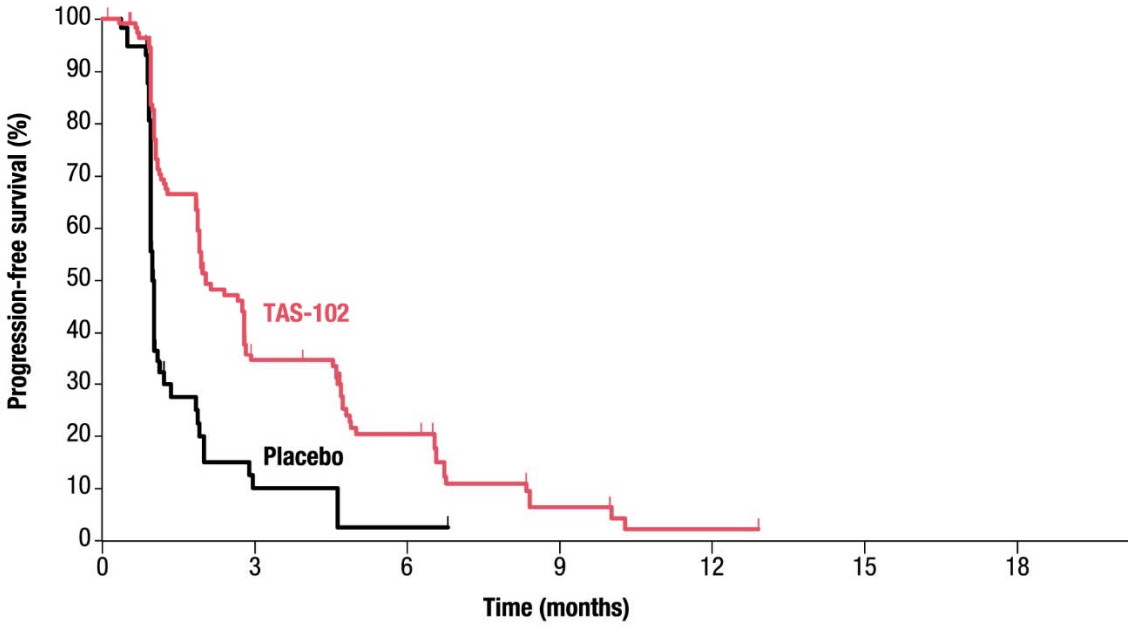
Secondary endpoints

Progression-free survival

Radiological assessment of response was conducted at Week 4, 8 and 12 after treatment initiation and 8 weekly thereafter**.**

Median PFS assessed by independent review committee was 2.0 months in the trifluridine/tipiracil group compared with 1.0 month in the placebo group (HR 0.41; 95% CI 0.28 to 0.59; p < 0.0001). Median PFS assessed by investigators was 2.7 months in the trifluridine/tipiracil group compared with 1.0 month in the placebo group (HR 0.35; 95% CI 0.25 to 0.50; p < 0.0001).

Figure 14: Kaplan-Meier curves of progression-free survival in the Phase II trial (ITT population)



No. at Risk					
TAS-102	112	31	17	4	1
Placebo	57	4	1	0	0

Key: TAS-102, trifluridine/tipiracil.
Source: Yoshino et al. 2012.[3]

Time to treatment failure

Based on the independent radiological image assessment, the median time to treatment failure (TTF) was 1.9 months for the trifluridine/tipiracil group versus 1.0 month in the placebo group (HR 0.40; 95% CI 0.28 to 0.56; $p < 0.0001$).

Based on the investigators' assessment, the median TTF was 2.7 months in the trifluridine/tipiracil group versus 1.0 month in the placebo group (HR 0.34; 95% CI 0.24 to 0.49; $p < 0.0001$).

Response rates

Table 23 shows the response rate and disease control rate determined by independent radiological image assessment, based on RECIST 1.0. There were no CR patients in either of the groups, but one PR patient was recognised in the trifluridine/tipiracil group, with a 0.9% response rate (95% CI 0.0 to 4.9%).

The disease control rates were 43.8% (95% CI 34.4% to 53.4%) and 10.5% (95% CI 4.0% to 21.5%) in the trifluridine/tipiracil and placebo groups, respectively, and the difference was statistically significant (p < 0.0001).

Table 23: Best overall response (independent radiological image assessment) in the Phase II trial (ITT population)

Response (RECIST version 1.0)	Trifluridine/tipiracil (N = 112) n	%	Placebo (N = 57) n	%	p-value[a]
Complete response (CR)	0	0	0	0	
Partial response (PR)	1	-0.9	0	0	
Stable disease (SD)	48	-42.9	6	-10.5	
Progression of disease (PD)	53	-47.3	44	-77.2	
Not evaluable	10	-8.9	7	-12.3	
Response rate (CR+PR)	1	-0.9	0	0	1
95% CI (%)		[0.0, 4.9]		[0.0, 6.3]	
Disease control rate (CR+PR+SD)	49	-43.8	6	-10.5	<0.0001
95% CI (%)		[34.4, 53.4]		[4.0, 21.5]	

Key: CI, confidence interval.
Notes: [a] Fisher's Exact Test.
Source: Phase II CSR.[42]

Duration of response

Table 24 shows the duration of response determined by the investigator, based on RECIST 1.0. For the trifluridine/tipiracil and placebo groups, 109 and 56 patients, respectively, were evaluated (excluding patients for which the best overall response had not been established because treatment was ongoing at the cut-off point of 31 January 2011). Partial response was seen in one patient in the trifluridine/tipiracil group; however, the patient was still continuing on treatment as of the cut-off point. The number of patients for the calculation of duration of complete response was 0 in both groups because CR was not observed. The median duration of stable disease was 80 days (range: 2 to 472 days) and 29 days (range: 14 to 184 days) in the trifluridine/tipiracil and placebo groups, respectively (p < 0.0001 by the t-test).

Table 24: Duration of response and complete response in the Phase II trial (ITT population)

		Trifluridine/ tipiracil (N = 112)	Placebo (N = 57)	p-value§
Duration of overall response (days)*	n	0	0	-
	Mean	-	-	
	Median	-	-	
	Range [min, max]	-	-	
Duration of overall complete response (days)†	n	0	0	-
	Mean	-	-	
	Median	-	-	
	Range [min, max]	-	-	
Duration of stable disease (days)‡	n	109	56	<0.0001
	Mean	107.8 (92.3)	44.4 (35.8)	
	Median	80.0	29.0	
	Range [min, max]	[2 , 472]	[14 , 184]	

Notes: *: Duration of overall response (days) = (date PD first noted - date CR or PR criteria first met) + 1; †: Duration of overall complete response (days) = (date recurrent disease first noted - date CR criteria first met) + 1; ‡: Duration of stable disease (days) = (date PD first noted - date of treatment start) + 1; §: t test.

Source: Phase II CSR.[42]

4.7.2 Phase III results – RECOURSE

RECOURSE was a Phase III, double-blind global study comparing trifluridine/tipiracil plus BSC and placebo plus BSC in refractory colorectal cancer.[12]

All primary and secondary efficacy endpoints for this study are relevant to the decision problem and are presented in this section.

Primary endpoint

Original survival analysis

The primary analysis of OS included survival follow-up data obtained through the date of the 571st death observed in the study. A total of 574 deaths were included in the primary analysis of OS based on a cut-off date of 24 January 2014 (4 patients died on the calendar day of the 571st event).

At the time of analysis, events were observed for 364 (68.2%) patients in the trifluridine/tipiracil group and 210 (78.9%) patients in the placebo group. Among patients with censored survival data, the median follow-up for OS was 8.29 months (range: 1.8 to 19.0 months).

The addition of trifluridine/tipiracil to BSC resulted in a statistically significant improvement in OS compared to placebo plus BSC (Table 25 and Figure 15). The median OS was 7.1 months in the trifluridine/tipiracil group and 5.3 months in the placebo group (HR 0.68; 95% CI 0.58 to 0.81; p < 0.0001). At 6 months, 58% of the patients in the trifluridine/tipiracil group and 44% of the patients in the placebo group were alive; at 12 months, 27% and 18%, respectively, were alive.

As shown in Figure 15, the separation of the OS curves for trifluridine/tipiracil and placebo is maintained throughout the duration of the follow-up period.

Table 25: Overall survival in RECOURSE

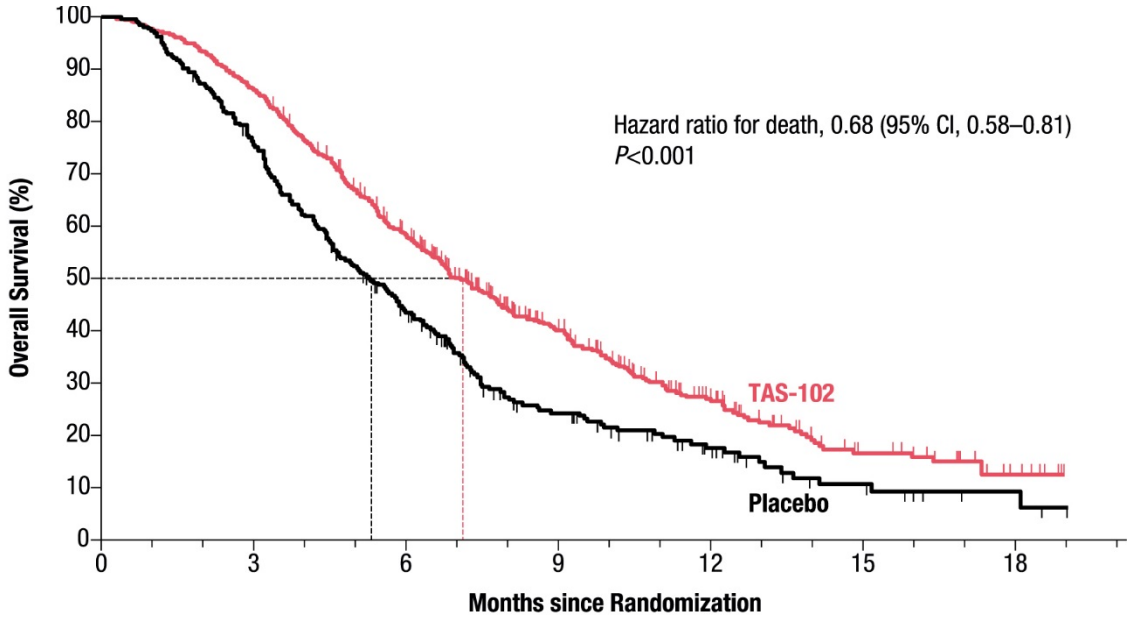
Parameter	Trifluridine/tipiracil (N = 534)		Placebo (N = 266)	
Number (%) of patients by censoring status				
Total	534 (100)		266 (100)	
Not censored (dead)	364 (68.2)		210 (78.9)	
Censored	170 (31.8)		56 (21.1)	
Survival (months)[a] [95% CI][b]				
Twenty-fifth percentile	4.1	[3.8, 4.6]	3.1	[2.6, 3.4]
Median	7.1	[6.5, 7.8]	5.3	[4.6, 6.0]
Seventy-fifth percentile	12.3	[11.1, 13.8]	8.6	[7.5, 11.1]
Hazard ratio [95% CI]	0.68 [0.58, 0.81]			
p-value[c]	<0.0001 (1-sided and 2-sided)			
Percent (%) of patients surviving[a] [95% CI][d]				
At 3 months	86.0	[82.7, 88.6]	75.1	[69.4, 79.9]
At 6 months	57.8	[53.5, 61.9]	43.5	[37.4, 49.4]
At 9 months	40.1	[35.6, 44.6]	24.2	[18.9, 29.9]
At 12 months	26.2	[22.2,31.1]	17.6	[12.7, 23.1]

Key: CI, confidence interval.

Notes: [a] Kaplan-Meier estimates; [b] Methodology of Brookmeyer and Crowley; [c] stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region); [d] using log-log transformation methodology of Kalbfleisch and Prentice.

Source: RECOURSE CSR.[12]

Figure 15: Overall survival in RECOURSE



No. at Risk							
TAS-102	534	459	294	137	64	23	7
Placebo	266	198	107	47	24	9	3

Key: TAS-102, trifluridine/tipiracil.

Note: Image is from the NEJM publication, rounding rules for this publication mean that the p-value quoted is different from the RECOURSE CSR

Source: Mayer et al. 2015.[2]

Updated survival analysis

An updated survival analysis based on a data cut-off of 08 October 2014 is presented in Table 26 and Figure 16. For this final survival analysis, 89% of the 800 patients randomly assigned to trifluridine/tipiracil or placebo had died, adding 138 additional events to the 574 events included in the original analysis. The updated median OS was 7.2 months in the trifluridine/tipiracil group and 5.2 months in the placebo group (HR 0.69; 95% CI 0.59 to 0.81; p < 0.0001). At 12 months, survival was 27.1% and 16.6% for trifluridine/tipiracil and placebo, respectively. OS benefit appears to be maintained for all patients in the trial regardless of prognostic status at trial entry.

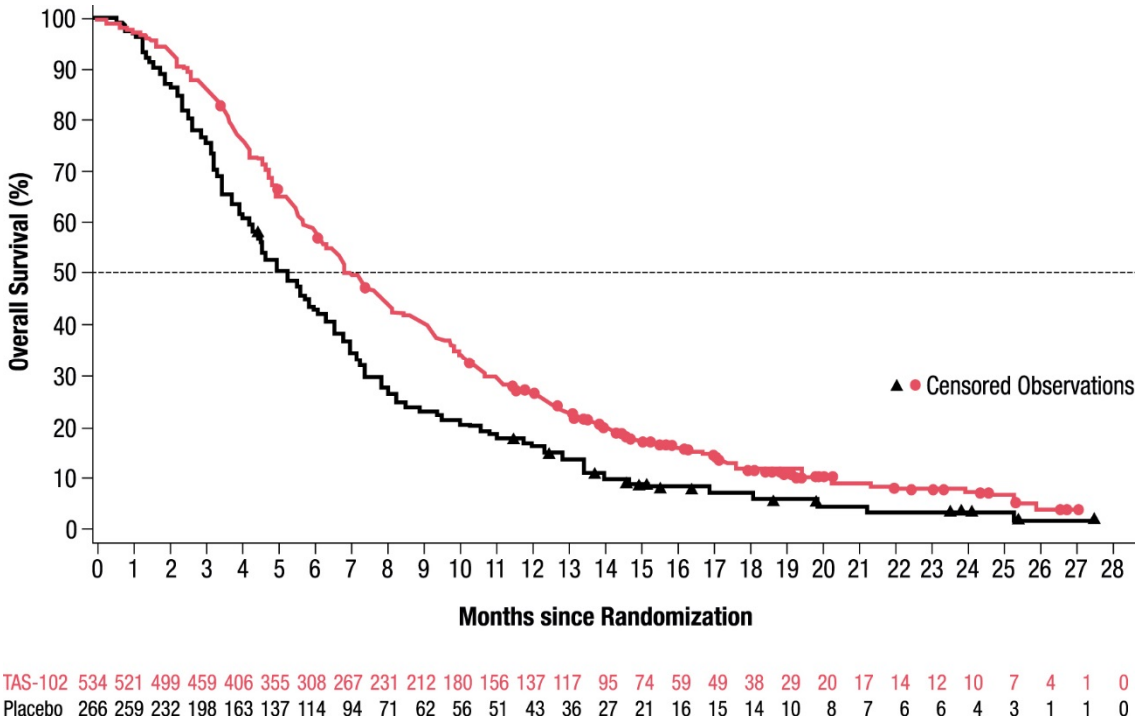
These results appear particularly meaningful in this heavily pre-treated and chemotherapy-refractory population and represent an average survival gain of approximately 50%.

Table 26: Updated survival analysis in RECOURSE, 08 October 2014

	Original analysis		Updated analysis	
	Trifluridine/tipiracil	Placebo	Trifluridine/tipiracil	Placebo
	(N = 534)	(N = 266)	(N = 534)	(N = 266)
Median OS, months	7.1	5.3	7.2	5.2
(95% CI)	(6.5-7.8)	(4.6-6.0)	(6.6-7.8)	(4.6-5.9)
Hazard ratio	0.68		0.69	
(95% CI)	(0.58-0.81)		(0.59-0.81)	
p-value (1-sided)	<0.0001		<0.0001	
1-year survival, %	26.6	17.6	27.1	16.6
(95% CI)	(22.2-31.1)	(12.7-23.1)	(23.3-30.9)	(12.4-21.4)

Key: CI, confidence interval; OS, overall survival.
Source: Mayer et al. 2016.[11]

Figure 16: Updated survival analysis in RECOURSE (ITT population)



Key: ITT, intention-to-treat; TAS-102, trifluridine/tipiracil.
Source: Mayer et al. 2016.[11]

Secondary endpoints

Progression-free survival

The addition of trifluridine/tipiracil to BSC resulted in a statistically significant improvement in PFS compared to placebo plus BSC (Table 27 and Figure 17). The median PFS was 2.0 months for the trifluridine/tipiracil group and 1.7 months for the placebo group (HR 0.48; 95% CI 0.41 to 0.57; 1-sided and 2-sided p < 0.0001).

Although median PFS was similar for the two treatment groups, the percentage of patients who remained progression-free was consistently higher for the trifluridine/tipiracil group than for the placebo group, starting at the time of the initial post baseline tumour assessment, i.e., at 2 months. At this point, the percentage of patients remaining progression-free was 47.3% for the trifluridine/tipiracil group compared to 20.8% for the placebo group. At 4 months, the percentage of patients progression-free was 25.0% for the trifluridine/tipiracil group compared with 4.7% for the placebo group; and at 6 months, the percentage of patients progression-free was 15.1% for the trifluridine/tipiracil group compared with 1.4% for the placebo group.

Table 27: Radiological progression-free survival in RECOURSE (ITT population)

Parameter	Trifluridine/tipiracil (N = 534)		Placebo (N = 266)	
Number (%) of patients by censoring status				
Total	534 (100)		266 (100)	
Not censored (PFS event)	472 (88.4)		251 (94.4)	
Progressed	432 (80.9)		226 (85.0)	
Death	40 (7.5)		25 (9.40	
Censored	62 (11.6)		15 (5.6)	
Discontinued follow-up	0 (0)		2 (0.8)	
Initiated other anti-tumour therapy	14 (2.6)		6 (2.3)	
Missed visit (>91 days since last response)	14 (2.6)		5 (1.9)	
Follow-up on-going at time of analysis	34 (6.4)		2 (0.8)	
Progression-free survival (months)[a] [95% CI][b]				
Twenty-fifth percentile	1.7	[1.7, 1.8]	1.5	[1.4, 1.6]
Median	2.0	[1.9, 2.1]	1.7	[1.7, 1.8]
Seventy-fifth percentile	4.0	[3.8, 5.4]	1.9	[1.9, 2.0]

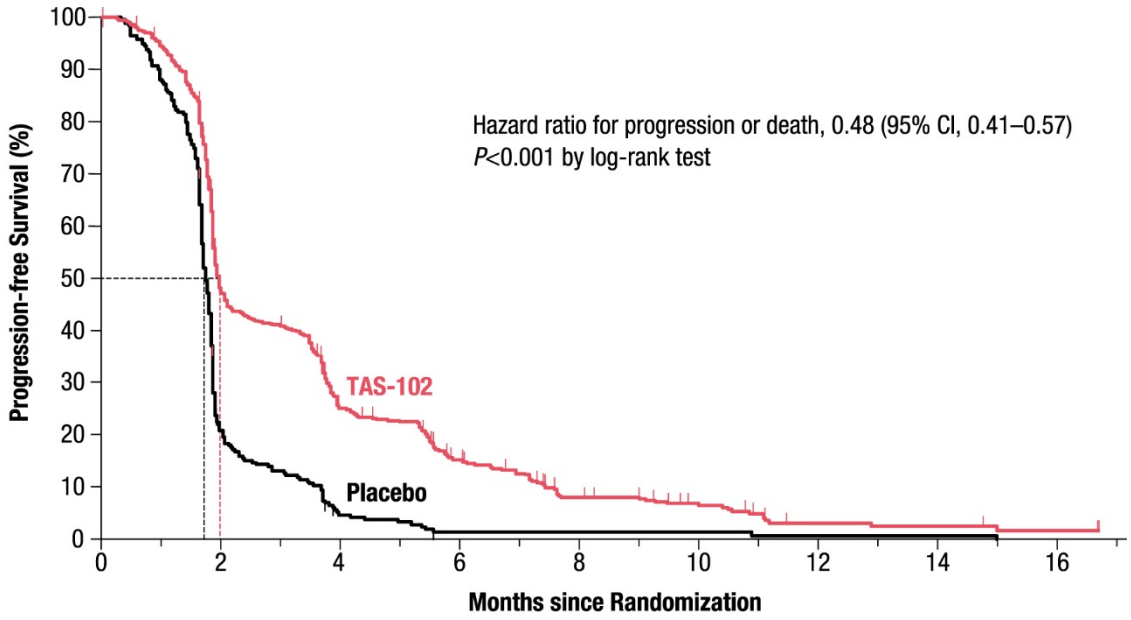
Parameter	Trifluridine/tipiracil (N = 534)		Placebo (N = 266)	
Hazard ratio [95% CI]	0.48 [0.41, 0.57]			
p-value[c]	<0.0001 (1-sided and 2-sided)			
Percent (%) of patients progression free[a] [95% CI][d]				
At 3 months	47.3	[42.9, 51.5]	20.8	[16.0, 26.0]
At 6 months	25.0	[21.3, 28.8]	4.7	[2.5, 7.9]
At 9 months	15.1	[12.1, 18.5]	1.4	[0.4, 3.7]
At 12 months	8.0	[5.7, 10.8]	1.4	[0.4, 3.7]

Key: CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival.

Notes: [a] Kaplan-Meier estimates; [b] Methodology of Brookmeyer and Crowley; [c] Stratified log-rank test (strata: KRAS status, time since diagnosis of first metastasis, region); [d] Using log-log transformation methodology of Kalbfleisch and Prentice.

Source: RECOURSE CSR.[12]

Figure 17: Progression-free survival in RECOURSE



Key: TAS-102, trifluridine/tipiracil.

Note: Image is from the NEJM publication, rounding rules for this publication mean that the p-value quoted is different from the RECOURSE CSR

Source: Mayer et al. 2015.[2]

Time to treatment failure (TTF)

As shown in Table 28, the results for TTF were consistent with those for PFS considering the small number of patients who discontinued treatment for reasons other than disease progression or death. The median TTF was 1.9 months for the

trifluridine/tipiracil group versus 1.7 months for the placebo group (HR 0.50; 95% CI 0.42 to 0.58; p < 0.0001).

Table 28: **Time to treatment failure in RECOURSE (ITT population)**

Parameter	Trifluridine/tipiracil (N = 534)		Placebo (N = 266)	
Number (%) of patients by censoring status				
Total	534 (100)		266 (100)	
Not censored	494 (92.5)		261 (98.1)	
Radiological progression	417 (78.1)		221 (83.1)	
Death	9 (1.7)		7 (2.6)	
Discontinued study treatment	68 (12.7)		33 (12.4)	
Censored	40 (7.5)		5 (1.9)	
Initiated other anti-tumour therapy	8 (1.5)		3 (1.1)	
Follow-up on-going at time of analysis	32 (6.0)		2 (0.8)	
Time to treatment failure (months)[a] [95% CI][b]				
Twenty-fifth percentile	1.7	[1.6, 1.7]	1.5	[1.4, 1.6]
Median	1.9	[1.9, 2.0]	1.7	[1.7, 1.8]
Seventy-fifth percentile	3.9	[3.8, 5.1]	1.9	[1.9, 2.0]
Hazard ratio [95% CI]	0.50 [0.42, 0.58]			
p-value[c]	<0.0001			

Key: CI, confidence interval; ITT, intention-to-treat.
Notes: [a] Kaplan-Meier estimates; [b] Methodology of Brookmeyer and Crowley; [c] Stratified log-rank test.
Source: RECOURSE CSR.[12]

Overall response rate (ORR) / Disease control rate (DCR)

In the tumour-response (TR) population (502 patients in the trifluridine/tipiracil group and 258 in the placebo group), eight patients in the trifluridine/tipiracil group had a partial response, and one patient in the placebo group was reported to have a complete response, resulting in objective response rates of 1.6% with trifluridine/tipiracil and 0.4% with placebo (p = 0.29). However, there was a substantial difference in the percentage of patients with best overall response of SD (42.4%, trifluridine/tipiracil; 15.9%, placebo) leading to a significant difference in DCR between the trifluridine/tipiracil and placebo groups (27.7%; 95% CI 21.5 to 34.0; p < 0.0001), see Table 29.

Table 29: Best overall response rate/disease control rate in RECOURSE (TR population)

Parameter	Trifluridine/tipiracil (N = 534)		Placebo (N = 266)	
Best overall response (ORR)	**n (%)**	**95% CI[a]**	**n (%)**	**95% CI[a]**
Complete or partial	8 (1.6)	0.7, 3.1	1 (0.4)	0.0, 2.1
Complete	0 (0.0)		1 (0.4)	
Partial	8 (1.6)		0 (0.0)	
Stable disease	213 (42.4)		41 (15.9)	
Progressive disease - radiological	260 (51.8)		195 (75.6)	
Not evaluable[b]	21 (4.2)		21 (8.1)	
Complete, partial or stable disease (DCR)	221 (44.0)	39.6, 48.5	42 (16.3)	12.0, 12.4
Difference in ORR (Trifluridine/tipiracil - placebo) [95% CI[c]]	1.2 [-0.1, 2.5]			
p-value[d]	0.2862			
Difference in DCR (Trifluridine/tipiracil - placebo) [95% CI[c]]	27.7 [21.5, 34.0]			
p-value[d]	<0.0001			

Key: CI, confidence interval; DCR, disease control rate; ORR, overall response rate; TR, tumour response.

Notes: TR population – The assessment of ORR was based on investigator review of radiological images and was restricted to patients with measurable disease (at least 1 target lesion) at baseline and with at least one tumour evaluation while on study treatment.

[a] Exact two-sided confidence interval based on Clopper-Pearson methodology; [b] Patients with a cancer-related death but no tumour evaluation while on study treatment; [c] Normal approximation; d Fisher's Exact test (two-sided).

Source: RECOURSE CSR.[12]

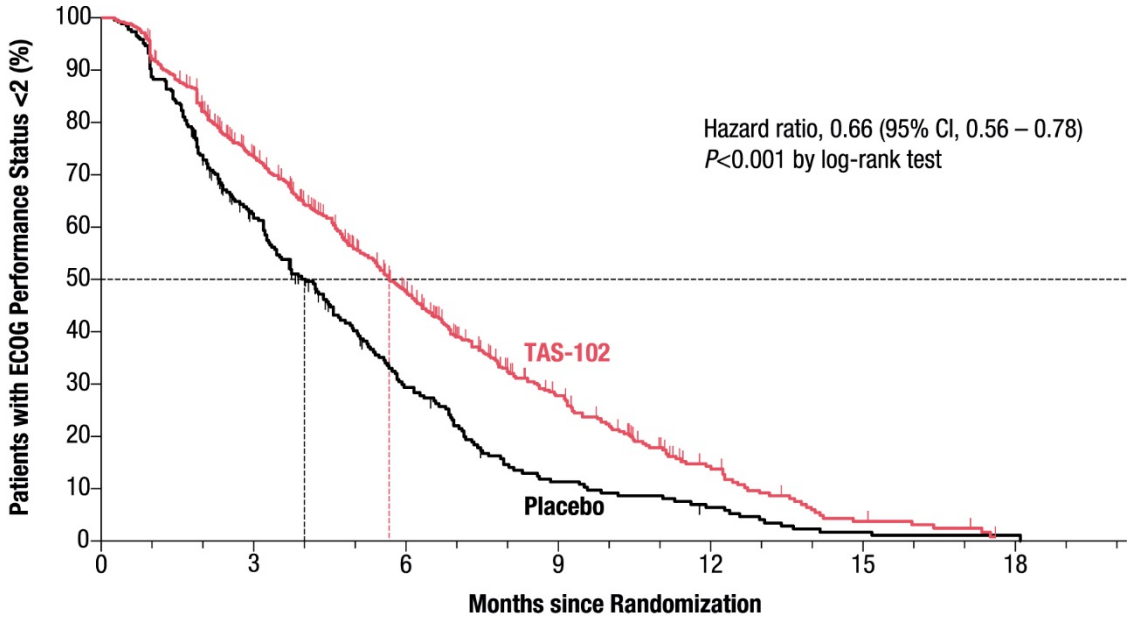
ECOG performance status

The RECOURSE trial measured time to deterioration of performance status (PS) as a measure of the effectiveness of trifluridine/tipiracil.[12] PS is a physician-reported measure of patient wellbeing, which has been shown to be a prognostic indicator of survival in mCRC patients.[12] It is favoured as a robust method of assessing how the disease and treatment affect the daily wellbeing of the patient.[43]

Results from RECOURSE demonstrate that trifluridine/tipiracil prolonged the time patients retained their good PS versus BSC, in addition to the observed survival benefit. The median time to ECOG PS ≥2 (ECOG PS 2 = ambulatory and capable of all self-care but unable to carry out any work activities) was 5.7 months for the

trifluridine/tipiracil group versus 4.0 months for the placebo group (HR 0.66; 95% CI 0.56 to 0.78; p < 0.0001) (Figure 18).This suggests that patients who received trifluridine/tipiracil had an improvement of their overall survival that was not at the expense of deterioration in PS.

Figure 18: **Time to ECOG performance status of ≥2 in RECOURSE (ITT population)**



No. at Risk							
TAS-102	534	352	188	84	28	7	0
Placebo	266	134	57	21	11	3	1

Key: ITT, intention-to-treat; TAS-102, trifluridine/tipiracil.

Note: Image is from the NEJM publication, rounding rules for this publication mean that the p-value quoted is different from the RECOURSE CSR

Source: Mayer et al. 2015.[2]

Post study anti-tumour treatment

There was no crossover in RECOURSE. The treatment groups were similar with respect to treatments received during follow-up after discontinuation of study treatment including post-treatment use of regorafenib (Table 30). Therefore, this was not a confounding factor with respect to OS results. This also suggests that, following tumour progression in patients who have received trifluridine/tipiracil, a significant number of patients were still well enough to receive further treatment.

A full list of anti-tumour agents administered in the first post-treatment regimen received are listed in Appendix 4.

Table 30: **Non-study anti-tumour treatments received after the end of the treatment period in RECOURSE (ITT population)**

Treatment	Number (%) of patients		
	Trifluridine/tipiracil (N = 534)	Placebo (N = 266)	Total (N = 800)
Surgery	6 (1.1)[a]	5 (1.9)	11 (1.4)
Surgery or systemic anti-cancer therapy	224 (41.9)	118 (44.4)	342 (42.8)
Radiotherapy	0	0	0
Any systemic therapy	222 (41.6)	113 (42.5)	335 (41.9)
Number of regimens			
1	170 (31.8)	88 (33.1)	258 (32.3)
2	41 (7.7)	22 (8.3)	63 (7.9)
≥3	11 (2.1)	3 (1.1)	14 (1.8)
Any regorafenib containing regimen	84 (15.7)	41 (15.4)	125 (15.6)
No regorafenib containing regimens	138 (25.8)	72 (27.1)	210 (26.3)

Key: ITT, intention-to-treat.

Notes: [a] Includes four patients who had surgery plus other systemic anti-cancer therapy, and two patients who had surgery only.

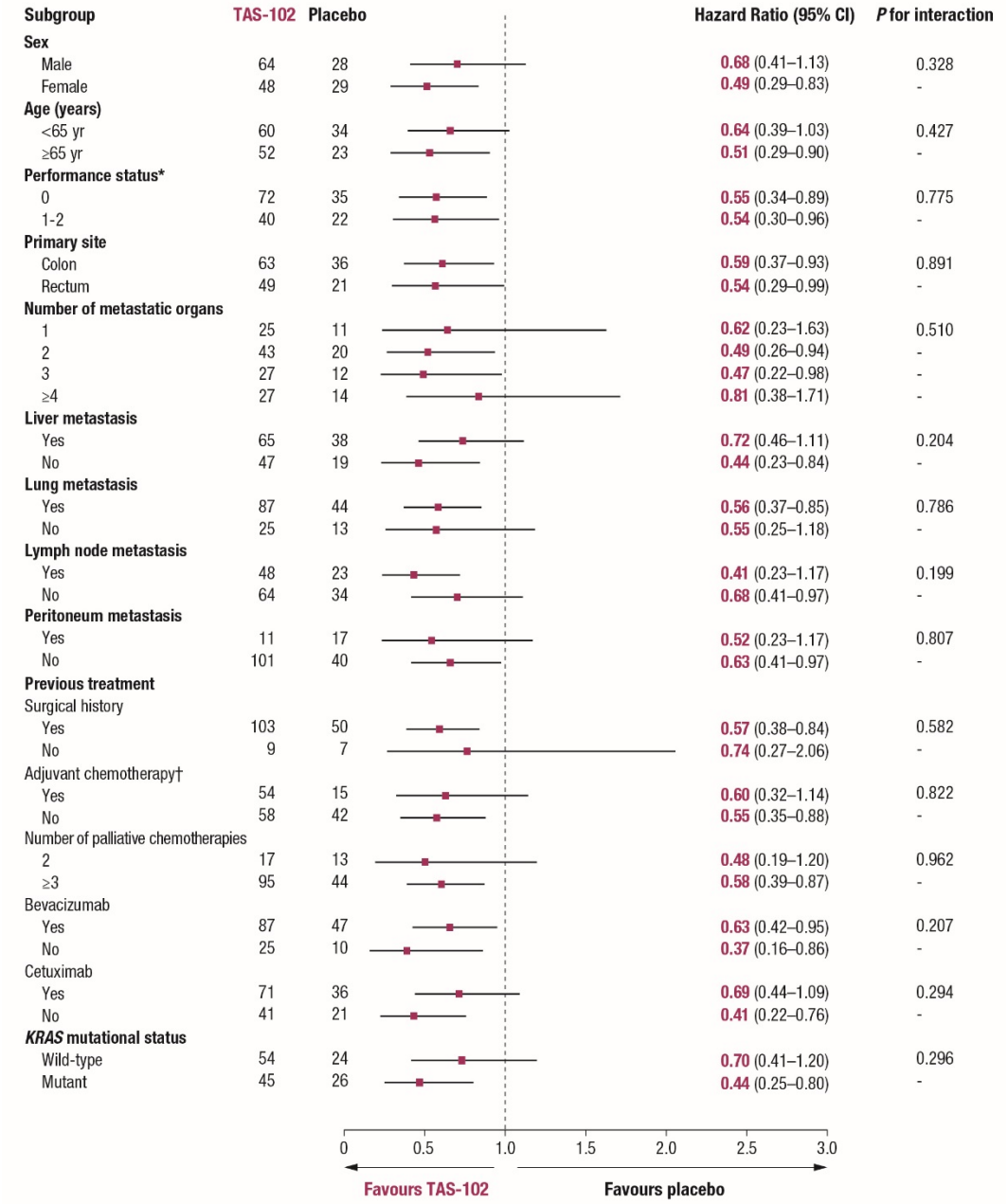
Source: RECOURSE CSR.[12]

4.8 Subgroup analysis

4.8.1 Phase II subgroup analysis

In the prespecified subgroup analyses for OS, the effect of trifluridine/tipiracil was similar in all categories, although not all improvements were significant (Figure 19).[3, 42]

Figure 19: Overall survival in prespecified subgroups in the Phase II trial

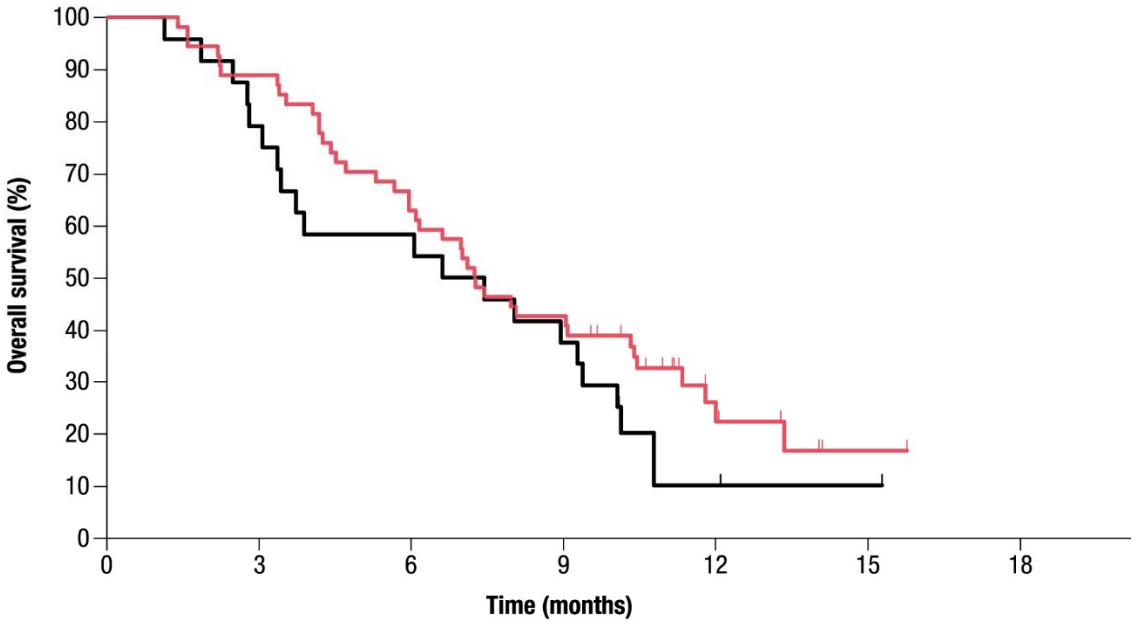


Key: TAS-102, trifluridine/tipiracil**.**
Notes: *Eastern Cooperative Oncology Group criteria.
†More patients received adjuvant chemotherapy in the trifluridine/tipiracil group than in the placebo group, but this difference had no effect on the assessment of overall survival with the Cox proportional hazards model with one variable (p = 0.605); there was no interaction (p = 0.822).
Source: Yoshino et al. 2012.[3]

Subgroup analysis by KRAS mutation status

KRAS status was available for 149 patients (99 patients in the trifluridine/tipiracil group, 50 patients in the placebo group). In the subset of patients with *KRAS* wild-type, median OS was 7.2 months for trifluridine/tipiracil and 7.0 months for placebo (HR 0.70; 95% CI 0.41 to 1.20; p = 0.191) (Figure 20). In the subset of patients with the *KRAS* mutation, median OS was 13.0 and 6.9 months for the trifluridine/tipiracil and placebo groups, respectively (HR 0.44; 95% CI 0.25 to 0.80; p = 0.0056) (Figure 21). There was no evidence of a differential treatment effect between wild-type and mutant groups (p = 0.296).

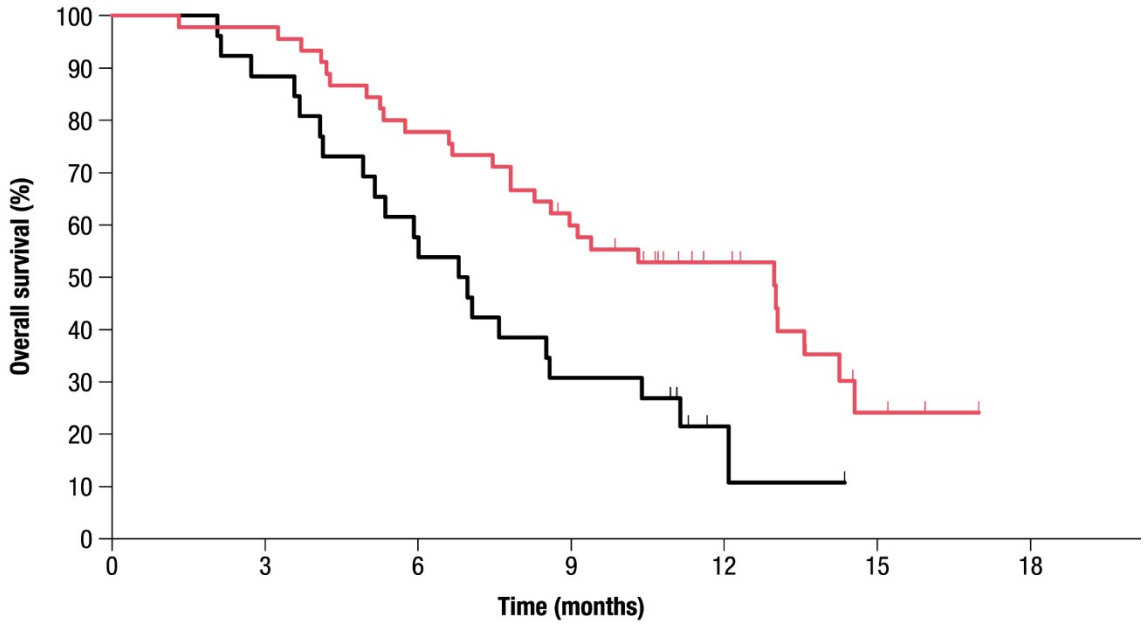
Figure 20: Overall survival of patients with wild-type *KRAS* in the Phase II trial



No. at Risk						
TAS-102	54	48	34	23	6	1
Placebo	24	19	14	9	2	1

Key: TAS-102, trifluridine/tipiracil (red line).
Source: Yoshino et al. 2012.[3]

Figure 21: Overall survival of patients with mutant KRAS in the Phase II trial



No. at Risk						
TAS-102	45	44	35	26	14	4
Placebo	26	23	15	8	2	0

Key: TAS-102, trifluridine/tipiracil (red line).

Source: Yoshino et al. 2012.[3]

In the *KRAS* wild-type patients, the median PFS was 1.9 months (95% CI 1.1 to 2.8) and 1.0 month (95% CI 1.0 to 1.1) in the trifluridine/tipiracil and placebo groups, respectively. For the *KRAS* wild-type patients, the HR obtained by the Cox proportional hazards model was 0.40 (95% CI 0.23 to 0.69) in the trifluridine/tipiracil group, versus the placebo group (p = 0.0004). For the *KRAS* mutant-type patients, the median PFS was 2.8 months (95% CI 1.9 to 4.7) and 1.0 month (95% CI 1.0 to 1.2) in the trifluridine/tipiracil and placebo groups, respectively, and the HR was 0.34 (95% CI 0.19 to 0.61), p-value <0.0001. The p-value for the interaction for these two groups (0.772) indicated no evidence for a differential treatment difference between *KRAS* wild-type and *KRAS* mutant.

4.8.2 Phase III subgroup analysis – RECOURSE

Subgroup analysis of OS by stratification group

Table 31 shows the pre-specified subgroup analysis of OS by stratification factor. The analysis consistently favours trifluridine/tipiracil with HRs ranging from 0.58 to 0.84.

Table 31: Overall survival by stratification groups in RECOURSE (ITT population)

	Trifluridine/tipiracil (N = 534)			Placebo (N = 266)				
	Survival (months)			Survival (months)				
Subgroup (based on IWRS)	**n**	**Median**	**95% CI**	**n**	**Median**	**95% CI**	**HR**	**95% CI**
KRAS status								
Wild-type	262	8.0	6.9, 9.2	131	5.7	4.5, 6.6	0.58	0.45, 0.74
Mutant type	272	6.5	5.6, 7.1	135	4.9	4.2, 6.1	0.80	0.63, 1.02
Time since diagnosis of first metastases								
<18 months	111	4.9	4.1, 5.9	55	3.8	3.3, 5.2	0.84	0.58, 1.21
≥18 months	423	7.8	6.9, 8.8	211	5.8	4.9, 6.4	0.64	0.53, 0.78
Geographic region								
Asia (Japan)	178	7.8	7.0, 9.1	88	6.7	5.1, 7.5	0.75	0.57, 1.00
Western (Australia, Europe, US)	356	6.5	5.9, 7.8	178	4.8	4.2, 5.7	0.64	0.52, 0.80

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; IWRS, Interactive Voice/Web Response System.
Source: RECOURSE CSR.[12]

Other pre-specified subgroups of OS

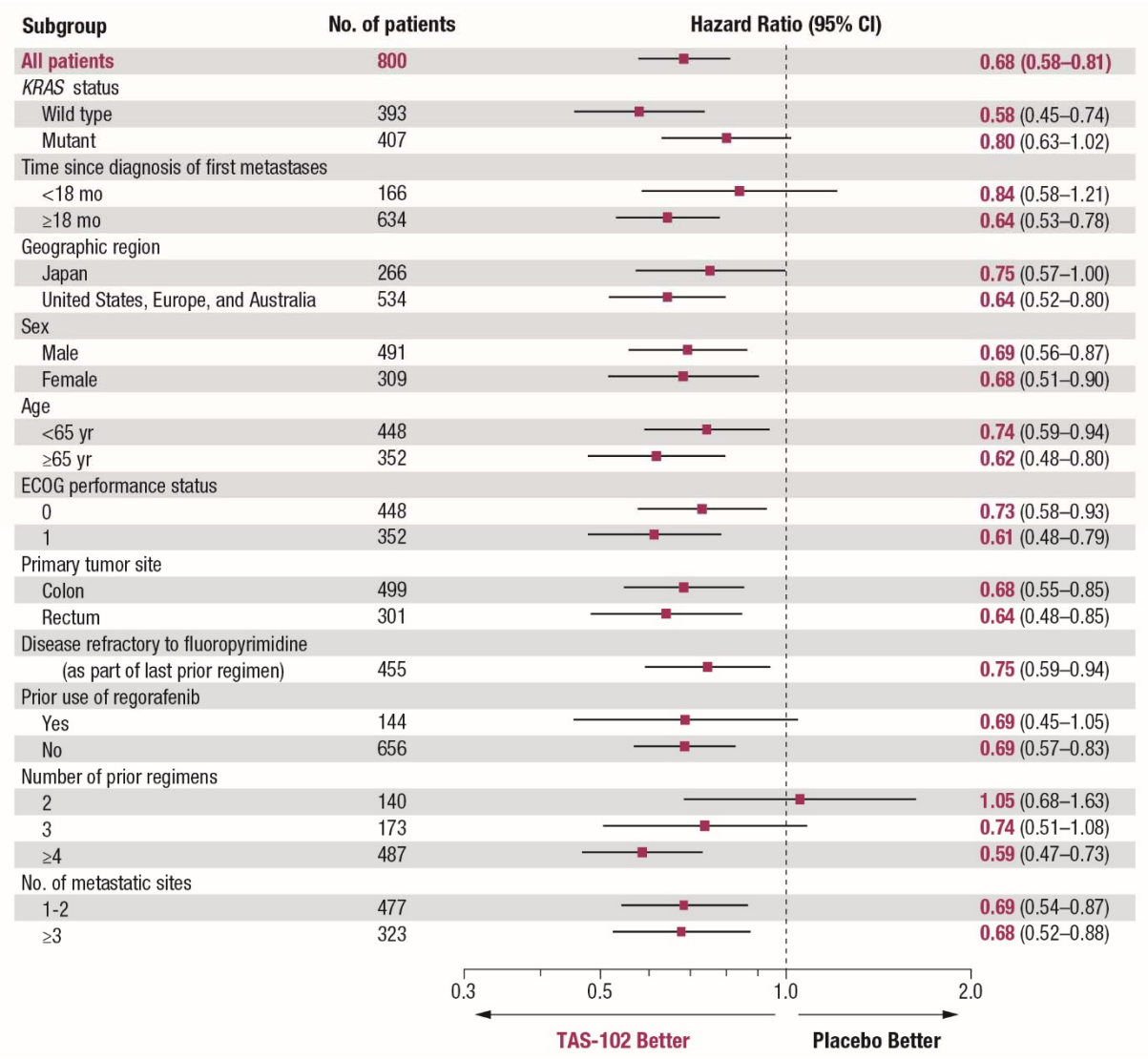
RECOURSE examined eleven pre-specified subgroups for OS. In general, the results for OS were consistent across pre-specified subgroups including age (<65 years, ≥65 years), race, gender, *BRAF* status, primary tumour site (colon, rectum), baseline ECOG score, number of metastatic sites (1-2, ≥3) and geographic sub-region (Australia, Europe, the US), with HRs ranging from 0.49 to 0.75. For some parameters, such as *BRAF* status and race, the small sample sizes precluded any meaningful analyses. There was only one subgroup where the HR for that group was greater than one for OS (two prior treatment regimens: HR 1.05; 95% CI 0.68 to 1.63). This subgroup was the smallest of those examined, and given that the trial was event driven for OS, it may be that there are only a few events within the group. As evidenced by the very wide confidence interval, there is considerable imprecision in the estimate of the HR.

According to the European Medicines Agency (EMA) guideline on the investigation of subgroups in clinical trials, there is currently no widely accepted definition of consistency, and only identification of a potential lack of effect within one subgroup should not be used as a basis for regulatory actions.[44] As more subgroups are analysed, there is an increase in the probability that an inconsistent treatment effect is seen by chance. In addition, there is no biological plausibility for such a subgroup effect, as trifluridine/tipiracil is a non-targeted chemotherapeutic agent.

The EMA guideline states that “a reassuring pattern of results is where all point estimates from subgroup analyses are rather similar to the overall effect with all confidence intervals overlapping with the confidence interval for the overall effect”.[44] As Figure 22 shows, the confidence intervals for all subgroups overlap with the overall trial result again, suggesting homogeneity of effect.

Approximately 61% (n = 485) of all patients in the ITT population received a fluoropyrimidine as part of their last treatment regimen prior to randomisation. Of these, 455 (94%) were refractory to the fluoropyrimidine at that time. As shown in Figure 22, among these patients, risk reduction in OS with trifluridine/tipiracil remained favourable and statistically significant (HR 0.75). Of the 800 randomised patients, 144 (18%) had received prior treatment with regorafenib. As shown in Figure 22, risk reduction in OS with trifluridine/tipiracil was the same for both groups (HR 0.69 for those with and without prior regorafenib use).[12] These data suggest that the activity of trifluridine/tipiracil is maintained irrespective of prior treatment regimens.

Figure 22: Forest plot of the pre-specified subgroups for OS in RECOURSE



Key: TAS-102, trifluridine/tipiracil.
Source: Mayer, et al. 2015.[2]

Multivariate analysis of OS

In addition to the three stratification factors (KRAS status, geographic region, and time since diagnosis of first metastasis), ten potential prognostic factors (BRAF status, age, race, gender, primary tumour site, ECOG PS, number of prior regimens, number of metastatic sites, refractory to last prior regimen when it contained fluoropyrimidine, and prior regorafenib use) were evaluated at the request of the regulators (EMA) in a multivariate model that excluded treatment, using a forward stepwise selection process, for its OS prognostic significance (p-value <0.10 to enter

the model and “stay” in the model) based on the ITT population. From the list above, the following six factors were identified to be of prognostic value: the three stratification factors (by default), primary tumour site, ECOG PS, and number of metastatic sites.[12] None of these factors demonstrated any interaction with treatment when treatment was added in the model (treatment interaction p-value >0.20 for all factors). There was no evidence of heterogeneity of treatment effect for OS across any of the subgroups examined.

Subgroup analysis of PFS

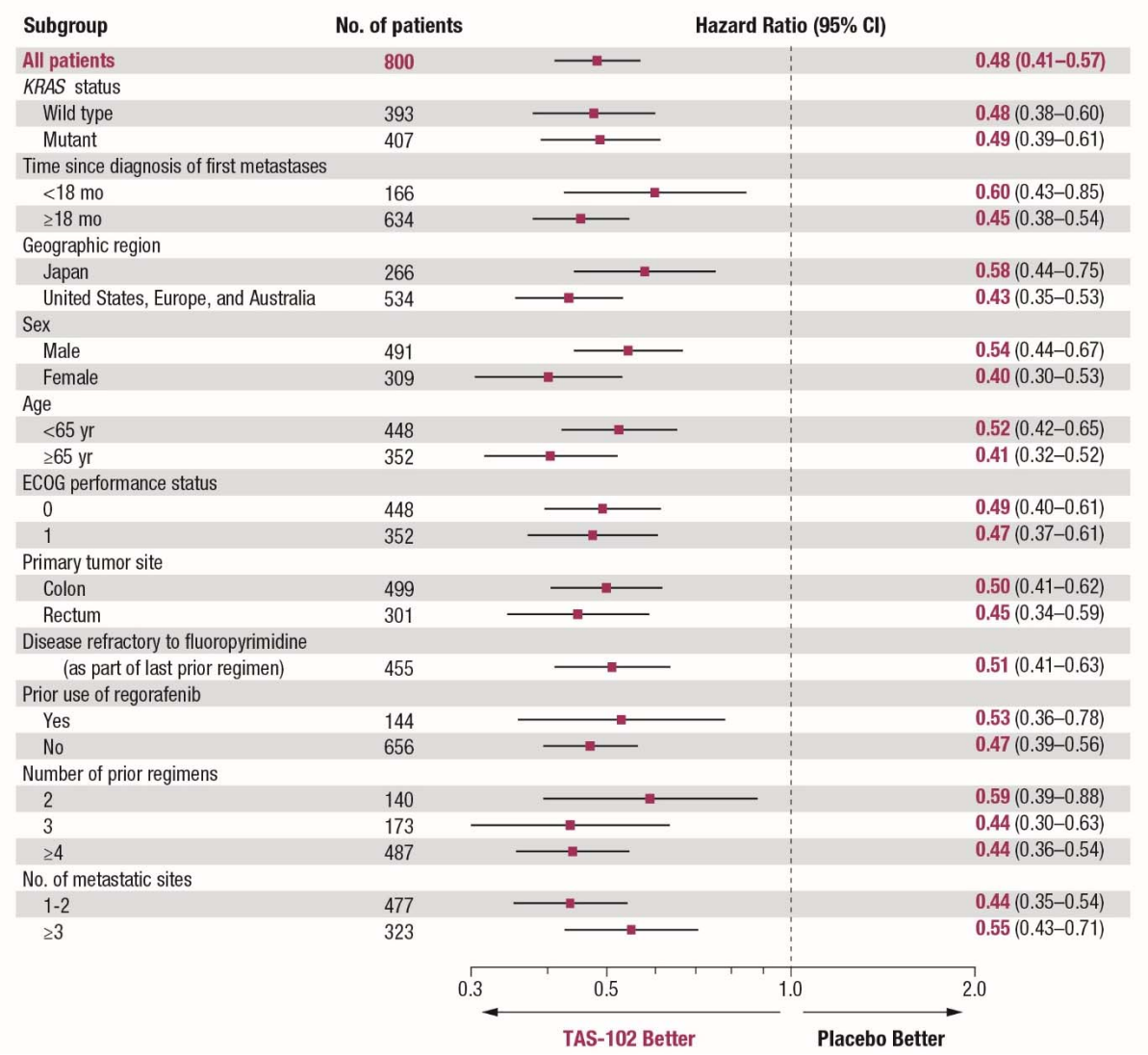
Treatment effects for the pre-specified subgroups for PFS were highly consistent with all confidence intervals well below 1 and HRs ranging from 0.43 to 0.60 (Table 32).

Table 32: Progression-free survival by stratification groups in RECOURSE (ITT population)

	Trifluridine/tipiracil (N = 534)			Placebo (N = 266)				
	PFS (months)			PFS (months)				
Subgroup (based on IWRS)	**N**	**Median**	**95% CI**	**N**	**Median**	**95% CI**	**HR**	**95% CI**
KRAS status								
Wild-type	262	2.1	1.9, 2.7	131	1.7	1.7, 1.8	0.48	0.38, 0.60
Mutant type	272	1.9	1.9, 2.1	135	1.8	1.7, 1.8	0.49	0.39, 0.61
Time since diagnosis of first metastases								
<18 months	111	1.8	1.7, 1.9	55	1.7	1.6, 1.7	0.60	0.43, 0.85
≥ 18 months	423	2.1	2.0, 3.1	211	1.8	1.7, 1.8	0.45	0.38, 0.54
Geographic region								
Asia (Japan)	178	2.0	1.9, 2.6	88	1.8	1.7, 1.9	0.58	0.44, 0.75
Western (Australia, Europe, US)	356	2.0	1.9, 2.2	178	1.7	1.7, 1.8	0.43	0.35, 0.53

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; IWRS, Interactive Voice/Web Response System; PFS, progression-free survival.
Source: RECOURSE CSR.[12]

Figure 23: Progression-free survival by subgroup in RECOURSE



Key: TAS-102, trifluridine/tipiracil.
Source: Mayer et al. 2015.[2]

Geographic subgroup analysis

A pre-specified analysis was performed to compare outcomes (OS, PFS) and safety according to geographic sub-region, although the study was not powered for each of these comparisons (Table 33 and Figure 24).[40]

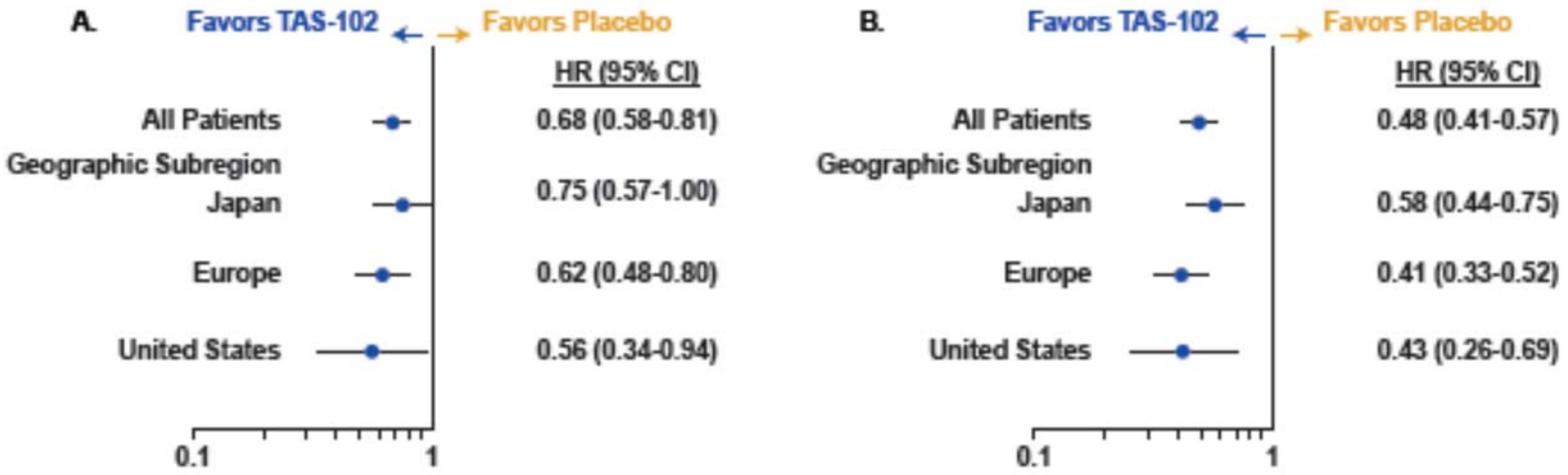
These data show that the OS and PFS benefits observed in each geographic subgroup randomised to trifluridine/tipiracil and placebo (US, EU, and Japan) were similar to the overall RECOURSE population. There is no evidence of a difference in efficacy based on ethnicity.

Table 33: Overall survival and progression-free survival in RECOURSE – overall population and by geographic sub-region (ITT population)

	US		EU		Japan		Overall	
ITT	Trifluridine/tipiracil (n = 64)	Placebo (n = 35)	Trifluridine/tipiracil (n = 271)	Placebo (n = 132)	Trifluridine/tipiracil (n = 179)	Placebo (n = 88)	Trifluridine/tipiracil (n = 534)	Placebo (n = 266)
Median OS, months	6.5	4.3	6.8	4.9	7.8	6.7	7.1	5.3
OS HR (95%, CI)	0.56 (0.34-0.94) p -0.0277		0.62 (0.48-0.90) p -0.0002		0.75 (0.57-1.00) p -0.047		0.68 (0.58-0.81) p <0.0001	
Median PFS, months	2.8	1.7	2.0	1.7	2.0	1.8	2.0	1.7
PFS HR (95% CI)	0.43 (0.26-0.69) p -0.0004		0.41 (0.33-0.52) p <0.0001		0.58 (0.44-0.75) p <0.0001		0.48 (0.41-0.57) p <0.0001	

Key: CI, confidence interval; EU, Europe; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; US, United States
Source: Ohtsu et al. 2015.[40]

Figure 24: Forest plots for (A) overall survival and (B) progression-free survival by geographic sub-region in RECOURSE



Key: CI, confidence interval; HR, hazard ratio.

Source: Ohtsu et al. 2015.[40]

Age-based subgroup analysis

A pre-specified analysis was performed to compare the efficacy OS and PFS and safety of trifluridine/tipiracil compared to placebo in patients with mCRC ≥65 and <65 years of age, although the study was not powered specifically for these comparisons.[41]

In addition, retrospective analyses of patients ≥70, <70, and ≥75 years of age were also performed (Table 34).

These data show that the OS and PFS benefits observed in each age subgroup randomised to trifluridine/tipiracil and placebo were similar to the overall RECOURSE population. There is no evidence of a difference in efficacy based on age.

Table 34: Overall survival and progression-free survival by age group in RECOURSE

	Age <65 years		Age ≥65 years		Age <70 years		Age ≥70 years	
	Trifluridine/tipiracil (n = 300)	Placebo (n = 148)	Trifluridine/tipiracil (n = 234)	Placebo (n = 118)	Trifluridine/tipiracil (n = 406)	Placebo (n = 210)	Trifluridine/tipiracil (n = 128)	Placebo (n = 56)
Median OS, months	7.1	5.7	7.0	4.6	7.1	5.3	7.0	4.7
HR (95% CI)	0.74 (0.59-0.94)		0.62 (0.49-0.90)		0.70 (0.57-0.85)		0.65 (0.45-0.94)	
p-value	0.0130		0.0002		0.0003		0.0231	
Median PFS, months	1.9	1.7	2.1	1.8	1.9	1.7	2.5	1.8
HR (95% CI)	0.52 (0.42-0.65)		0.41 (0.32-0.52)		0.49 (0.41-0.59)		0.44 (0.30-0.63)	
p-value	<0.0001		<0.0001		<0.0001		<0.0001	

Key: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
Source: Van Cutsem et al. 2015.[41]

4.8.3 Subpopulation analysis

During assessment of the marketing authorisation, the CHMP was interested in whether there were specific subpopulations that may have a greater benefit from trifluridine/tipiracil. In response, exploratory analyses were undertaken to assess the treatment effect in low to high risk patients according to a clinically-based prognostic risk-score for OS.[19]

Clinical prognostic risk scores

The prognostic risk score for each patient was derived using the final multivariate regression model for OS that was established after stepwise selection from all predefined potentially prognostic factors (RECOURSE CSR Section 11.2.1.4[12]) and described earlier (Section 4.8.2).

The final model containing the six chosen factors, but excluding treatment, was used to estimate the prognostic risk score for each patient. The survival hazard for each patient was estimated based on the patient characteristics for each of six factors; that is, whether the patient's diagnosis of first metastasis was less than 18 months versus 18 months or more, whether the ECOG PS was 0 versus 1, or whether the number of metastatic sites was 1 to 2 versus 3.

As a simplified example, the ECOG PS HR in the stepwise model that excluded treatment was 0.60, which meant that a patient with ECOG status 0 had a 40% lower chance of dying at any given time compared to a patient with ECOG status 1.

Once the survival hazard (prognostic score) for each patient was estimated with all six factors included in the model, but excluding treatment, they were categorised in 4 quartiles that each included about 25% of the overall patient population, ranging from high risk (high hazard – higher risk for death) to low risk (low hazard – lower risk for death).

A sensitivity analysis was also performed that used only the placebo patients in the ITT population to identify factors of prognostic value (first step in the methodology described earlier). The resulting model again included six factors; the only difference was that the factor 'Primary Tumour site' was replaced by 'Race (Black vs non-Black).' Despite the difference in one of the six factors, the OS results by risk quartile presented in Table 35 remained almost identical.

Table 35: Overall survival by risk quartile

Risk quartile	Trifluridine/tipiracil			Placebo			HR (trifluridine/tipiracil vs placebo)
	n	%	Median OS	n	%	Median OS	
Q1 (Lowest)	158	29.6	10.5	77	28.9	7.1	0.67
Q2	112	21	8.5	59	22.1	6.0	0.58
Q3	139	26	6.5	56	21.1	5.0	0.74
Q4 (Highest)	125	23.4	4.6	74	27.8	3.5	0.56

Key: HR, hazard ratio; Q, quartile.

Source: Summary of CHMP Day 120 Clinical Major Objection.[19]

The OS results for the subgroups defined based on the survival prognostic score demonstrate that the clinical benefit of trifluridine/tipiracil is consistently maintained in all patients, irrespective of their survival prognosis, as captured by the prognostic risk score. For patients with a better or worse prognosis upon entering the trial, the OS benefit of trifluridine/tipiracil over placebo appears to have been maintained. Therefore, prognostic categorisation of the patients *a priori* does not provide a predictive marker for subpopulations of patients who do or do not benefit from trifluridine/tipiracil.

Additional prognostic factors in mCRC

An extensive literature review was undertaken to explore various plausible prognostic factors and their possible application to the RECOURSE population and fluoropyrimidine-based treatments to identify a sub-population who would most benefit from trifluridine/tipiracil. These assessments included the role of microsatellite instability and other tumour characteristics, e.g. *RAS* mutation status, *BRAF* mutation status, 18q deletion, proliferative activity and other molecular markers.

Currently, no predictive marker has been identified in the mCRC setting to clearly define subpopulations that would derive greater or less benefit from trifluridine/tipiracil.

4.9 Meta-analysis

Individual patient pooled analysis from Phase II and RECOURSE

A pooled analysis using individual patient data was conducted for the Phase II and RECOURSE trials, examining OS and PFS.

Method

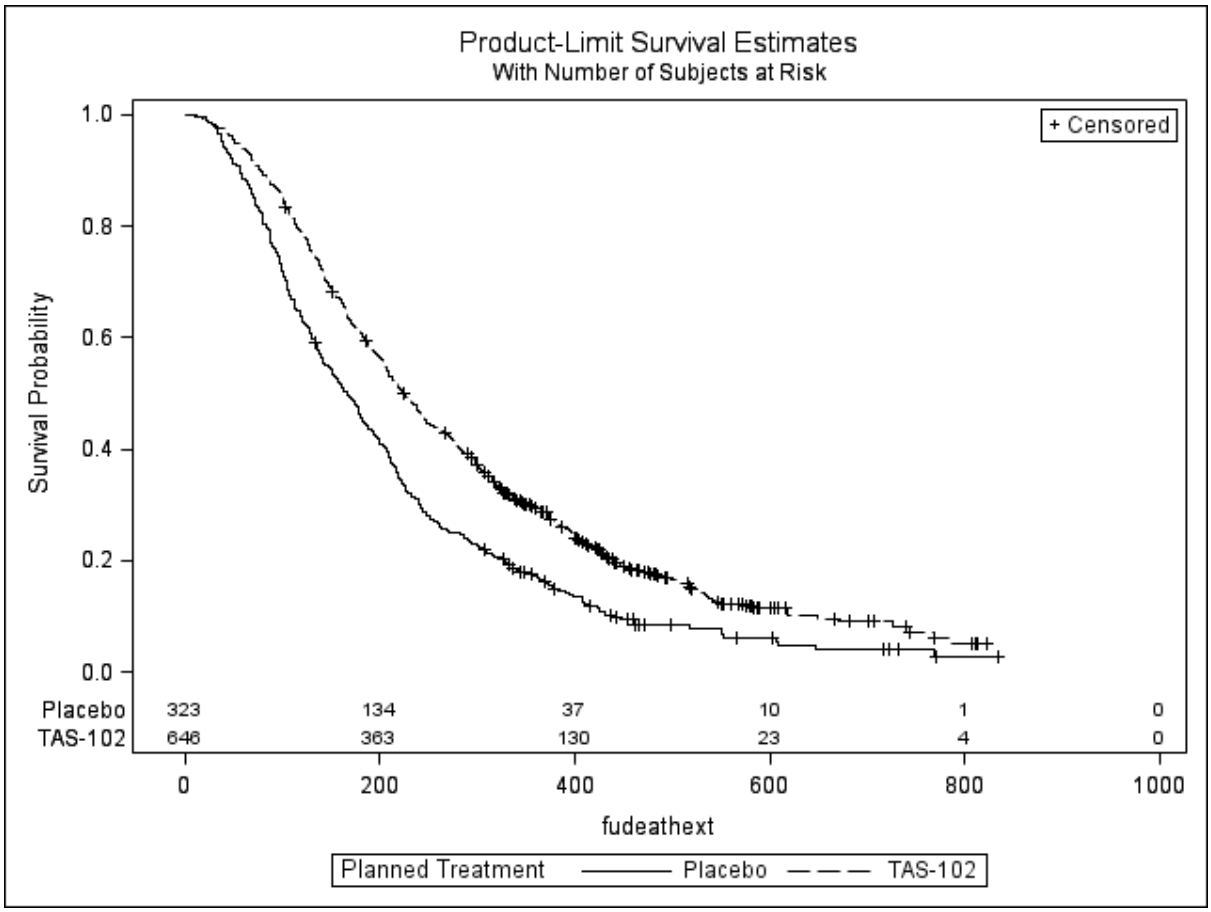
The published analyses were replicated for OS and PFS according to the methods described in the published papers.[2, 3] A pooled analysis was conducted using a log rank test and Kaplan-Meier survival curves described for patients randomised to trifluridine/tipiracil and placebo, combining the patients from both trials. The pooled analysis of OS was the primary analysis. Cox models were constructed for the pooled data set. For OS, the primary analysis, all available cases form RECOURSE were used; i.e., the 712 deaths reported in the latest data-cut in October 2014 (rather than the prespecified cut off for the RECOURSE primary outcome of 571 events).[11]

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). The assumption of constant proportional hazards was examined using the Assess statement in Proc PHREG.

Results

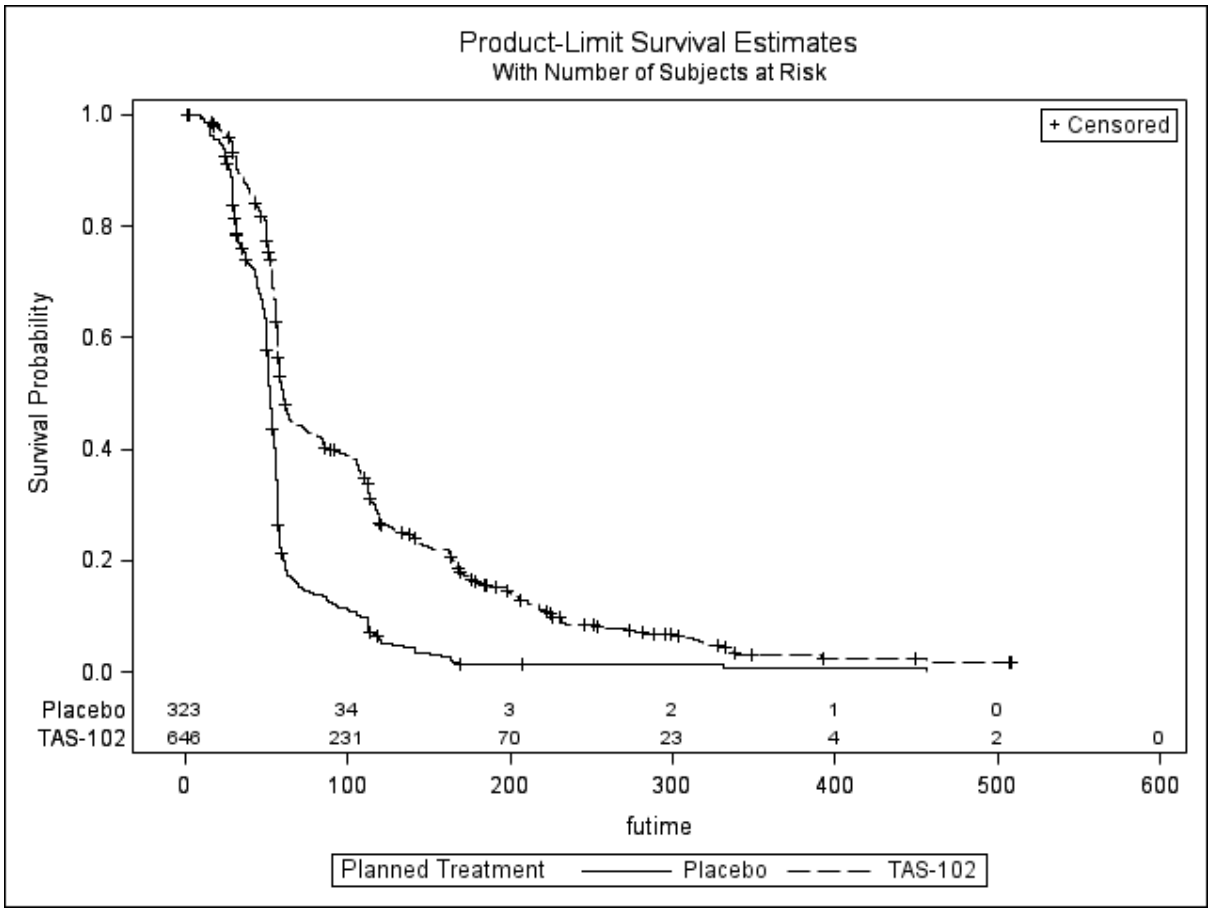
In total, 297/323 (92.0%) in the placebo group and 538/646 (83.3%) in the trifluridine/tipiracil group died. Mean follow-up death or censorship was 241.6 days. The corresponding numbers for progression were 300/323 (92.9%) in the placebo group, and 563/646 (87.2%) in the patients randomised to trifluridine/tipiracil. The Kaplan-Meyer survival curves by randomised group for the pooled data set for OS and PFS are described in Figure 25 and Figure 26, respectively.

Figure 25: Survival by randomised condition – overall survival



Key: OS, overall survival.

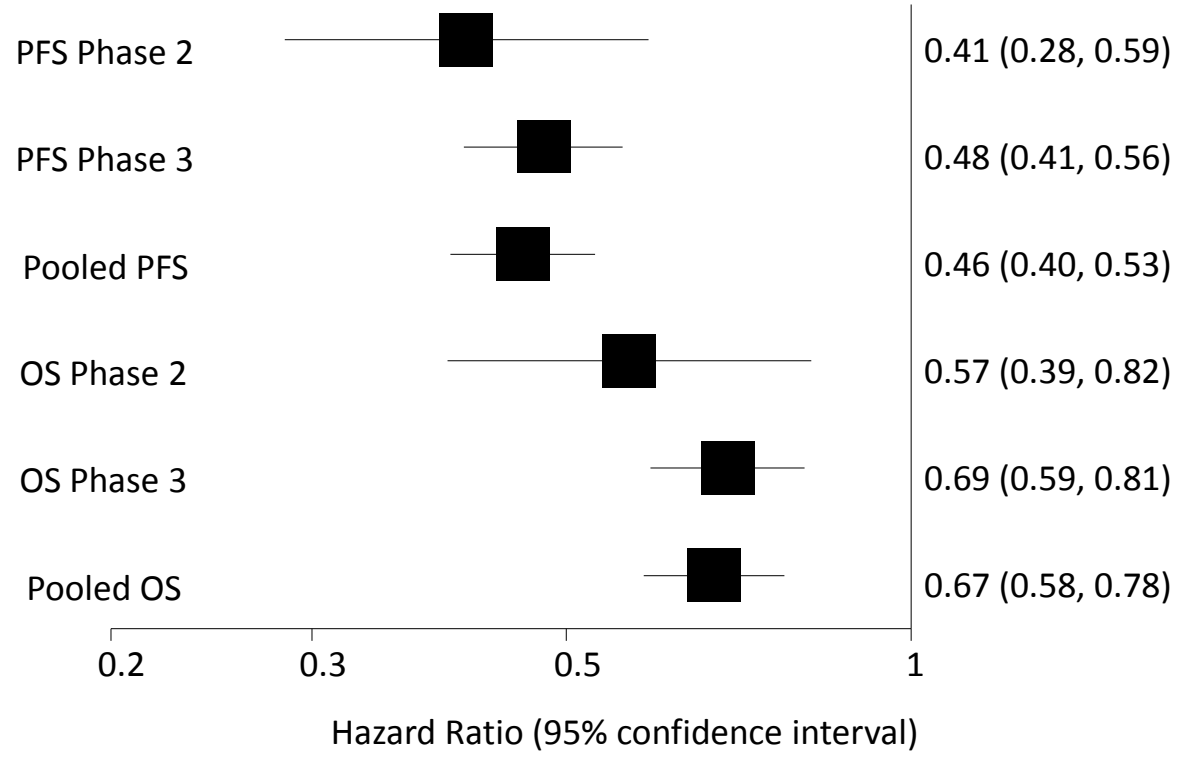
Figure 26: Survival by randomised condition – progression-free survival



Key: PFS, progression-free survival.

The hazard ratios for each trial and the pooled hazard ratios for OS and PFS are described in Figure 27. This forest plot clearly shows that there is no evidence of heterogeneity across the two trials.

Figure 27: Hazard ratio and 95% CI by trial and pooled overall survival and progression-free survival



Key: OS, overall survival; PFS, progression-free survival.

Note: Phase III is RECOURSE

The hazard ratios for the effects of randomisation to trifluridine/tipiracil on OS and PFS are described in Table 36. These demonstrate a 33% reduction in the risk of death and a 54% reduction in the risk of progression in heavily pre-treated and refractory patients with mCRC.

Table 36: Effects of randomisation to trifluridine/tipiracil or placebo

Outcome	Hazard ratio	Lower 95% CI	Upper 95% CI	P
OS	0.673	0.584	0.776	<0.0001
PFS	0.458	0.396	0.530	<0.0001

Key: OS, overall survival; PFS, progression-free survival.
Note: p-value derived from the log-rank test.

Summary

This analysis shows that the treatment effect of trifluridine/tipiracil is consistent across both trials for OS and PFS. The results show a significant reduction in the risk of death (HR 0.67; 95% CI 0.58 to 0.78; $p < 0.0001$) and progression (HR 0.46; 95% CI 0.40 to 0.53; $p < 0.0001$).

4.10 Indirect and mixed treatment comparisons

Not applicable to the decision problem for this appraisal.

4.11 Non-randomised and non-controlled evidence

Table 37: List of relevant non-randomised and non-controlled studies

Study number	Objective	Population	Intervention	Comparator	Primary study reference	Justification for inclusion
No study number. Kotani D et al. 2015[45]	To retrospectively investigate the characteristics and clinical outcomes of patients with mCRC in clinical practice	Patients with mCRC treated with trifluridine/tipiracil after standard therapies	Trifluridine/tipiracil	None	Kotani D et.al. Safety and efficacy of trifluridine/tipiracil monotherapy in clinical practice for patients with mCRC: experience at a single institution	Population relevant to the decision problem
No study number Muro K et al. 2015[46]	Post marketing surveillance. Safety monitoring as spontaneous ADR reports from attending clinicians	Patients with mCRC if they are refractory to all standard chemotherapies	Trifluridine/tipiracil	None	Muro K et al. Initial safety survey report from early post-marketing phase vigilance on trifluridine/tipiracil for mCRC	Population relevant to the decision problem
Key: ADR, adverse drug reaction; mCRC, metastatic colorectal cancer.						

4.11.1 Safety and efficacy of trifluridine/tipiracil monotherapy in clinical practice – Kotani et.al.

Patients and methods

The clinical records of patients with mCRC who had been treated with trifluridine/tipiracil after standard therapies at a Japanese clinic from May 2014 to January 2015 were examined.[45] All patients had presented with histologically confirmed colorectal adenocarcinoma. The retrospective study was conducted under an institutional review board waiver in accordance with the Japanese Ethical Guidelines for Epidemiological Research.

The baseline characteristics were collected for each patient as follows: age, sex, tumour histological type, ECOG PS, primary site, site of metastasis, number and regimen of previous treatments, time from the start of systemic chemotherapy, and status of *KRAS* exons 2, 3, and 4 and NRAS exons 2, 3, and 4, if available.

The dose intensity was defined as the cumulative dose (mg/m^2) divided by the number of weeks from initial treatment to discontinuation or the cut-off date. The relative dose intensity was defined as the dose intensity (mg/m^2 per week) divided by the regulated dose (175 mg/m^2 per week), similar to the dose used in the trifluridine/tipiracil pivotal clinical trials.[2, 3]

Given that this study is an observational, real-world study, descriptive statistics were used to help quantify some of the differences seen. Due to the nature of the retrospective analysis it is not possible to provide details of the patient flow.

Results

Patient characteristics and treatment

A total of 55 patients (median age, 66 years; range, 38-78 years; 27 men [49.1%]) with mCRC had received treatment with trifluridine/tipiracil during the study period. Of the 55 patients, 23, 26, and 6 had an ECOG PS of 0, 1, and 2, respectively. *KRAS* exon 2 wild-type and all *RAS* (*KRAS* exon 2, 3, and 4 and *NRAS* exon 2, 3, and 4) wild-type accounted for 33 (60.0%) and 26 (47.3%) patients, respectively. Of the 55 patients, 32 (58.2%) had been treated with regorafenib before receiving trifluridine/tipiracil. Almost all available agents, except for regorafenib, had been used before trifluridine/tipiracil treatment.

Initially, trifluridine/tipiracil was administered at the full dose in 53 patients (96.4%). Two patients started with reduced doses at the investigator's discretion. Ten patients (18.2%) required ≥1 dose reduction, mainly because of neutropenia. Twenty-three patients (41.8%) required a treatment delay of ≥4 days, predominantly because of neutropenia, with a median treatment delay of 7 days (range, 6-27 days). The mean dose intensity of trifluridine/tipiracil was 154.4 mg/m^2/week, and its relative dose intensity was 88.2%. The treatment after discontinuation of trifluridine/tipiracil was as follows: regorafenib for 8 (14.5%), clinical trials for 7 (12.7%), rechallenge with oxaliplatin and fluoropyrimidine for 1 (5.5%), and irinotecan combined with panitumumab for 1 patient (1.8%). Subsequent regorafenib treatment was given to 34.8% of patients without previous regorafenib treatment.

Safety

The safety profiles were evaluated for all 55 patients (Table 38). No Grade 4 non-haematological adverse events occurred. The most frequent Grade 3 or 4 adverse events were neutropenia, leucopenia, and anaemia. Twelve patients (21.8%) were given granulocyte colony-stimulating factor (G-CSF). Febrile neutropenia developed in 3 patients (5.5%), 2 of whom had a history of infection, including urinary or biliary tract infection, during previous treatment. Emergency hospital admission was required for 13 patients (23.6%). Of these events, 3 were associated with trifluridine/tipiracil treatment (febrile neutropenia, anaemia, or fatigue), but 10 were disease related. No treatment-related deaths occurred.

Table 38: Frequency of adverse events – Kotani et al.

Adverse events n (%)	Any Grade	Grade ≥3	Previous Regorafenib		No Previous Regorafenib	
			Any Grade	Grade ≥3	Any Grade	Grade ≥3
Haematological						
Neutropenia	35 (63.6)	23 (41.8)	16 (50.0)	12 (37.5)	19 (82.6)	11 (47.8)
Leucopenia	43 (78.2)	15 (27.2)	24 (75.0)	6 (18.8)	19 (82.6)	9 (39.1)
Anaemia	53 (96.4)	13 (23.6)	31 (96.9)	8 (25.0)	22 (95.7)	5 (21.7)
Thrombocytopenia	26 (47.3)	1 (1.8)	13 (40.6)	0	13 (56.5)	1 (4.3)
Non-haematological						
Fatigue	31 (56.4)	2 (3.6)	18 (56.3)	2 (6.3)	13 (56.5)	0
Anorexia	20 (36.4)	0	14 (43.8)	0	6 (26.1)	0
Nausea	16 (29.1)	0	10 (31.3)	0	6 (26.1)	0
Infection	7 (12.7)	3 (5.5)	6 (18.8)	2 (6.3)	2 (8.7)	1 (4.3)
Vomiting	4 (7.3)	0	4 (12.5)	0	0	0
Diarrhoea	3 (5.5)	0	2 (6.3)	0	1 (4.3)	0
Febrile neutropenia	3 (5.5)	3 (5.5)	1 (3.1)	1 (3.1)	2 (8.7)	2 (8.7)

Efficacy

The median interval from the start of trifluridine/tipiracil treatment to the first evaluation by computed tomography was 1.8 months. With a median follow-up of 6.0 months, the median PFS and OS were 2.0 months (95% CI 1.7 to 2.3 months) and 5.3 months (95% CI 3.5 to 7.2 months), respectively.

Among the 54 patients with measurable disease at baseline, 2 (3.7%) achieved a partial response (37.3% or 44.8% with tumour shrinkage, with a 6- or 5.8-month response duration, respectively). Eighteen patients had stable disease, seven were not evaluable by computed tomography because of clinical progressive disease in the investigator's judgment, and one was transferred to a different hospital.

The overall response rate and disease control rate (DCR), defined as complete response, partial response, or stable disease, were 3.7% and 37.0%, respectively.

Conclusion

The study findings have shown that the efficacy and safety of trifluridine/tipiracil monotherapy in patients with mCRC in a real-world setting was comparable to that seen in the RECOURSE trial.

4.11.2 Initial safety survey report

Details of the poster titled "Initial safety survey report from early post-marketing phase vigilance on trifluridine/tipiracil for metastatic colorectal cancer (mCRC)" are shown in Table 39.[46]

Given that this study was an observational, real-world study, descriptive statistics were used to help quantify some of the differences seen. Currently, these data are available only in poster format; therefore, we cannot comment on the patient flow through the study.

Table 39: Baseline characteristics for patients in post-marketing surveillance

Characteristics	N=3,420
Age (years)*	66 (24-92)
<70 ≧70	2149 1270
Sex	
Male	2065 (60.4%)
Female	1355 (39.6%)
ECOG performance status	
0 or 1	3,396 (99.3%)
2	21 (0.6%)
3	3 (0.1%)
Body Mass Index	21.9 (12.5-42.7) (kg/m^2)

Source: Safety survey report.[46]

In the post-marketing surveillance survey, 370 AEs were observed in 219 patients on the basis of spontaneous reports by attending physicians; these included 89 serious adverse events (SAEs) in 51 patients and 281 non-SAEs in 183 patients. A significant increase in either SAE or non-SAE in patients equal to or more than 70 years was not apparent compared to those in patients younger than 70 years. A total of 162 of 167 AEs (97.0%) were confirmed to have recovered or to be recovering.

The AEs and safety profile of trifluridine/tipiracil observed in this study in daily practice was similar to those from recent trifluridine/tipiracil RCTs.[2, 3] There were no unexpected safety signals.

Table 40: Number of adverse events during post-marketing surveillance

AEs	Number of AEs		
	Non-SAEs	SAEs	Total
Haematological			
Neutropenia	70	7	77
Leucopenia	25	3	28
Thrombocytopenia	14	9	23
Anaemia	12	8	20
Febrile neutropenia	1	18	19
Interactions	0	6	6
Others	5	7	12
Non-haematological			
Nausea	31	2	33
Anorexia	27	4	31
Diarrhoea	20	5	25
Fatigue	17	0	17
Vomiting	11	2	13
Interstitial lung disease	0	7	7
Others	48	11	59

Key: AE, adverse event; SAE, severe adverse event.
Source: Safety survey report.[46]

4.12 Adverse reactions

When comparing any treatment intended to improve survival to BSC, it is likely that active treatment will produce an increased number of AEs.

The prevalent AEs of trifluridine/tipiracil were consistent with the mechanism of action for fluoropyrimidines: bone marrow-related (anaemia, neutropenia, and thrombocytopenia) as well as gastrointestinal-related (nausea, vomiting, and diarrhoea). While these are significant AEs that affect quality of life, the majority of these events were mild to moderate, had limited impact on treatment continuity, were treated without requiring hospitalisation, and discontinuation rates were low.

The main AEs reported in the Phase II and RECOURSE trials are reported in Sections 4.12.1 and 4.12.2.

4.12.1 Phase II safety evaluation

Safety evaluation was performed for 170 patients (113 patients in the trifluridine/tipiracil group, 57 patients in the placebo group).[42] Adverse events were noted in 109 patients (96.5%) in the trifluridine/tipiracil group (95% CI 91.2 to 99.0) and in 40 patients (70.2%) in the placebo group (95% CI 56.6 to 81.6), $p < 0.0001$. There were no treatment-related deaths in this study, and there was no case of early death within 30 days after the start of study treatment either in the trifluridine/tipiracil or placebo group. SAEs were reported in 21 patients (18.6%) in the trifluridine/tipiracil group (95% CI 11.9 to 27.0) and in five patients (8.8%) in the placebo group (95% CI 2.9 to 19.3), $p = 0.116$. Thus, there was no significant difference between the number of SAEs reported in the trifluridine/tipiracil and placebo groups.

AE data for the Phase II trial (All events and Grade ≥3) are presented in Table 41 and Table 42

.

Table 41: Adverse events with a frequency of at least 3% in the safety population from the Phase II trial

All grades AE	Trifluridine/tipiracil			Placebo			ARR %	Lower 95% CI (%)	Upper 95% CI (%)	Relative risk	Lower 95% CI	Upper 95% CI
	n	Number of events	%	n	Number of events	%						
Neutropenia	113	81	71.7	57	1	1.8	-69.9	-79.0	-60.88171	40.858407	5.717671	291.97368
Leucopenia	113	86	76.1	57	2	3.5	-72.6	-81.5	-63.69497	21.690265	5.3799205	87.448804
Anaemia	113	82	72.6	57	9	15.8	-56.8	-68.5	-45.06592	4.5958702	2.3463402	9.0021143
Lymphopenia	113	39	34.5	57	7	12.3	-22.2	-34.5	-9.969509	2.8103666	1.2742619	6.1982238
Thrombocytopenia	113	44	38.9	57	1	1.8	-37.2	-47.5	-26.85969	22.19469	3.0746404	160.21525
Fatigue	113	66	58.4	57	24	42.1	-16.3	-31.2	-1.423903	1.3871681	0.8903895	2.1611164
Diarrhoea	113	43	38.1	57	12	21.1	-17.0	-30.6	-3.423503	1.8075221	0.9697142	3.3691744
Nausea	113	73	64.6	57	16	28.1	-36.5	-50.4	-22.71223	2.3014381	1.3674365	3.8733916
Anorexia	113	70	61.9	57	19	33.3	-28.6	-43.0	-14.26938	1.8584071	1.1440505	3.0188151
Febrile neutropenia	113	5	4.4	57	0	0.0	-4.4	-6.0	-2.869652	NE	NE	NE
Vomiting	113	38	33.6	57	14	24.6	-9.1	-22.5	4.3234027	1.369153	0.7553223	2.4818278

Keys: AE, adverse event; ARR, absolute risk reduction; CI, confidence interval; NE, not estimable.
Notes: Trial data from Yoshino et al. 2012.[3] Calculations not possible when absolute risk in placebo group = 0. Data are n (%). The safety population included all patients who received at least one dose of the study treatment.

Table 42: Adverse events Grade ≥3 with a frequency of at least 3% in the safety population from the Phase II trial

Grade ≥3 AE	Trifluridine/tipiracil			Placebo			*ARR %*	Lower 95% CI *(%)*	Upper 95% CI *(%)*	Relative risk	Lower 95% CI	Upper 95% CI
	n	Number of events	%	n	Number of events	%						
Neutropenia	113	57	50.4	57	0	0.0	-50.4	-59.6	-41.2	NE	NE	NE
Leucopenia	113	32	28.3	57	0	0.0	-28.3	-35.8	-20.9	NE	NE	NE
Anaemia	113	19	16.8	57	3	5.3	-11.6	-19.4	-3.7	3.2	1.0	10.7
Lymphopenia	113	11	9.7	57	2	3.5	-6.2	-11.7	-0.8	2.8	0.6	12.4
Thrombocytopenia	113	5	4.4	57	0	0.0	-4.4	-6.0	-2.9	NE	NE	NE
Fatigue	113	7	6.2	57	2	3.5	-2.7	-7.0	1.7	1.8	0.4	8.4
Diarrhoea	113	7	6.2	57	0	0.0	-6.2	-8.3	-4.1	NE	NE	NE
Nausea	113	5	4.4	57	0	0.0	-4.4	-6.0	-2.9	NE	NE	NE
Anorexia	113	5	4.4	57	2	3.5	-0.9	-4.7	2.9	1.3	0.2	6.5
Febrile neutropenia	113	5	4.4	57	0	0.0	-4.4	-6.0	-2.9	NE	NE	NE
Vomiting	113	4	3.5	57	0	0.0	-3.5	-4.8	-2.3	NE	NE	NE

Keys: AE, adverse event; ARR, absolute risk reduction; CI, confidence interval; NE, not estimable.
Notes: Trial data from Yoshino et al. 2012.[3] Calculations not possible when absolute risk in placebo group = 0. Data are n (%). The safety population included all patients who received at least one dose of the study treatment.

4.12.2 Phase III safety evaluation – RECOURSE

The overall incidence of adverse events was similar for the trifluridine/tipiracil and placebo treatment groups (98.3% and 93.2%, respectively), while the incidence of treatment-related AEs was higher in the trifluridine/tipiracil group than in the placebo group (85.7% and 54.7%, respectively), as was the incidence of Grade ≥3 AEs (69.4% and 51.7%, respectively). However, there were favourable trends in the differences between the trifluridine/tipiracil and placebo groups with respect to incidence of SAEs (29.6% and 33.6%, respectively), AEs/SAEs listed as the primary reason for discontinuation of study treatment (3.6% and 1.5%, respectively) and fatal AEs (3.2% and 11.3%, respectively).

Adverse event data for RECOURSE (All events and Grade ≥3) are presented in Table 43 and Table 44.

Table 43: All adverse events within RECOURSE published data

All grades AE*	Trifluridine/tipiracil			Placebo			ARR %	Lower 95% CI (%)	Upper 95% CI (%)	Relative risk	Lower 95% CI	Upper 95% CI
	n	Number of events	%	n	Number of events	%						
Any event	533	524	98.3	265	247	93.2	-5.1	-8.7	-1.5	1.1	1.0	1.1
Any serious event	533	158	29.6	265	89	33.6	3.9	-9.4	17.3	0.9	0.7	1.1
Nausea†	533	258	48.4	265	63	23.8	-24.6	-38.9	-10.3	2.0	1.6	2.6
Vomiting†	533	148	27.8	265	38	14.3	-13.4	-25.0	-1.8	1.9	1.4	2.7
Decreased appetite†	533	208	39.0	265	78	29.4	-9.6	-23.8	4.6	1.3	1.1	1.6
Fatigue†	533	188	35.3	265	62	23.4	-11.9	-25.4	1.6	1.5	1.2	1.9
Diarrhoea†	533	170	31.9	265	33	12.5	-19.4	-31.4	-7.5	2.6	1.8	3.6
Abdominal pain†	533	113	21.2	265	49	18.5	-2.7	-13.5	8.1	1.1	0.8	1.5
Fever†	533	99	18.6	265	37	14.0	-4.6	-14.3	5.1	1.3	0.9	1.9
Asthenia†	533	97	18.2	265	30	11.3	-6.9	-16.2	2.4	1.6	1.1	2.4
Febrile neutropenia**	533	20	3.8	265	0	0.0	-3.8	-5.1	-2.4	0	0	0
Stomatitis**	533	43	8.1	265	17	6.4	-1.7	-7.3	4.0	1.3	0.7	2.2
Hand-foot syndrome**	533	12	2.3	265	6	2.3	0.0	-2.6	2.6	1.0	0.4	2.6
Cardiac ischaemia** ‡	533	2	0.4	265	1	0.4	0.0	-0.9	0.9	1.0	0.1	10.9
Neutropenia§	528	358	67.8	263	2	0.8	-67.0	-76.1	-58.0	89.2	22.4	355.1
Leucopenia§	528	407	77.1	263	12	4.6	-72.5	-81.5	-63.5	16.9	9.7	29.4
Anaemia§	528	404	76.5	263	87	33.1	-43.4	-55.7	-31.2	2.3	1.9	2.8
Thrombocytopenia§	528	223	42.2	263	21	8.0	-34.3	-46.5	-22.0	5.3	3.5	8.1
Increase in alanine aminotransferase level§	526	126	24.0	263	70	26.6	2.7	-9.4	14.7	0.9	0.7	1.2

All grades AE*	Trifluridine/tipiracil			Placebo			ARR %	Lower 95% CI (%)	Upper 95% CI (%)	Relative risk	Lower 95% CI	Upper 95% CI
	n	Number of events	%	n	Number of events	%						
Increase in aspartate aminotransferase level§	524	115	21.9	262	91	34.7	12.8	0.8	24.8	0.6	0.5	0.8
Increase in total bilirubin§	526	186	35.4	262	69	26.3	-9.0	-22.7	4.7	1.3	1.1	1.7
Increase alkaline phosphatase level§	526	205	39.0	262	118	45.0	6.1	-8.7	20.8	0.9	0.7	1.0
Increase in creatinine level§	527	71	13.5	263	32	12.2	-1.3	-9.5	6.9	1.1	0.7	1.6

Key: AE, adverse event; ARR, absolute risk reduction; CI, confidence interval.
Notes: Trial data from Mayer et al. 2015.[2]
* All adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
† Adverse events of any grade that are listed as most common occurred in 10% or more of patients in the trifluridine/tipiracil group and in a greater percentage in that group than in the placebo group.
** Events associated with fluoropyrimidine treatment.
‡ Events included acute myocardial infarction, angina pectoris, and myocardial ischaemia.
§ The denominator for the percentage of patients with laboratory abnormalities is the number of patients with at least one post baseline measurement during treatment.

Table 44: Adverse events Grade ≥3 within RECOURSE published data

Grade ≥3 AE	Trifluridine/tipiracil			Placebo			*ARR %*	Lower 95% CI *(%)*	Upper 95% CI *(%)*	Relative risk	Lower 95% CI	Upper 95% CI
	n	Number of events	%	n	Number of events	%						
Any event	533	370	69.4	265	137	51.7	-17.7	-31.5	-3.9	1.3	1.2	1.5
Nausea†	533	10	1.9	265	3	1.1	-0.7	-2.7	1.2	1.7	0.5	6.0
Vomiting†	533	11	2.1	265	1	0.4	-1.7	-3.2	-0.2	5.5	0.7	42.1
Decreased appetite†	533	19	3.6	265	13	4.9	1.3	-2.5	5.2	0.7	0.4	1.4
Fatigue†	533	21	3.9	265	15	5.7	1.7	-2.5	5.9	0.7	0.4	1.3
Diarrhoea†	533	16	3.0	265	1	0.4	-2.6	-4.4	-0.8	8.0	1.1	59.7

Grade ≥3 AE	Trifluridine/tipiracil			Placebo			*ARR %*	Lower 95% CI *(%)*	Upper 95% CI *(%)*	Relative risk	Lower 95% CI	Upper 95% CI
	n	Number of events	%	n	Number of events	%						
Abdominal pain†	533	13	2.4	265	10	3.8	1.3	-1.8	4.5	0.6	0.3	1.5
Fever†	533	7	1.3	265	1	0.4	-0.9	-2.2	0.3	3.5	0.4	28.1
Asthenia†	533	18	3.4	265	8	3.0	-0.4	-3.6	2.9	1.1	0.5	2.5
Febrile neutropenia**	533	20	3.8	265	0	0.0	-3.8	-5.1	-2.4	NE	NE	NE
Stomatitis**	533	2	0.4	265	0	0.0	-0.4	-0.5	-0.2	NE	NE	NE
Cardiac ischemia** ‡	533	1	0.2	265	1	0.4	0.2	-0.6	1.0	0.5	0.0	7.9
Neutropenia§	528	200	37.9	263	2	0.8	-37.1	-46.8	-27.4	49.8	12.5	199.0
Leucopenia§	528	113	21.4	263	12	4.6	-16.8	-25.5	-8.1	4.7	2.6	8.3
Anaemia§	528	96	18.2	263	87	33.1	14.9	3.8	26.0	0.5	0.4	0.7
Thrombocytopenia§	528	27	5.1	263	21	8.0	2.9	-2.2	7.9	0.6	0.4	1.1
Increase in alanine aminotransferase level§	526	10	1.9	263	70	26.6	24.7	18.7	30.7	0.1	0.0	0.1
Increase in aspartate aminotransferase level§	524	23	4.4	262	91	34.7	30.3	23.1	37.6	0.1	0.1	0.2
Increase in total bilirubin§	526	45	8.6	262	69	26.3	17.8	9.6	26.0	0.3	0.2	0.5
Increase alkaline phosphatase level§	526	42	8.0	262	118	45.0	37.1	28.4	45.7	0.2	0.1	0.2
Increase in creatinine level§	527	5	0.9	263	32	12.2	11.2	6.9	15.5	0.1	0.0	0.2

Key: AE, adverse event; ARR, absolute risk reduction; CI, confidence interval; NE, not estimable.
Notes: Trial data from Mayer et al. 2015.[2] Calculations not possible when absolute risk in placebo group = 0.
* All adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
† Adverse events of any grade that are listed as most common occurred in 10% or more of patients in the trifluridine/tipiracil group and in a greater percentage in that group than in the placebo group.
** Events associated with fluoropyrimidine treatment.
‡ Events included acute myocardial infarction, angina pectoris, and myocardial ischaemia.
§ The denominator for the percentage of patients with laboratory abnormalities is the number of patients with at least one post baseline measurement during treatment.

Table 45 represents the overall safety/tolerability and clinical outcome impact for trifluridine/tipiracil therapy.[19] Considering the increased treatment exposure in the trifluridine/tipiracil group (mean of 13 weeks in trifluridine/tipiracil vs 7 weeks in placebo), the exposure-adjusted treatment-related AE incidence is shown based on a 100 patient-years exposure rate. Excluding neutropenia and thrombocytopenia, all other differences in AE rates between the two groups are reduced once adjusted for the degree of exposure.

Table 45: Overall safety/tolerability and clinical outcome impact for trifluridine/tipiracil therapy

Adverse event	Treatment-related incidence rate (%) All/Grade ≥3		Exposure-adjusted incidence rate[a] All/Grade ≥3		Clinical events outcome: hospitalisation		Impact on therapy continuity no. of pts. D/C	
	Trifluridine/ tipiracil	Placebo	Trifluridine/ tipiracil[b]	Placebo[c]	Trifluridine/ tipiracil	Placebo	Trifluridine/ tipiracil	Placebo
Anaemia	31.5/12.2	4.5/1.9	98.2/38.0	21.7/9.0	2.10%	0	2	0
Neutropenia	28.7/20.1	0	89.5/62.6	0.0/0.0	0.60%	0	1	0
Thrombocytopenia	5.6/1.7	0.4/0.4	17.5/5.3	1.8/1.8	0.40%	0	0	0
Diarrhoea	23.6/2.3	9.1/0.0	73.7/7.0	43.4/0.0	0.80%	0	2	1
Nausea	39.4/0.9	10.9/0.0	122.8/2.9	52.4/0.0	0.60%	0	1	0
Vomiting	20.1/0.6	4.5/0.0	62.6/1.8	21.7/0.0	1.10%	0	2	0

Key: D/C, discontinuing therapy; pts, patients.
Notes: [a] Incidence rate is calculated as patients/100 patient years; [b] For trifluridine/tipiracil, patient years = 171.0; [c] For placebo, patient years = 55.3. patient years = total days of safety exposure (first dose through last dose + 30 days) from all patients in the group combined divided by 365.25.
Source: Taiho Pharmaceutical Company Ltd, 2015[19]

Dose reductions and delays in cycle initiation

In total, 73 (13.7%) patients in the trifluridine/tipiracil group had at least one dose reduction during treatment. Adverse events leading to dose reduction were reported for 72 of these patients. The most frequent AEs leading to dose reduction in the trifluridine/tipiracil group were neutropenia (17, 3.2%), anaemia (11, 2.1%), decreased neutrophil count (10, 1.9%), febrile neutropenia (10, 1.9%), fatigue (8, 1.5%), and diarrhoea (7, 1.3%). In the placebo group, 3 (1.1%) patients had a single dose reduction, with 2 reporting AEs leading to dose reduction (1 anaemia; 1 bronchopneumonia). However, across all cycles, 94.4% (503/533) of patients in the trifluridine/tipiracil group and 93.6% (248/265) of patients in the placebo group received ≥80% of their target cycle dose.

Across all cycles, 289 (54.2%) patients in the trifluridine/tipiracil group had AEs that resulted in interruptions in dosing, dose delays and/or dose reductions compared to 36 (13.6%) patients in the placebo group. In the trifluridine/tipiracil group, the most frequent AEs leading to interruptions/delays and/or dose reductions were decreased neutrophil count (109 patients, 20.5%), neutropenia (106 patients, 19.9%), and anaemia (29 patients, 5.4%). In the placebo group, the most frequent AEs leading to these outcomes (in at least 3 patients) were decreased appetite (5 patients, 1.9%) and pyrexia (3 patients, 1.1%). Table 46 below summarises the main reasons for cycle delays, with the top four groups accounting for more than 85% of delays.

Clinical experts have reported that interruptions in dosing, dose delays and/or dose reductions are common in patients receiving chemotherapy for mCRC as well as other cancers.[4] They have indicated that the data presented are in line with what they would expect for patients receiving treatment for mCRC at third line and beyond.

Table 46: Main reasons for cycle delays within RECOURSE

	AE All grades (n)	%	AE Grade ≥3 (n)	%
Blood and lymphatic system disorders	106	48.0	78	62.4
Gastrointestinal disorders	29	13.1	14	11.2
General disorders and administration site conditions	28	12.7	5	4
Infections and infestations	24	10.9	9	7.2
Hepatobiliary disorders	9	4.1	4	3.2
Metabolism and nutrition disorders	9	4.1	6	4.8
Renal and urinary disorders	4	1.8	2	1.6
Nervous system disorders	3	1.4	2	1.6
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2	0.9	1	0.8
Vascular disorders	2	0.9	2	1.6
Cardiac disorders	1	0.5	1	0.8
Injury, poisoning and procedural complications	1	0.5	0	0
Musculoskeletal and connective tissue disorders	1	0.5	1	0.8
Psychiatric disorders	1	0.5	0	0
Reproductive system and breast disorders	1	0.5	0	0
Total AEs	221		125	

Key: AE, adverse event.

Note: Patients could have more than one AE. Groups shown in shaded rows account for more than 85% of delays.

Source: RECOURSE CSR.[12]

4.12.3 Other considerations

The CHMP assessor noted that gastrointestinal AEs (diarrhoea, nausea and vomiting) were potentially undertreated in RECOURSE.[19]

Diarrhoea

Diarrhoea is a condition that can impact a patient's quality of life. The overall incidence of diarrhoea for all grades was higher in the trifluridine/tipiracil arm compared with placebo, as well as for Grade 3 or higher, although the incidence was 3%. The protocol did not require prophylactic therapy.

The reported use of concomitant anti-diarrhoeal drugs for diarrhoea was low, at approximately 40% in the overall population, while approximately 75% of patients who had Grade 3/4 diarrhoea received treatment. Nonetheless, only 2 patients discontinued trifluridine/tipiracil due to diarrhoea during the study; (one on placebo; Table 14.3.1.3 RECOURSE CSR)[12], indicating that the vast majority of patients were able to tolerate and manage the diarrhoea caused by trifluridine/tipiracil.

Nausea and vomiting

Nausea and vomiting are other side effects that can affect quality of life. Concomitant use for anti-emetics was low at approximately 30% in the overall population, while approximately 50% in the patients who experienced Grade 3 or higher nausea or vomiting received therapy. However, only three patients discontinued trifluridine/tipiracil due to nausea or vomiting (Table 14.3.1.3 RECOURSE CSR).[12]

The above findings are consistent with the overall finding that only 3.6% of trifluridine/tipiracil patients discontinued their therapy primarily due to adverse effects compared to 1.5% on placebo.

In conclusion, the use of anti-symptomatic therapeutic measures for nausea, vomiting, and diarrhoea in RECOURSE was relatively low. Therefore, an appropriate and earlier utilisation of anti-symptomatic drugs may further reduce the incidence and/or severity of these side effects.

4.13 Interpretation of clinical effectiveness and safety evidence

Treatments that confer a survival benefit are needed in patients with heavily pre-treated mCRC.[3] Patients with mCRC at third line and beyond have a life expectancy of approximately 6 months.[1-3, 5] Currently, no treatments are recommended by NICE or the CDF to treat patients at this stage of the disease, and therefore, BSC is the only available option. Discussion with clinical experts has determined that clinicians who wish to provide further treatment to patients at this line of therapy may give capecitabine or chemotherapy re-challenge. However, neither have an evidence base to support usage in patients who are refractory to 5-FU or other chemotherapy-based regimens. This is the group of patients relevant to the decision problem for this appraisal.

The evidence for the effectiveness and safety of trifluridine/tipiracil comes from one of the largest international multi-centre trials in advanced mCRC performed to date. It is supported by a Phase II trial in a similar patient population of mCRC patients which was the trial used for registration purposes in Japan. In these heavily pre-treated populations, it is very rare to see complete or partial response to therapy.[4] Therefore, the emphasis will be on maintenance of stable disease, a clinically meaningful increase in OS within the context of expected overall survival and a treatment that can be managed from a tolerability perspective. Both trials were conducted in a patient population that is relevant to the decision problem for this appraisal and are consistent with the proposed marketing authorisation. The meta-analysis presented in Section 4.9 demonstrates that the treatment effect of trifluridine/tipiracil is consistent across both trials for both OS and PFS.

Trifluridine/tipiracil improves OS when compared to BSC in patients with advanced mCRC; within RECOURSE, the median was 1.8 months (7.1 vs 5.3 months; HR 0.68; 95% CI 0.58 to 0.81, $p < 0.0001$). An updated survival analysis based on a data-cut off of October 2014 confirmed that the OS benefits were maintained, with improvement in median OS increasing to 2 months (7.2 vs 5.2 months: HR 0.69; 95% CI 0.59 to 0.81; $p < 0.0001$). Survival modelling calculations presented in this submission (Section 5.3.3) estimate that the mean survival gain for RECOURSE patients is 3.0 months (Trifluridine/tipiracil 10.7 months; 95% CI 9.8 to 11.7 and placebo 7.7 months; 95% CI 6.8 to 8.8). When combining individual patient data from

Phase II and RECOURSE, the mean gain in survival increases to 3.2 months (Trifluridine/tipiracil 11.1 months; 95% CI 10.2 to 12.0 and placebo 7.9 months; 95% CI 7.0 to 8.8). This demonstrated ability to extend mCRC patients' lives at such a late stage of the disease offers a real therapeutic option for patients who currently only have BSC (treatments to help manage the side effects and symptoms of cancer) as an alternative, giving patients at the end of their life approximately a 50% gain in life expectancy. The improvement in survival at 1 year surpasses 10% (27.1% vs 16.6% for trifluridine/tipiracil and placebo, respectively) which represents a relative improvement of over 60%. Results from the trials also showed that patients treated with trifluridine/tipiracil experienced a delay in tumour growth (PFS) compared to those not receiving the compound.[2, 3] The PFS in RECOURSE had a HR of 0.48 (95% CI 0.41 to 0.57; $p < 0.0001$), and there was a significant difference in disease control rate (DCR) between the trifluridine/tipiracil and placebo groups of 27.7% (95% CI 21.5 to 34.0; $p < 0.0001$). These clinically meaningful efficacy outcomes are mainly driven by disease stabilisation.

The mortality risk reduction and prolongation of survival with trifluridine/tipiracil were consistent among all patient subgroups based on stratification factors, baseline disease characteristics, and demographics except in instances where small sample sizes within a subgroup precluded meaningful estimates. Consistent with the primary mechanism of action of trifluridine/tipiracil, which differs from that of conventional fluoropyrimidines, a significant increase in OS was demonstrated in patients who were refractory to conventional fluoropyrimidines received as part of their last regimen prior to randomisation.

A potential limitation of the RECOURSE trial is that patients were required to have received chemotherapy with bevacizumab prior to entry into the trial. Recent changes to the CDF-approved list and NICE guidance means that patients in England would not be able to receive bevacizumab prior to treatment with trifluridine/tipiracil.[5, 32] A number of patients in the Phase II trial had not received bevacizumab or cetuximab (22% and 37%, respectively), which have recently been delisted from the CDF (along with panitumumab) and are therefore not available for this line of treatment in England. These data provide insight into the efficacy of trifluridine/tipiracil in patients who have received all NICE recommended, available chemotherapy, but who have not necessarily received biological agents and

demonstrate that efficacy is maintained. This was discussed with clinical experts at a recent advisory board, and the feedback was that tumours in patients who had received fewer treatment options were likely to be less resistant to additional therapy.[4]

The statistical methods used in the Phase II and RECOURSE trials, both in terms of design and analysis, are correct and valid for each study in question. RECOURSE is representative of Western populations; within the study, 271 of patients receiving trifluridine/tipiracil were from the EU, which was the largest geographical group in the trial. Additionally, RECOURSE demonstrated that trifluridine/tipiracil is effective in all subgroups of patients with no evidence of treatment heterogeneity of any subgroup either for OS or PFS. Although the Phase II trial was performed in a Japanese population, there is no evidence to suggest that trifluridine/tipiracil shows different activity in different patient populations (Section 4.8). Therefore, the results are generalisable and relevant to the decision problem.

The combination of trifluridine/tipiracil provides an innovative method to administer trifluridine, which has not previously been available orally due to its rapid degradation. The accessibility of this compound for terminally ill patients with mCRC in England would add to the treatment options available for these patients. Trifluridine/tipiracil will provide patients another medication to fight their cancer and extend survival, and if positively appraised, it will represent the only available evidence-based chemotherapy in third-line treatment for patients. The mean OS gain (3.2 months for the pooled analysis and 3.0 for RECOURSE) represents a significant survival gain for patients with a life expectancy of approximately 6 months, which is an important gain for patients receiving end-of-life treatment.

Trifluridine/tipiracil is generally well tolerated; the most common Grade ≥3 adverse event in clinical trials was myelosuppression, which was managed with treatment delays, dose reductions and, rarely, growth factor support. This adverse event profile is also mirrored in clinical practice, as seen from real-world use in Japan and the US, where trifluridine/tipiracil has been used in more than 12,000 patients with mCRC to date. Despite the addition of new therapy at this late stage in treatment of terminally ill patients, there was no increase in hospitalisations for patients treated with trifluridine/tipiracil compared to placebo, demonstrating its tolerability.

4.13.1 End of life

The patients relevant to the decision problem for this appraisal have a life expectancy of substantially less than 6 months. Evidence for end-of-life criteria is provided in Table 47.

Table 47: End-of-life criteria

<table>
<tr><th>Criterion</th><th>Data available</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>1. Final appraisal determination NICE TA242, Section 4.4.19.[5]
“For metastatic colorectal cancer that has progressed after first-line treatment, the Committee agreed that the technologies fulfil the first criterion related to life expectancy, because estimates of life expectancy from people randomised to best supportive care in the second-line setting were less than 12 months”
2. Hoyle et al. 2013[1]
Describes the cost-effectiveness analysis of cetuximab, cetuximab plus irinotecan, and panitumumab for third and further lines of treatment for KRAS wild-type patients with mCRC. This reports a mean OS for BSC of 0.51 years (6.2 months)
3. Mean OS (RECOURSE[2])
The mean OS in the BSC arm was 0.64 years (7.7 months)
4. Mean OS pooled analysis (RECOURSE and Yoshino[3])
The mean OS in the BSC arm was 0.66 years (7.9 months)</td></tr>
<tr><td>There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment</td><td>The estimates of OS are based on mature survival data. The proportion of patients who had died in the RECOURSE and Phase II trials were 89.0% and 72.9%, respectively.[3, 11]
1. Mean OS - Pooled analysis
<table>
<tr><th></th><th>Days</th><th>Months</th></tr>
<tr><td>Trifluridine/tipiracil</td><td>338</td><td>11.1</td></tr>
<tr><td>BSC</td><td>240</td><td>7.9</td></tr>
<tr><td>Incremental</td><td>98</td><td>3.2</td></tr>
</table>
2. Mean OS (RECOURSE)
<table>
<tr><th></th><th>Days</th><th>Months</th></tr>
<tr><td>Trifluridine/tipiracil</td><td>326</td><td>10.7</td></tr>
<tr><td>BSC</td><td>234</td><td>7.7</td></tr>
<tr><td>Incremental</td><td>92</td><td>3.0</td></tr>
</table></td></tr>
<tr><td>The treatment is licensed or otherwise indicated for small patient populations</td><td>1. Section 3.4.2 and Section 6.1
Based on the epidemiological data that are available for mCRC and expert clinical opinion, it is estimated that approximately 2,600 patients may receive further active therapy at third line or beyond (i.e. where trifluridine/tipiracil may be considered). Currently, this</td></tr>
</table>

Criterion	Data available
	treatment comprises capecitabine, chemotherapy re-challenge or clinical trials 2. Market research Pharmacor (Decision Resources Group) determined that the number of patients in the UK with mCRC (*KRAS* wild-type and *KRAS* mutation-positive) who would be treated at third line or beyond was 2,490. Further details of the survey are available in Appendix 5.
Key: BSC, best supportive care; mCRC, metastatic colorectal cancer; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival.	

4.14 Ongoing studies

Trifluridine/tipiracil has an active and on-going clinical development programme. In the current indication, a study in Chinese and South East Asian patients (TERRA – ClinicalTrials.gov identifier: NCT01955837) was due for completion at the end of 2015, with a clinical study report estimated to be available in summer 2016. This study mirrors RECOURSE, but in a different geographical setting. Given the efficacy across all ethnicities and populations in which trifluridine/tipiracil has been tested in to date, we anticipate that the results from this study will mirror those of RECOURSE in terms of efficacy and adverse events.

5 Cost effectiveness

5.1 Published cost-effectiveness studies

A systematic review of the published literature was conducted to identify cost-effectiveness studies assessing the treatment of patients with mCRC with trifluridine/tipiracil compared with BSC as third-line or later treatment.

The following electronic databases were searched on the 26 October 2015: Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, EMBASE (Ovid), and the Cochrane library (Ovid), consisting of the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, the NHS Economic Evaluation Database (NHS EED), the Database of Abstracts of Reviews of Effects (DARE), and HTA.

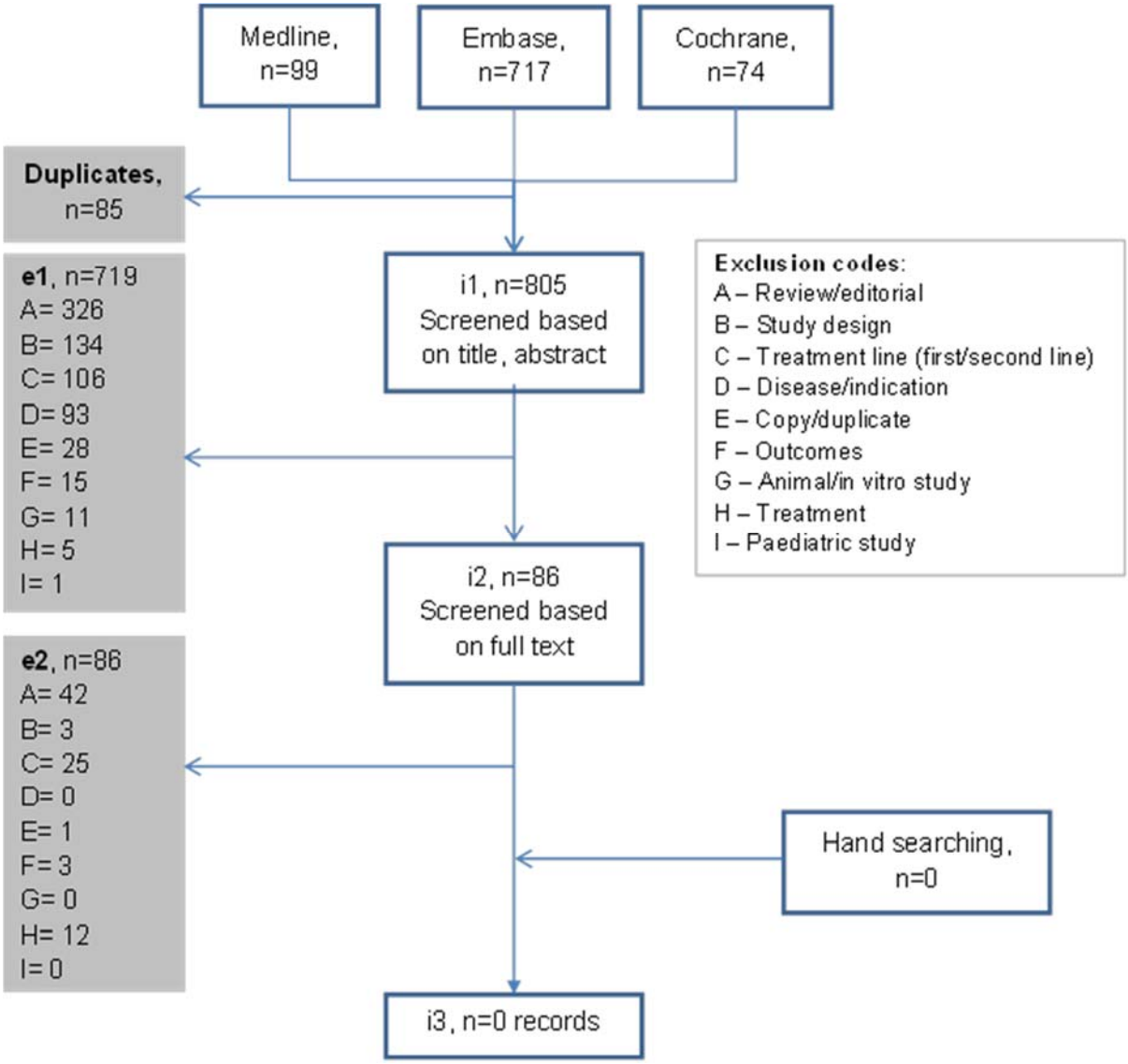
Electronic searches were supplemented by hand searching reference lists of included publications and conference proceedings. Any relevant abstracts identified through the electronic database search or supplementary hand searching were checked for available associated posters.

Full details of the search are provided in Appendix 6.

In total, 890 papers were identified through the electronic searches. Upon the removal of duplicate papers, 805 titles and abstracts were reviewed. Eighty-six were ordered for full paper review, all of which were excluded, resulting in no relevant papers for final inclusion (Figure 28).

No additional relevant publications were identified via hand searching.

Figure 28: Schematic for the systematic review of cost-effectiveness evidence



5.2 De novo analysis

5.2.1 Patient population

In accordance with the anticipated licence, trifluridine/tipiracil is 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 chemotherapy, anti-VEGF biological therapies, and anti-EGFR therapies.[7] This is reflective of the population discussed in the decision

problem and the scope, as well as in the clinical trials from which efficacy data are derived to inform the model (discussed in Section 4.7).

As a result of this licence, it is expected that trifluridine/tipiracil will be given from third line, because patients will have received prior therapy, as discussed in Section 3.3.

5.2.2 Model structure

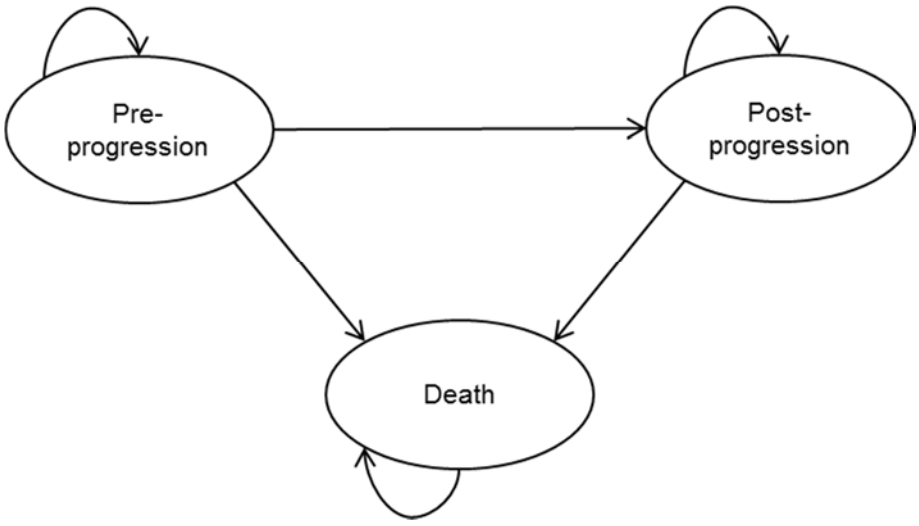
A partitioned-survival (area under the curve) model was constructed in Microsoft Excel® consisting of the following health states:

- Pre-progression
- Post-progression
- Death

Model health states were selected in accordance with the clinical pathway of care (discussed further in Section 3.3) and are comparable to the structure used in other late-stage cancer models. This structure is identical for patients treated with trifluridine/tipiracil or comparator therapies as the structure is based on disease progression.

The possible routes patients may flow through the model are presented in Figure 29.

Figure 29: Model structure



The likelihood of patients transitioning between the health states is determined via PFS curves that are fitted to the clinical trial data. All patients enter the model in the 'Pre-progression' health state and remain in this state until disease progression or death. Patients are not permitted to transition from the 'Post-progression' to the 'Pre-progression' health state. Patients are able to transition to the 'Dead' state from any other health state. The model operates on a daily cycle length to ensure the accuracy of survival estimates, which is particularly important given the extremely poor prognosis of patients, and means that a half-cycle correction is not required.

Table 48: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	10 years	Lifetime horizon – after this time <1% of patients are alive.
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case[47]
Discount of 3.5% for utilities and costs	Yes	
Perspective (NHS/PSS)	NHS	
Key: NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; QALYs, quality-adjusted life years.		

5.2.3 Intervention technology and comparators

The intervention, trifluridine/tipiracil, is implemented in the model as per the expected marketing authorisation and is reflective of the decision problem described in Section 1.1. Trifluridine/tipiracil is an orally administered combination of trifluridine, a thymidine-based nucleic acid analogue, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride. Trifluridine/tipiracil is administered at a dose of 35mg/m^2 twice daily, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period. This treatment cycle is repeated every 4 weeks.[7]

The comparator considered in this economic evaluation is BSC. Currently, there is no recommended treatment for patients covered by the anticipated licence for trifluridine/tipiracil, hence the choice of primary comparator for the economic evaluation. This is consistent with the comparator used in the pivotal Phase III trial RECOURSE and the Phase II trial.[2, 3] A sensitivity analysis is also provided

comparing trifluridine/tipiracil to regorafenib, which although licensed, is not recommended by NICE or the CDF for mCRC.

As per the RECOURSE trial protocol and the anticipated licence, treatment with trifluridine/tipiracil is continued until the determination of RECIST-defined disease progression, clinical progression, the development of severe adverse events, withdrawal from the study, death, or a decision by the treating physician that discontinuation would be in the patient's best interest.[2, 48]

5.3 Clinical parameters and variables

Clinical data from the pivotal Phase III trial RECOURSE and the Phase II trial were used to inform the model base case. Both trials were multicentre, double-blind and randomised-controlled trials in which patients were assigned in a 2:1 ratio to receive trifluridine/tipiracil or placebo, along with BSC.[2, 3]

Data utilised from the trial include:

- PFS
- OS
- Time on treatment (ToT) (incorporation of treatment delay, RECOURSE only)
- Body surface area (BSA) (used for drug costing, RECOURSE only)
- Dose reductions (used for drug costing, RECOURSE only)
- AE rates (RECOURSE only)

5.3.1 Efficacy data

Within the model, efficacy data may be derived from the following sources:

- The Phase III trial (RECOURSE)
- The Phase II trial
- Pooled data from both trials.

In the model base case, pooled data from both trials was selected as the source of efficacy data in the interest of utilising the maximum amount of data, as both trials were multicentre, randomised, placebo-controlled registration studies with very

similar protocols and thus both are relevant to the decision problem. Notably both trials also randomised 2:1, with the pooling of studies therefore providing a meaningful increase in the number of placebo-treated subjects.

Parametric survival curves were fitted to trial data to determine the probability of a patient experiencing an event over time (i.e. progression or death) in line with the NICE DSU guidelines.[49] Survival data are relatively mature (89.0 % in RECOURSE and 72.9% in the Phase II); however, extrapolation allowed long-term estimates of treatment effects to be appropriately implemented into the model. The best-fitting curves were identified via visual inspection, Akaike Information Criterion (AIC) scores and plausibility of long-term outcomes.

Two types of curve fits were produced: unstratified by treatment and stratified by treatment. The unstratified curves included a covariate for treatment within the model, whereas the stratified curves were stratified by treatment such that two separate curve fits were produced.

5.3.2 Progression-free survival

A variety of curve fits were applied to the PFS data in the model. The AIC goodness of fit statistics are presented in Table 49.

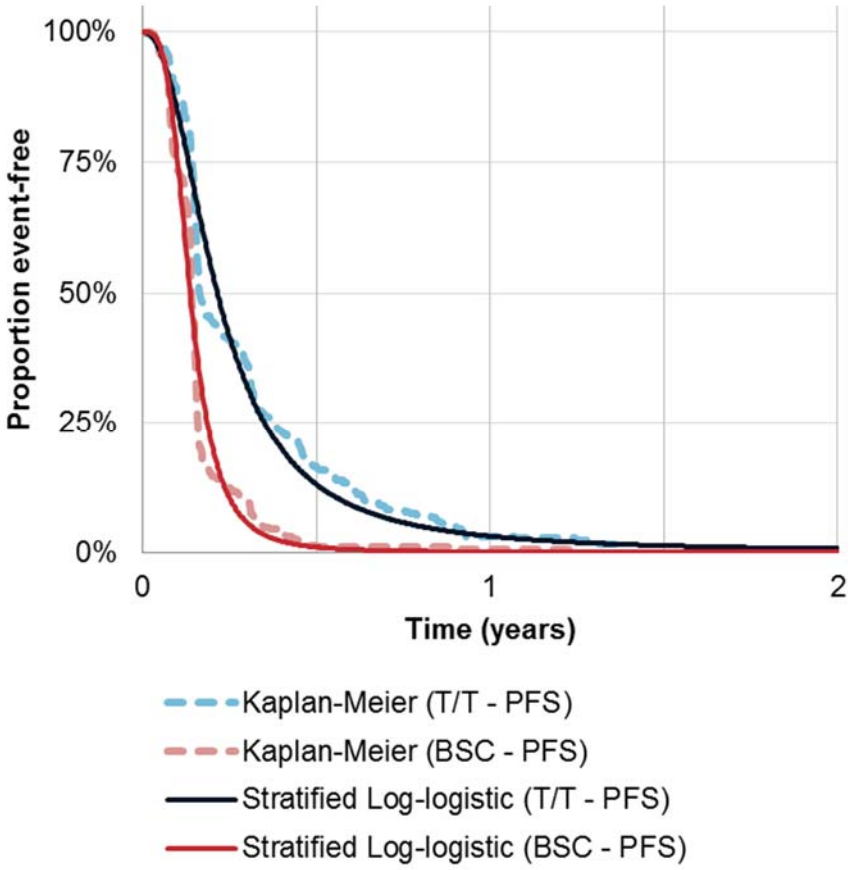
Table 49: Progression-free survival – goodness of fit statistics

Model	AIC
Stratified log-logistic	9,331
Stratified generalised gamma	9,352
Stratified log-normal	9,356
Log-logistic	9,385
Generalised gamma	9,403
Log-normal	9,407
Stratified Weibull	9,589
Weibull	9,607
Stratified Gompertz	9,754
Gompertz	9,759
Exponential	9,773
Extreme value	9,855
Stratified extreme value	9,857
Key: AIC, Akaike Information Criterion.	

From these goodness of fit statistics, the stratified log-logistic distribution demonstrates the best statistical fit while also having a good visual fit, and was used in the model base case (Figure 30).

Alternative curve fits were explored in sensitivity analysis, with complete curve fits presented in Appendix 7. Due to the completeness of the Kaplan-Meier data the choice of curve fit does not significantly impact the ICER. The 5 next best fitting alternative curve fits producing ICERs within ±8% of the base case ICER (ICERs presented in Section 5.8.3).

Figure 30: Progression-free survival – chosen curve fits (2 years)



Key: BSC, best supportive care; PFS, progression-free survival; T/T, trifluridine/tipiracil.

5.3.3 Overall survival

Two options exist for the choice of OS from RECOURSE in the model:

- Original OS
- Updated OS

The primary analysis (original OS) included survival follow-up data obtained from randomisation through to the date of the 571st death observed in the study. If a patient was still alive after the 571st death date, they were censored in the primary analysis. Updated OS considers the time from randomisation through to the last known alive date (with no capping at the 571st death date), which gives additional data on patients.

In the model base case, the updated OS is used, which has an additional 138 deaths, with 89% of the cohort having died. The choice of OS source only affects the OS from RECOURSE; therefore, if the pooled population is selected, the OS from the Phase II trial remains unchanged (i.e. there is only one data cut available). Sensitivity analyses are presented using the original data for completeness, and in comparison with the published trial data (although the results do not change noticeably).

A variety of curve fits were applied to the OS data in the model. The curve fits and the respective AIC goodness of fit statistics are presented in Table 50.

Table 50: Overall survival – goodness of fit statistics

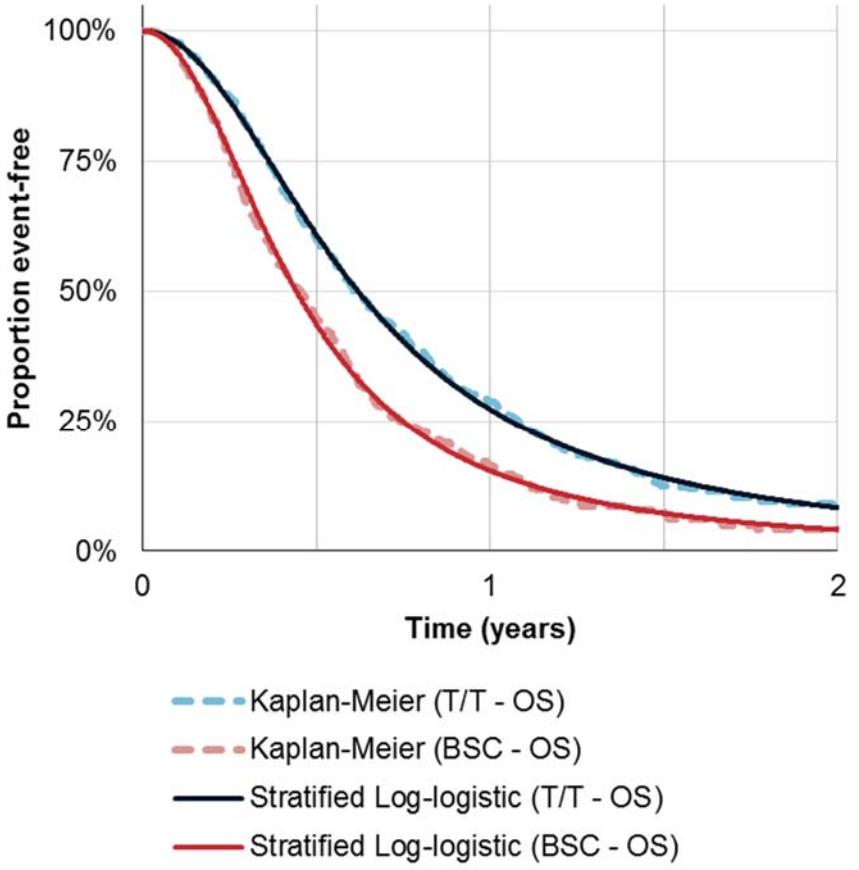
Model	AIC
Log-logistic	10,896
Stratified log-logistic	10,898
Generalised gamma	10,899
Stratified generalised gamma	10,901
Log-normal	10,903
Stratified log-normal	10,905
Weibull	10,957
Stratified Weibull	10,958
Gompertz	11,040
Stratified Gompertz	11,041
Stratified extreme value	11,060
Extreme value	11,063
Exponential	11,079
Key: AIC, Akaike Information Criterion.	

From these goodness of fit statistics, both the log-logistic and stratified log-logistic curves demonstrate the best statistical fit, with regards to AIC. However, the stratified log-logistic distribution shows a better visual fit for both OS and PFS, as it was the chosen curve for PFS and demonstrates very small differences in the estimation of OS. Given that within both trials randomisation was not equal (2:1), it may also be considered more appropriate to utilise stratified curves.

For consistency with PFS, while also maintaining good visual and statistical fit, the stratified log-logistic model was used in the model base case (its AIC is only 2 worse than unstratified log-logistic, the best fitting AIC). These curve fits are shown in Figure 31 and Figure 32.

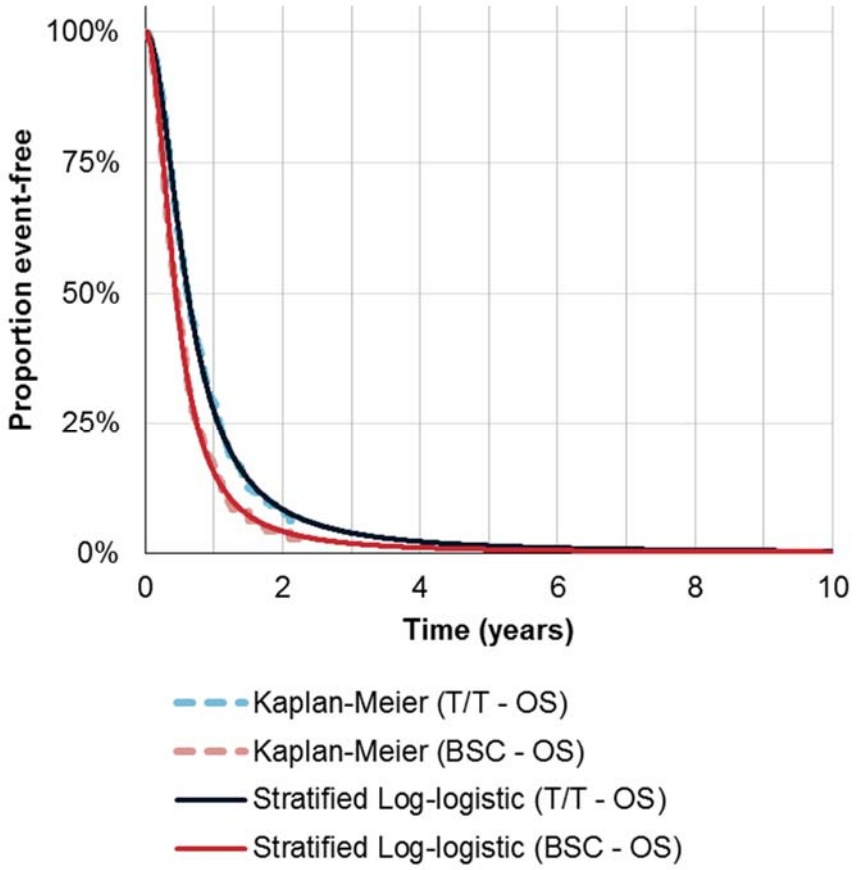
Alternative relatively well fitting curve fits were explored in sensitivity analysis, with curve fits presented in Appendix 7. As previously mentioned, due to the completeness of the Kaplan-Meier data the choice of curve fit does not significantly impact the ICER. The 5 next best fitting alternative curve fits producing ICERs within ±8% of the base case ICER (ICERs presented in Section 5.8.3).

Figure 31: Overall survival – chosen curve fits (2 years)



Key: BSC, best supportive care; OS, overall survival; T/T, trifluridine/tipiracil.

Figure 32: Overall survival – chosen curve fits (10 years)



Key: BSC, best supportive care; OS, overall survival; T/T, trifluridine/tipiracil.

It is noted that the long-term plausibility of the log-logistic distribution should be justified given that the curves typically predict long tails, which may not be clinically justified in some disease areas. However, Kaplan-Meier data are mature (with approximately 10% (T/T) and 5% (BSC) of patients still alive at the end of each curve); therefore, even if this is the case, OS would not be vastly over-predicted.

Table 51 shows the proportion of patients predicted to be alive on both trifluridine/tipiracil and BSC at 2, 5, 8 and 10 years.

Table 51: Proportion of patients alive at different time points in the model

Treatment	Percentage of patients alive at			
	2 years	5 years	8 years	10 years
Trifluridine/tipiracil	8.34%	1.37%	0.53%	0.33%
Best supportive care	4.11%	0.63%	0.24%	0.15%

From published data, it can also be seen that 5-year survival for patients diagnosed with Stage IV colorectal cancer (CRC) is 7-8%.[50] The average time for all patients from diagnosis to study initiation was 35.2 months (i.e. approximately 3 years).[51] The predicted survival at 2 years for patients in the model (using the extrapolated log-logistic curve) are given in Table 51, and are therefore consistent with these published figures.

The proportions of patients alive on BSC in the model at this time are slightly lower than those reported in the published data, since these data consider time from diagnosis rather than time from initiation of third-line treatment. Therefore, the extrapolated figures demonstrate lower proportions alive at coincidental time points as expected, demonstrating face validity in regards to the expected prognosis of patients in this setting.

The results of the survival analysis are presented in Table 52 and Table 53.

Table 52: Mean overall survival – pooled analysis

Treatment	Trifluridine/tipiracil	BSC	Difference
Mean OS	11.1 months	7.9 months	3.2 months
95% CI	(10.2-12.0)	(7.0-8.8)	
Key: BSC, best supportive care; CI, confidence interval; OS, overall survival.			

Table 53: Mean overall survival – RECOURSE

Treatment	Trifluridine/tipiracil	BSC	Difference
Mean OS	10.7 months	7.7 months	3.0 months
95% CI	(9.8-11.7)	(6.8-8.8)	
Key: BSC, best supportive care; CI, confidence interval; OS, overall survival.			

5.3.4 Time on treatment

ToT was not explicitly reported in either of the clinical trials from which efficacy data were derived. Therefore, to estimate ToT, PFS was adjusted according to delays in treatment initiation. By adjusting PFS in this way, the average treatment cycle length considered in the model incorporates both the duration of the anticipated treatment cycle (as defined by the clinical trial protocols) as well as the mean average delay in treatment initiation per cycle.

Treatment with trifluridine/tipiracil is continued until disease progression, clinical progression, the development of severe adverse events (AEs), withdrawal from the study, death, or a decision by the treating physician that discontinuation would be in the patient's best interest.[2] It is noted that not all of these factors have been included in our estimation of ToT due to lack of available data, and we would therefore consider our derivation of ToT to be an over-estimate of the observed ToT.

In addition to informing our estimation of ToT, the incorporation of treatment delays into the model facilitated the implementation of additional medical resource use for patients who experience a delay in treatment. This additional medical resource use applies for all patients, regardless of treatment received, and therefore, the average delay in treatment initiation was calculated for both trifluridine/tipiracil and BSC patients.

Trifluridine/tipiracil is administered at a dose of 35mg/m^2 twice daily, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period. This regimen is repeated every 4 weeks.[2, 7] To account for delays in treatment initiation, the average treatment delay was added to the anticipated treatment cycle length of 28 days.

In total, there were 752 cycles of treatment for patients on trifluridine/tipiracil in which a treatment delay was experienced, out of 1,828 total cycles of treatment received. The average delay in starting treatment, given that a patient has experienced a delay, was 6.61 days. Therefore, the average delay in trifluridine/tipiracil treatment initiation per treatment cycle was calculated as shown below:

$$\frac{(n\ of\ delayed\ cycles * average\ delay) + (n\ of\ non-delayed\ cycles * 0)}{Total\ n\ of\ cycles}$$

This process was repeated for treatment with placebo in the RECOURSE trial to obtain an average treatment delay for patients on BSC in the model.

The average delay in treatment initiation per cycle experienced by patients in the model is given in Table 54.

Table 54: Average delay in treatment initiation

	Trifluridine/tipiracil	BSC
Total number of cycles	1828	598
Total number of delayed cycles	752	228
Average delay in treatment initiation for delayed patients	6.61 days	3.67 days
Average delay in treatment initiation for all patients (A)	2.72 days	1.40 days
Protocol treatment cycle length (B)	28 days	28 days
Applied treatment cycle length in model (A+B)	30.72 days	29.40 days

5.3.5 Body surface area

The dosing of trifluridine/tipiracil is based on patient BSA, and therefore, estimation of the distribution around patient BSA for patients with late-stage mCRC was required. BSA was taken from clinical trial data to inform the dosing of trifluridine/tipiracil in the model.

Patients were categorised into the groups shown in Table 55 and dosed accordingly. The distribution of BSA used in the model base case was derived from a log-normal fit to the distribution of BSA in the RECOURSE trial, to produce a more realistic estimate of the distribution of patient BSA. The non-parameterised distribution of BSA from RECOURSE was also explored, as well as the application of a log-normal fit of BSA from general population data, both of which were explored as scenario analyses.[52]

Clinicians at the advisory board indicated that patients with mCRC would be expected to lose weight, given their disease status, and therefore agreed with the use of a lower estimate of BSA compared with the general population particularly at the line of treatment relevant to the decision problem.[4]

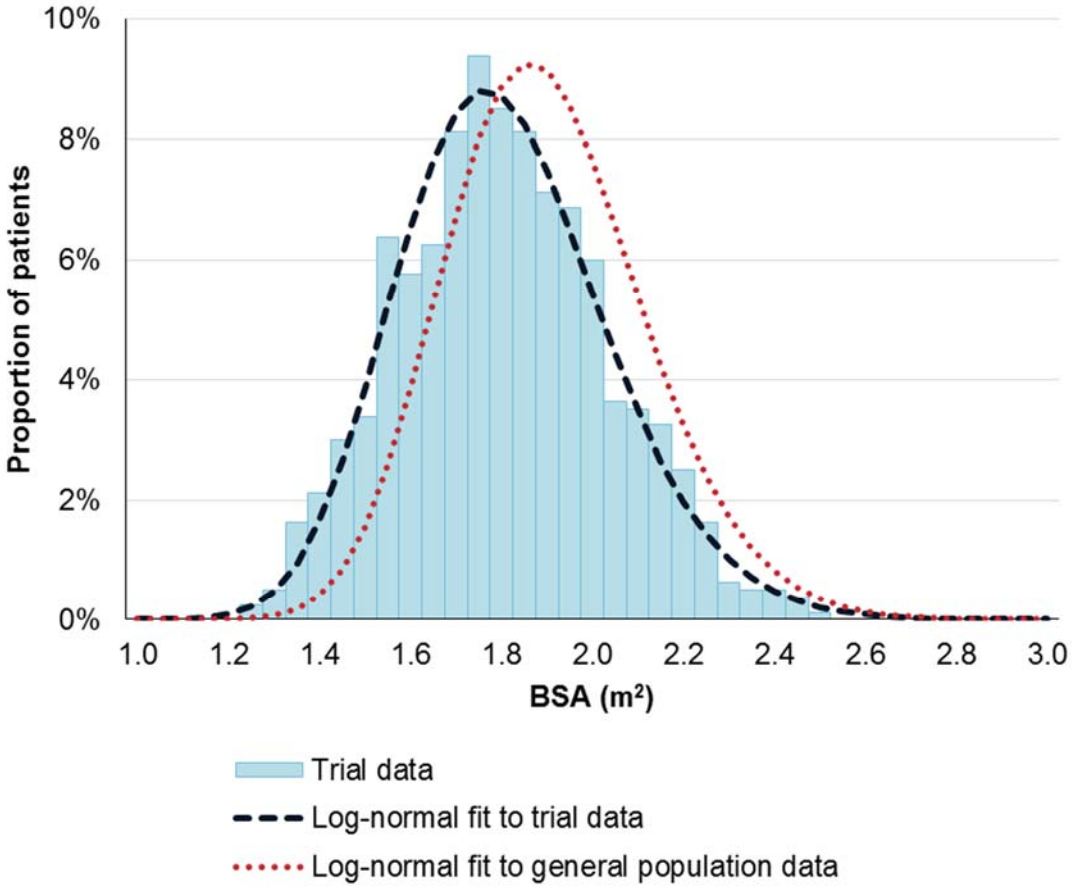
Table 55: Dosing of trifluridine/tipiracil

BSA (m^2)	Distribution of BSA		
	RECOURSE data	Log-normal fit to RECOURSE data	Log-normal fit to general population data*
< 1.07	0.00%	0.00%	0.00%
1.07 - 1.22	0.13%	0.19%	0.01%
1.23 - 1.37	2.38%	2.15%	0.39%
1.38 - 1.52	9.25%	9.55%	3.58%
1.53 - 1.68	19.88%	22.47%	14.70%
1.69 - 1.83	27.00%	25.97%	25.26%
1.84 - 1.98	21.38%	20.57%	26.14%
1.99 - 2.14	12.63%	12.13%	18.35%
2.15 - 2.29	5.75%	4.72%	7.82%
≥2.30	1.63%	2.25%	3.75%

Key: BSA, body surface area.
Notes: *General population data applies to Health Survey for England data sourced by Porter et al. 2015.[52]

The distributions of BSA are shown in Figure 33.

Figure 33: Distribution of body surface area



Key: BSA, body surface area.

5.3.6 Dose reductions

In the RECOURSE trial, 53 (9.9%) patients treated with trifluridine/tipiracil had a single dose reduction, 18 (3.4%) had two reductions, and two (0.4%) had three reductions.[12] To account for these dose reductions, the proportion of patients receiving each dose for a given treatment cycle was adjusted in the subsequent treatment cycles.

All patients were expected to receive the dose of trifluridine/tipiracil based on BSA in the first cycle of treatment. After this, 9.9% of patients from each dosing group were moved down to the dosing group below for the second cycle of treatment. This process was repeated for the third and fourth cycles (moving 3.4% and 0.4% of patients, respectively), after which it was assumed that all patients remained on their current dose until discontinuation of treatment. It is expected that some patients may

have their dose reduced by more than this amount, but there are no data available to estimate dose reductions in clinical practice.

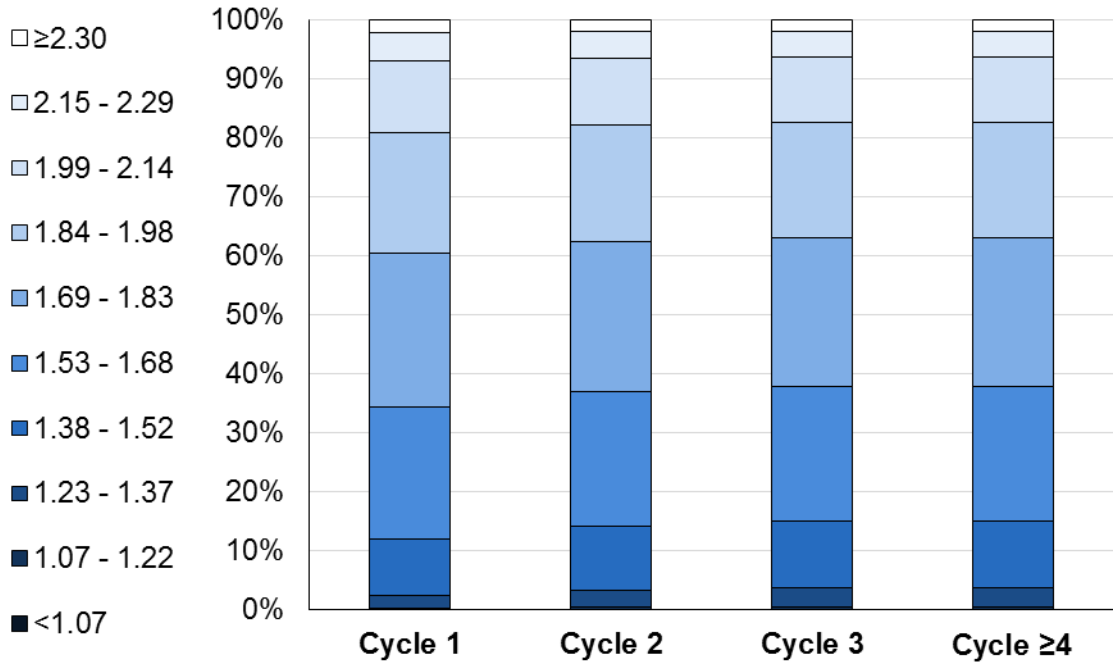
The proportion of patients receiving each dose of trifluridine/tipiracil per cycle are shown in Table 56. The proportion of patients receiving each dose of trifluridine/tipiracil in the first treatment cycle is taken from the log-normal fit to BSA data from the RECOURSE trial, as shown previously.

Table 56: Proportion of patients receiving trifluridine/tipiracil

Dosage (mg; 2x daily)	Cycle 1	Cycle 2	Cycle 3	Cycle 4+
35	0.00%	0.02%	0.04%	0.04%
40	0.19%	0.38%	0.47%	0.48%
45	2.15%	2.88%	3.15%	3.18%
50	9.55%	10.83%	11.24%	11.28%
55	22.47%	22.82%	22.91%	22.91%
60	25.97%	25.44%	25.25%	25.22%
65	20.57%	19.73%	19.45%	19.42%
70	12.13%	11.40%	11.16%	11.14%
75	4.72%	4.47%	4.39%	4.38%
80	2.25%	2.03%	1.96%	1.95%

To demonstrate the effect of applying dose reductions in the model, these data are also shown in Figure 34.

Figure 34: Proportion of patients receiving trifluridine/tipiracil by BSA category



Key: BSA, body surface area.

5.3.7 Adverse event rates

All common AEs recorded in RECOURSE were included in the model. AEs were classified as "common" if they occurred in 10% or more of patients receiving trifluridine/tipiracil, and in a higher proportion of these patients compared with BSC patients.[2] AEs and their associated rates of incidence in the RECOURSE trial are presented in Table 57.

Table 57: Adverse events in RECOURSE

AE	T/T (n = 533)				BSC (n = 265)			
	Any grade		Grade ≥3		Any grade		Grade ≥3	
	n	%	n	%	n	%	n	%
Any event	**524**	**98.3%**	**370**	**69.4%**	**247**	**93.2%**	**137**	**51.7%**
Any serious event	**158**	**29.6%**			**89**	**33.6%**		
Nausea	258	48.4%	10	1.9%	63	23.8%	3	1.1%
Vomiting	148	27.8%	11	2.1%	38	14.3%	1	0.4%
Decreased appetite	208	39.0%	19	3.6%	78	29.4%	13	4.9%
Fatigue	188	35.3%	21	3.9%	62	23.4%	15	5.7%

AE	T/T (n = 533)				BSC (n = 265)			
	Any grade		Grade ≥3		Any grade		Grade ≥3	
	n	%	n	%	n	%	n	%
Any event	**524**	**98.3%**	**370**	**69.4%**	**247**	**93.2%**	**137**	**51.7%**
Any serious event	**158**	**29.6%**			**89**	**33.6%**		
Diarrhoea	170	31.9%	16	3.0%	33	12.5%	1	0.4%
Abdominal pain	113	21.2%	13	2.4%	49	18.5%	10	3.8%
Fever	99	18.6%	7	1.3%	37	14.0%	1	0.4%
Asthenia	97	18.2%	18	3.4%	30	11.3%	8	3.0%
Febrile neutropenia	20	3.8%	20	3.8%	0	0.0%	0	0.0%
Stomatitis	43	8.1%	2	0.4%	17	6.4%	0	0.0%
Hand-foot syndrome	12	2.3%	0	0.0%	6	2.3%	0	0.0%
Cardiac ischaemia	2	0.4%	1	0.2%	1	0.4%	1	0.4%
Neutropenia	358/ 528	67.8%	200/ 528	37.9%	2/ 263	0.8%	2/ 263	0.8%
Leucopenia	407/ 528	77.1%	113/ 528	21.4%	12/ 263	4.6%	12/ 263	4.6%
Anaemia	404/ 528	76.5%	96/ 528	18.2%	87/ 263	33.1%	87/ 263	33.1%
Thrombocytopenia	223/ 528	42.2%	27/ 528	5.1%	21/ 263	8.0%	21/ 263	8.0%
Increase in alanine aminotransferase level	126/ 526	24.0%	10/ 526	1.9%	70/ 263	26.6%	70/ 263	26.6%
Increase in aspartate aminotransferase level	115/ 524	21.9%	23/ 524	4.4%	91/ 262	34.7%	91/ 262	34.7%
Increase in total bilirubin	186/ 526	35.4%	45/ 526	8.6%	69/ 262	26.3%	69/ 262	26.3%
Increase alkaline phosphatase level	205/ 526	39.0%	42/ 526	8.0%	118/ 262	45.0%	118/ 262	45.0%
Increase in creatinine level	71/ 527	13.5%	5/ 527	0.9%	32/ 263	12.2%	32/ 263	12.2%

Key: AE, adverse event; BSC, best supportive care; T/T, trifluridine/tipiracil.

The cost of treating adverse events is applied in the first cycle of the model as a one-off lump sum. These costs are discussed further in Section 5.5.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality of life data from clinical trials

Health-related quality of life (HRQL) data were not collected in either the Phase II trial or RECOURSE. In lieu of this, a systematic review was undertaken to obtain HRQL data from published literature.

5.4.2 Health-related quality of life studies

Identification of studies

A systematic review was conducted to identify HRQL studies from the published literature relevant to the decision problem; in particular, studies reporting EQ-5D health state utility values (in line with the NICE preferred method) relating to patients with advanced/mCRC receiving third-line treatment or beyond were considered eligible for inclusion.

The following electronic databases were searched: Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, EMBASE (Ovid), and the Cochrane Library (Ovid), consisting of the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), HTA, and NHS EED.

Electronic searches were supplemented by hand searching references of included publications and conference proceedings. Any relevant abstracts identified through the electronic database search or supplementary hand searching were checked for available associated posters.

Full details of the search are provided in Appendix 10.

In total, 547 papers were identified through the electronic searches. Upon the removal of duplicate papers, 464 titles and abstracts were reviewed. Twenty-eight were ordered for full paper review, of which 24 were excluded, resulting in four relevant papers for final inclusion (Figure 35).

No additional relevant publications were identified via hand searching. A full list of studies excluded on the basis of full publication review is available in Appendix 13 along with a rationale for exclusion.

Studies that met the inclusion criteria of the review

One study was presented as a full publication[53], and three were presented as abstracts[54-56], with one also having an available associated poster.[57] Countries from which the HRQL data were derived in the included studies include Canada (n = 2)[53, 57] and China (n = 1).[55] One study was multi-national and derived HRQL data from 16 countries in North America, Europe, Asia and Australia (4).[56]

The study populations in all four included studies consisted of adult patients with advanced/metastatic CRC. The line of therapy was clearly third-line and beyond in two studies.[55, 56] In two studies, HRQL data were based on patients from the CO.17 study and were reported to have advanced refractory disease.[53, 57] In the CO.17 trial, 18.2% of patients had received one or two previous lines of chemotherapy for metastatic disease, and the remaining 81.8% of patients had received ≥3 lines of previous chemotherapy.[58] These populations contained a proportion of patients being treated at second-line, albeit a minority; it is therefore unclear if the results from these studies are fully representative of the population of interest.[53, 57]

Interventions investigated in the studies included: cetuximab versus BSC alone (as part of the CO.17 trial) (n = 2)[53, 57] and regorafenib versus placebo (n = 2).[56] Utilities were measured at baseline, and at 4, 8, 16, and 24 weeks after randomisation in one study.[53] Utilities were expressed as least squares mean time-adjusted area under the curve (AUC) to represent the change in HRQL across the treatment period in two studies[55, 56]; however, it is unclear over what time period the change in utilities occurred. In one study, the follow-up period was not reported.[57]

Utilities were derived from the EQ-5D in two studies[55, 56], in line with the NICE reference case, and with the HUI3 in one study.[53] One study reported the use of a mapping algorithm to derive HUI3 utilities from the EORTC-QLQ-C30 and/or patient baseline characteristics.[57] Multivariable linear regression was used to construct the algorithm using stepwise selection. The regression analysis showed that HUI3 was significantly associated with four of the five functional scales, the pain scale, and the general health status scale of the EORTC-QLQ-C30. The mapping algorithm, consisting of these six scales, resulted in a model with an adjusted R2 of 0.61, leave-one-out-cross-validation mean error of -0.00014, mean absolute error of 0.11, and root mean squared error of 0.15.

The method of valuation was not clear in any of the included studies; as three included studies were abstracts, this may be due to limited reporting.

The results of the four included studies are provided in Table 58, and a summary of the relevance of the studies to the NICE reference case is provided in Table 59. Quality assessment of the included studies is provided in Appendix 13.

Figure 35: Schematic for the systematic review of health-related quality of life evidence

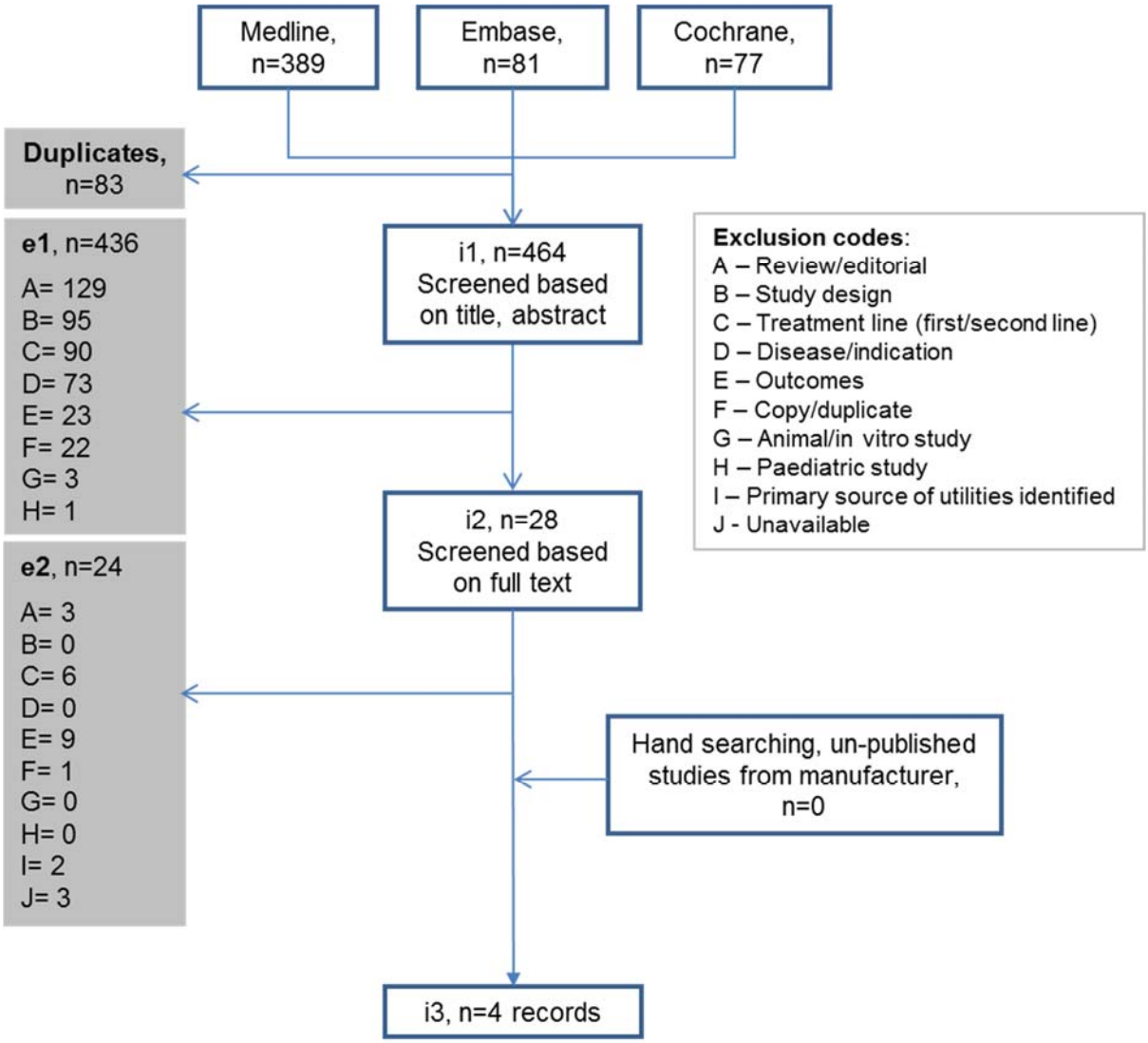


Table 58: Summary of health state utility values associated with patients with advanced/metastatic colorectal cancer

Study/ country	Population	Interventions/ comparators	Sample size	Mapping	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]	Discussion (summary of relevance to NICE reference case and quality assessment)
Chan, 2014[56] Canada	Patients with advanced refractory CRC	• Cetuximab + BSC • BSC	N = 545	A mapping algorithm was constructed to derive HUI3 from the EORTC-QLQ-C30 scale and/or baseline characteristics	HUI3	Patients with advanced refractory CRC; mean HUI3 utility	0.717 [0.235]	• This study does not meet the requirements of the NICE reference case; instead of the preferred EQ-5D, a mapping algorithm was used to derive HUI3 utilities, and the methods of elicitation and valuation were not clear. However, in the absence of higher quality evidence, the utilities reported may be considered useful for informing economic evaluation • It is unclear if the population is generalisable to a UK population of patients with advanced/metastatic CRC receiving treatment at third line or beyond; while patients had advanced disease, the treatment line was unclear • Limitations that may restrict the usefulness of the study for informing economic evaluation include: o The study was presented as an abstract/poster only, and there was limited reporting of details regarding the patient recruitment process, eligibility criteria and response rates
Chang 2015[58] China	Patients with mCRC whose disease progressed on standard treatments; must have had ≥2 prior standard treatments for metastatic disease[59] (CONCUR trial)	• Regorafenib • Placebo	N = 204	NA	EQ-5D *[Utility expressed as LSM time-adjusted AUC to represent change in HRQL across the treatment period]*	Patients with mCRC, regorafenib	0.70 (0.67, 0.73)	• This study may meet the requirements of the NICE reference case; utilities were derived using the preferred EQ-5D; however, the methods of elicitation and valuation were unclear • The study population consisted of Asian patients with mCRC receiving at least third-line treatment; however, it is unclear if the results are generalisable to a similar population in a UK setting • Limitations that may restrict the usefulness of the study for informing economic evaluation include: o The study was presented as an abstract only, and there was limited reporting of details regarding the patient recruitment process, eligibility criteria and response rates
						Patients with mCRC, placebo	0.74 (0.70, 0.78)	

Study/ country	Population	Interventions/ comparators	Sample size	Mapping	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]	Discussion (summary of relevance to NICE reference case and quality assessment)
Mittmann 2009[53] Canada	Patients with chemo-refractory CRC	• Cetuximab + BSC • BSC	N = 572	NA	HUI3	CRC patients, cetuximab + BSC, baseline	0.72 [0.23]	• This study does not meet the requirements of the NICE reference case, as the HUI3 was used instead of the preferred EQ-5D; however, in the absence of higher quality evidence, the utilities reported may be considered appropriate for informing economic evaluation • Utilities were derived directly from patients; however, the method of valuation was unclear • The study population consisted of patients with chemo-refractory CRC receiving treatment at second-line and beyond; only a small proportion of patients were receiving treatment at second-line, and so the results may be more representative of patients receiving third or subsequent line treatment • Many heavily pre-treated patients with advanced CRC have poor PS (ECOG 3-4) – the study population was a selected group of previously treated patients who still maintained a reasonable PS (ECOG 0-2); and therefore, results may not be generalisable to very ill patients • It is unclear how generalisable the results are to a UK setting as the study was conducted in Canada • Limitations which may restrict the usefulness of the study for informing economic evaluation include: o Lack of information reported regarding response rate to the HUI3, loss to follow up and missing data
						CRC patients, cetuximab + BSC, week 4 post-randomisation	0.73 [0.26]	
						CRC patients, cetuximab + BSC, week 8 post-randomisation	0.73 [0.24]	
						CRC patients, cetuximab + BSC, week 16 post-randomisation	0.73 [0.24]	
						CRC patients, cetuximab + BSC, week 24 post-randomisation	0.77 [0.22]	

Study/ country	Population	Interventions/ comparators	Sample size	Mapping	Instrument used to derive utilities	Health states	Utility score (95% CI) [SD]	Discussion (summary of relevance to NICE reference case and quality assessment)
						CRC patients, BSC, baseline	0.71 [0.24]	
						CRC patients, BSC, 4 weeks	0.68 [0.26]	
						CRC patients, BSC, 8 weeks	0.66 [0.28]	
						CRC patients, BSC, 16 weeks	0.63 [0.30]	
						CRC patients, BSC, 24 weeks	0.70 [0.24]	
Siena 2013[54] Multi-national (16 countries in North America, Europe, Asia, and Australia)	Adult patients with mCRC whose disease had progressed after all standard therapies (CORRECT trial)*	• Regorafenib • Placebo	N = 760	NA	EQ-5D *[Utility expressed as LSM time-adjusted AUC to represent change in HRQL across the treatment period]*	Patients with mCRC, regorafenib	0.67 (0.64, 0.70)	• This study may meet the requirements of the NICE reference case; utilities were derived using the preferred EQ-5D; however, the methods of elicitation and valuation were unclear • The study population consisted of patients with mCRC and the majority of the study population were receiving at least third-line treatment; however, it is unclear how generalisable the results are to a UK only setting • Limitations which may restrict the usefulness of the study for informing economic evaluation include: o The study was presented as an abstract only and there were was limited reporting of details regarding the patient recruitment process, eligibility criteria and response rates
						Patients with mCRC, placebo	0.67 (0.64, 0.70)	

Key: AUC, area under the curve; BSC, best supportive care; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EORTC-QLQ-C30, European organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36; EQ-5D, European Quality of Life-5 Dimensions; HRQL, health-related quality of life; HUI3, Health Utilities Index 3; LSM, least squares mean; (m)CRC, metastatic colorectal cancer; NA, not applicable; NICE, National Institute for Health and Care Excellence; NR, not reported; PS, performance status; SD, standard deviation; UK, United Kingdom.
Notes: *Following the discovery of this paper in the systematic literature search, the full trial paper for the CORRECT study was sourced, from which the utility values were taken. These utility values are discussed further in Section 5.4.4.[57]

Table 59. Relevance of identified health state utility value to NICE reference case

Study	Is the generic preference-based EQ-5D instrument used to describe health states?	Do patients describe the health states?	Are appropriate societal preferences used to value health states?	Is the TTO/SG method used to value health states?	Is the study consistent with NICE body reference cases?
Chan 2014[56]	No – a mapping algorithm was used to derive HUI3 utilities from the EORTC-QLQ-C30	Unclear	Unclear	Unclear	No – a mapping algorithm was used to derive HUI3 utilities from the EORTC-QLQ-C30, rather than the preferred EQ-5D, and the methods of elicitation and valuation were unclear
Chang 2015[58]	Yes	Unclear	Unclear	Unclear	This study may be consistent with the NICE reference case – the preferred EQ-5D was used to derive utilities; however, the methods of elicitation and valuation were unclear
Mittman 2009[53]	No – HUI3	Yes	Unclear	Unclear	No – although utilities were derived directly from patients, the HUI3 was used to measure HRQL instead of the preferred EQ-5D
Siena 2013[54]	Yes	Unclear	Unclear	Unclear	This study may be consistent with the NICE reference case – the preferred EQ-5D was used to derive utilities; however, the methods of elicitation and valuation were unclear

Key: EORTC-QLQ-C30, European organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36; EQ-5D, European Quality of Life-5 Dimensions; HRQL, health-related quality of life; HUI3, Health Utilities Index 3; NICE, National Institute for Health and Care Excellence; SG, standard gamble; TTO, time trade off.

5.4.3 Adverse reactions

AEs were generally mild and transient in the RECOURSE clinical trial, and trifluridine/tipiracil is associated with few serious adverse events.[2]

Given the lack of available evidence to inform the model in regards to disutilities associated with adverse events, the health state utilities chosen for the model base case incorporate the small changes in HRQL attributable to adverse event incidence. The impact of AEs on cost was also captured in the treatment delays experienced by patients (Section 5.3) and were costed as a lump sum in the first cycle of the model (Section 5.5).

5.4.4 Health-related quality of life data used in the cost-effectiveness analysis

In the model base case, health state utilities were taken from the CORRECT study of regorafenib monotherapy for previously treated mCRC (as this was conducted at the same disease stage) and the cetuximab NICE manufacturer submission for the first-line treatment of mCRC.[30] For all health states, the average of these two sources was taken. These utility values are summarised in Table 60.

Table 60: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	Justification
Pre-progression – on treatment	0.73 (0.01)	CORRECT study[57] and the cetuximab NICE manufacturer submission for the first-line treatment of mCRC.[30]
Pre-progression – BSC	0.74 (0.02)	
Post-progression – T/T	0.64 (0.01)	
Post-progression – BSC	0.64 (0.02)	
Dead	0	NICE reference case[47]
Key: BSC, best supportive care; N/A, Not applicable; NICE, National Institute for Health and Care Excellence; SE, standard error; T/T, trifluridine/tipiracil.		

Alternatively, health state utility values may be taken solely from the CORRECT study, or the cetuximab NICE manufacturer submission for the first-line treatment of mCRC.[30, 57] Utilities in the CORRECT study were 0.73 on treatment and 0.74 for patients on BSC. Following progression, utilities were 0.59 for all patients,

irrespective of previous treatment. Utilities in the cetuximab submission were 0.77 for first-line, 0.73 for second-line and 0.68 for third-line treatment. The utilities for second-line and third-line treatment (those used in the calculation of the mean) may be used in the model for the 'Pre-progression' and 'Post-progression' health states, respectively, as a scenario analysis.

The values provided in the model and sensitivity analyses aim to address the uncertainty surrounding HRQL for these patients, by providing a range of values, with the average of the two most appropriate sources used in the base case.

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

There have been two recent NICE technology appraisals in mCRC that are relevant to the decision problem (TA242 and ID794)[5, 60] ID794 is particularly relevant, with the assessment report becoming available in August 2015; we have therefore utilised the resource costs identified within this document. Additional resource use attributable to patients in this later line of therapy has been included based on published literature and expert opinion.

5.5.2 Intervention and comparators' costs and resource use

Drug costs

Trifluridine/tipiracil is available in 15mg or 20mg tablets, in pack sizes of 20 and 60. The unit costs of these pack sizes are presented in Table 61 at the list price.

Table 61: Unit costs of treatment

Treatment	Unit dose (mg)	Pack size	Unit cost	Source
Trifluridine/tipiracil	15	20	£500	Servier
		60	£1,500	
	20	20	£667	
		60	£2,000	

Dosage was based on BSA, with pack sizes available to cater for all doses, as shown in Table 62.

Table 62: Trifluridine/tipiracil given based on body surface area

Baseline BSA	Dosage (mg; 2x daily)	Tablets per dose		Packs given				Cost per cycle (list price)
		15mg	20mg	15mg		20mg		
				20	60	20	60	
<1.07	35	1	1	✓		✓		£1,167
1.07 - 1.22	40	0	2			✓✓		£1,333
1.23 - 1.37	45	3	0		✓			£1,500
1.38 - 1.52	50	2	1	✓✓		✓		£1,667
1.53 - 1.68	55	1	2	✓				£1,833
1.69 - 1.83	60	0	3				✓	£2,000
1.84 - 1.98	65	3	1		✓	✓		£2,167
1.99 - 2.14	70	2	2	✓✓		✓✓		£2,333
2.15 - 2.29	75	1	3	✓			✓	£2,500
≥2.30	80	0	4			✓	✓	£2,667

Key: BSA, body surface area.

As discussed in Section 5.3, some additional steps were applied to obtain the average cost per patient per treatment cycle of trifluridine/tipiracil. Initially, the distribution of patients' BSA was used to determine the weighted average cost per patient in the first cycle of treatment, which was calculated to be £2,032 at list price. Following this, the average cost per patient per treatment cycle was adjusted according to the proportion of patients who experienced a dose reduction in the RECOURSE trial. This applies to the average cost per patient for treatment cycle 2 onwards. The costs per treatment cycle for trifluridine/tipiracil are presented in Table 63.

Table 63: Cost of treatment per cycle (list price)

Treatment	Treatment cycle	Unit cost*	Source
Trifluridine/tipiracil	1	[redacted]	Servier
	2	[redacted]	
	3	[redacted]	
	4+	[redacted]	
Best supportive care		£0	No active treatment cost
Note: *based on average BSA in RECOURSE of 1.78m^2			

To all prices, the confidential discount of [redacted]% was then applied.

Medical resource use

Trifluridine/tipiracil is an oral therapy, and therefore does not require an outpatient appointment for administration. Resource use is associated with the disease, and is therefore discussed below.

Medical resource use (MRU) items were identified following consultation with clinical experts, due to the lack of published literature reporting robust estimates of the MRU of patients in this setting. MRU items were categorised by progression status.

Pre-progression

Patients receiving trifluridine/tipiracil are expected to attend an oral chemotherapy day case appointment once per treatment cycle. During this appointment, it is expected that patients receive their treatment for this cycle, undergo any routine tests and investigations as well as having a clinician appointment to review their treatment. For patients receiving BSC, it was assumed that patients would have an outpatient consultation with an oncologist per treatment cycle, as opposed to having a chemotherapy day case appointment.

For patients receiving trifluridine/tipiracil, delays in treatment initiation were associated with increased MRU. This increased MRU is caused by patients requiring breaks in treatment and potential down-dosing. These patients will therefore be expected to “re-attend” their standard chemotherapy day case appointment, and therefore incur the cost of doing so. This was costed in the model at the same time as the original appointment as an increased cost.

In addition to these MRU items for pre-progression patients, it was assumed that 25% of patients incurred the cost of a health home visitor per treatment cycle. This estimate is based on expert opinion from consultants in palliative care who are involved in patient care for patients in their last year of life.

Post-progression

Following progression, MRU is expected to change in accordance to the difference in need. Patients no longer attend the chemotherapy day case unit, or attend an outpatient appointment with an oncology consultant. The estimates in this section are based on expert opinion which was obtained through interviews conducted with consultants in palliative care and general practitioners.

Patients are expected to visit their general practitioner (GP) approximately once per month, along with being seen by a community nurse specialist and a health home visitor. Additionally, 25% of patients are expected to require a district nurse visit per week, equating to approximately one district nurse visit per month per patient. In addition to this, 25% of patients are expected to require a GP home consultation per month.

All other resource use costs (including social care for patients towards the end of life) are assumed to be captured in the end-of-life care cost applied for all patients upon death, as discussed in the section below. Full MRU costs are reported in Table 64.

Table 64: Summary of medical resource use

MRU item	Occurrence per treatment cycle†			Unit cost (£)	Reference
	Pre-P		PP		
	T/T	BSC			
Oral chemotherapy day case attendance*	1			192.32	NHS reference costs 2014-15: Day case and Regular Day/Night; SB11Z; Deliver exclusively oral chemotherapy[61]
Medical oncologist outpatient consultation		1		170.85	NHS reference costs 2014-15: 370; Medical Oncology - Outpatient, consultant led[61]
GP home consultation			0.25	96.92	PSSRU 2013: GP - per out of surgery visit lasting 23 minutes (without qualifications) - inflated using PSSRU 2015 inflation indices[62]
Community nurse specialist visit			1	44.00	PSSRU 2015: Nurse Specialist (Community) Cost per hour (without qualifications) - 10.4 (contact assumed to last 1 hour)[62]
Health home visitor	0.25	0.25	1	44.00	PSSRU 2015: Health Visitor Cost per hour (without qualifications) - 10.3 (contact assumed to last 1 hour)[62]
District nurse visit			1	44.00	PSSRU 2015: Health Visitor Cost per hour (without qualifications) - 10.1 (contact assumed to last 1 hour)[62]
GP surgery visit			1	37.00	PSSRU 2015: GP consultation (Per patient contact lasting 11.7 minutes, without qualifications) - 10.2[62]

Key: BSC, best supportive care; GP, general practitioner; MRU, medical resource use; NHS, National Health Service; PP, post-progression; Pre-P, pre-progression; PSSRU, Personal Social Services Research Unit; T/T, trifluridine/tipiracil.
Notes: * Patients who experience a delay in treatment initiation incur the cost of an additional oral chemotherapy day case attendance.
† MRU items are incurred according to an average unadjusted treatment cycle (i.e. 28 days). Adjustments for delays in treatment initiation are captured by the repeat chemotherapy day case attendance.

Using these occurrences per treatment cycle and unit costs, the average cost of MRU was calculated per treatment cycle. These average costs are presented in Table 65.

Table 65: Medical resource use by health state

Health state	Treatment	Average MRU cost
Pre-progression	Trifluridine/tipiracil	£203
	BSC	£182
Post-progression	All	£193
Key: BSC, best supportive care; MRU, medical resource use.		

End-of-life care resource use and cost

People with advanced cancer require a range of health, social and informal care during the final phases of life.[63] End-of-life care costs were taken from a modelling study by Round et al. to estimate the cost of caring for people with CRC at the end of life.[63] The cost taken from this source for end of life takes into account health care (£4,854), social care (£1,489) and charity care (£470), and excludes the cost of informal care as per the NICE reference case.[47]

The total cost of end-of-life care from this study was there £6,910, and was applied in the model as a lump sum upon death for both arms.

5.5.3 Health-state unit costs and resource use

The costs associated with each health state in the model are presented in Table 66.

Table 66: Health states and associated costs per treatment cycle

Health state	Items	Value		Reference in submission
		Trifluridine/tipiracil	BSC	
Pre-progression	Technology	[redacted]	£0	Table 63
	MRU*	£203	£182	Table 65
Progressed	Technology	£0		Table 63
	MRU	£193		Table 65
Non-health state costs applied as a lump sum	Adverse events†	£923	£426	Table 68
	End of life‡	£6,910		Section 5.5
	Post-progression treatmentΔ	£1,528		Table 69

Key: BSC, best supportive care; MRU, medical resource use.
Notes: * additional chemotherapy day case attendance applies for patients experiencing delays
† applied for all patients in the first model cycle.
‡ applied upon death.
Δ applied upon progression.

5.5.4 Adverse reaction unit costs and resource use

Costs were incurred for AEs if a given AE is actively treated in the NHS. Advice on which adverse events would be actively managed was verified with clinical and medical oncologists. The full list of AEs included in the model, whether or not they are actively treated, and the treatment costs are presented in Table 67.

Table 67: Adverse events included in the model

Adverse event	Actively treated		Cost of treatment		Reference (see notes for sources)	
	All grades	Grade ≥3	Grade ≤2	Grade ≥3	Grade ≤2	Grade ≥3
Nausea		✓		£158.43		**a**
Vomiting	✓	✓	£158.43	£158.43	**a**	**a**
Decreased appetite		✓		£158.43		**a**
Fatigue		✓		£158.43		**a**
Diarrhoea	✓	✓	£158.43	£158.43	**a**	**a**
Abdominal pain		✓		£139.52		**b**
Fever	✓	✓	£158.43	£158.43	**a**	**a**
Asthenia		✓		£158.43		**a**
Febrile neutropenia	✓	✓	£2,583.98	£2,583.98	**c**	**c**
Stomatitis		✓		£158.43		**a**
Hand-foot syndrome		✓		£158.43		**a**
Cardiac ischaemia	✓	✓	£158.43	£158.43	**a**	**a**
Neutropenia		✓		£1,227.95		**d**
Leucopenia		✓		£158.43		**a**
Anaemia		✓		£799.00		**e**
Thrombocytopenia		✓		£643.48		**f**

Key: DSU, Decision Support Unit; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.
Notes: a NHS Reference costs 14-15: Outpatient visit, general medicine[61];
b NHS Reference costs 14-15: Outpatient visit, pain management[61];
c NICE DSU report[64];
d NHS Reference costs 14-15: Average non-elective inpatient stay[61];
e PENTAG ERG Report for cetuximab[60];
f NHS Reference costs 14-15: Weighted cost of thrombocytopenia based on complications and comorbidities score.[61]

Applying these unit costs of treatment for AEs to the rates observed from the RECOURSE clinical trial (Section 5.3) yields the cost of treating AEs per treatment shown in Table 68.

Table 68: Cost of adverse events by treatment

Trifluridine/tipiracil	Best supportive care
£923	£426

5.5.5 Miscellaneous unit costs and resource use

Post-progression treatments

Following discontinuation of the study treatment, approximately 42% of patients in RECOURSE went on to receive non-study anti-tumour treatments. To account for the costs of post-progression treatment, analysis was undertaken using RECOURSE trial data to provide an estimate of the average cost of post-progression treatment per patient. The full details of this analysis are presented in Appendix 11.

The average cost of post-progression therapy is presented in Table 69. This cost is applied as a lump sum for patients upon progression. All other costs included in the cost-effectiveness analysis have been discussed in the previous sections. A sensitivity analysis is performed costing each arm separately, which shows minimal impact on the ICER.

Table 69: Average cost of post-progression therapy

Costing scenario	Trifluridine/tipiracil	Best supportive care
Assume same cost	£1,528	
Assume different cost	£1,549	£1,487

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

A summary of the base-case de novo analysis inputs is presented in Table 70.

Table 70: Summary of base-case de novo analysis inputs

Parameter	Value	Varied by	Reference
Model settings		**Section 5.2**	
Intervention	T/T	Not included in SA	Model setting
Comparator	BSC		
Model cycle length (days)	1		
Model time horizon (years)	10		
Annual discount rate: Costs	3.5%	Defined by guidance, OWSA only	
Annual discount rates: LYs	0%		
Annual discount rates: QALYs	3.5%		
Survival and progression		**Section 5.3**	
Mean delay in treatment initiation per patient per cycle (days) T/T	2.719	Triangular ± 20% of mean	Analysis of RECOURSE study data
Mean delay in treatment initiation per patient per cycle (days) BSC	1.399		
OS and PFS curve parameters	See Appendix 7		
Dosing		**Section 5.3**	
Dosing: Log-normal parameter: mean	0.571	Log-normal	Analysis of RECOURSE study data
Dosing: Log-normal parameter: SD	0.129		
Resource use (per treatment cycle)		**Section 5.5**	
Resource; PFS; T/T: Oral chemotherapy day case	1*	Triangular ± 20% of mean	Expert Opinion – based on consultation with clinical experts
Resource; PFS; T/T: Health home visitor	0.25		
Resource; PFS; BSC: Medical Oncologist outpatient consultation	1		
Resource; PFS; BSC: Health home visitor	0.25		
Resource; PPS: General Practitioner home consultation	0.25		
Resource; PPS: Community Nurse Specialist visit	1		
Resource; PPS: Health home visitor	1		
Resource; PPS: District nurse	1		
Resource; PPS: General Practitioner surgery visit	1		
Utilities		**Section 5.4**	
Utility: PFS: T/T	0.73	Beta	CORRECT study[57] and the cetuximab NICE manufacturer submission for the first-line treatment of mCRC.[30]
Utility: PFS: BSC	0.74		
Utility: PPS: T/T	0.64		

Parameter	Value	Varied by	Reference
Utility: PPS: BSC	0.64		
Costs		**Section 5.5**	
Cost: T/T 15mg (20 pack)	£500	Not included in SA	Servier
Cost: T/T 15mg (60 pack)	£1500		
Cost: T/T 20mg (20 pack)	£667		
Cost: T/T 20mg (60 pack)	£2000		
Dose reduction: After cycle 1	0.0993	Beta	Analysis of RECOURSE study data
Dose reduction: After cycle 2	0.0337		
Dose reduction: After cycle 3	0.00375		
Cost; Post-progression treatment: T/T	1528	Triangular ± 20% of mean	Analysis of RECOURSE study data. See Appendix 11
Cost; Post-progression treatment: BSC	1528		
Cost: Oral Chemotherapy	£192	Bounds from source	[61]
Cost: Medical oncologist	£171	Triangular ± 20% of mean	[62]
Cost: General Practitioner home consultation	£97		
Cost: Community Nurse Specialist visit	£44		
Cost: Health home visitor	£44		
Cost: District nurse	£44		
Cost: General Practitioner surgery visit	£37		
Cost: Hospice care	£6,910	Normal	[63]
Adverse events		**Section 5.5**	
AE: Total cost (T/T)	£923	Triangular ± 20% of mean	See Table 68
AE: Total cost (BSC)	£426	Triangular ± 20% of mean	

Key: AE, adverse event; BSC, best supportive care; LY, life year; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year; SA, sensitivity analysis; SD, standard deviation; T/T, trifluridine/tipiracil
Notes: * Additional resource use incurred for patients experiencing a dose reduction.

5.6.2 Assumptions

Table 71 contains the key assumptions made in the *de novo* economic model.

Table 71: Key model assumptions

<table>
<tr><th>Assumption</th><th>Rationale</th></tr>
<tr><td>Model cycle length</td><td>Daily cycle length used to enable accurate estimation of survival outcomes over the model time horizon. A longer time horizon was inappropriate for consideration due to the kinks in the curve caused by the frequency of progression assessment in the clinical trials.</td></tr>
<tr><td>Pooling of Phase II and Phase III trial data</td><td>The Phase III clinical trial (RECOURSE) and the Phase II clinical trial were both international, multicentre, double-blind, 2:1 randomised, placebo-controlled trials to investigate the efficacy and safety of trifluridine/tipiracil for pre-treated mCRC. Baseline patient characteristics were similar for both trials, with the following key features:
<table>
<tr><th rowspan="2">Characteristic</th><th colspan="2">Phase II</th><th colspan="2">RECOURSE</th></tr>
<tr><th>T/T
(n = 112)</th><th>BSC
(n = 57)</th><th>T/T
(n = 534)</th><th>BSC
(n = 266)</th></tr>
<tr><td>Age (median)</td><td>63</td><td>62</td><td>63</td><td>63</td></tr>
<tr><td>Male (%)</td><td>57</td><td>49</td><td>61</td><td>62</td></tr>
<tr><td>ECOG (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>0</td><td>64</td><td>61</td><td>56</td><td>55</td></tr>
<tr><td>1</td><td>33</td><td>37</td><td>44</td><td>45</td></tr>
<tr><td>2</td><td>3</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td colspan="5">Key: BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; T/T, trifluridine/tipiracil.</td></tr>
</table>
Furthermore, the majority (82.6%) of patients in the pooled dataset were recruited into the Phase III study. Therefore, the impact of incorporating Phase II patients is not extensively large. The meta-analysis presented in Section 4.9 demonstrates that there is no evidence of heterogeneity between the two trials.</td></tr>
<tr><td>Use of log-normal distribution fit to patient body surface area</td><td>The log-normal distribution has been used in published literature to estimate the distribution of body surface area across populations.[52, 65] A study by Murray et al. concluded that surface area fit well for both men and women, and is appropriate for use in public risk assessments.[65]</td></tr>
</table>

Medical resource use	Robust estimates of medical resource use for patients in this setting are not publically available, given the lack of alternative treatments available for which evidence may have previously been gathered. As a result of this, clinical expert advice was sought to estimate the anticipated medical resource use of these patients.
Utility values	As utility values were not reported in either of the clinical trials, external sources were necessarily sought out to inform health-related quality of life in the *de novo* economic model. The base case choice of utility values were taken as the mean of those from the CORRECT study of regorafenib, for the same indication of mCRC patients[57] and from the cetuximab NICE submission which also provided utilities for patients at this stage of disease. These utility values were chosen based on similarities of population, and hence compatibility with data used to populate the model. The utility values also incorporate a degree of disutility attributable to the increased incidence of adverse events for patients on active chemotherapy versus best supportive care. Although it is noted that the toxicity profiles for trifluridine/tipiracil and regorafenib differ substantially, these utility values were used as a conservative estimate of the anticipated utility associated with patients in pre-progression on active treatment in lieu of available data for patients on trifluridine/tipiracil.
Post-progression treatment	As there is no currently recommended treatment for the anticipated licence of trifluridine/tipiracil, the availability of information regarding treatment after this line is non-existent. To estimate the cost associated with any treatment received following discontinuation of trifluridine/tipiracil, data from RECOURSE was used to derive an estimate of the average cost of one cycle of treatment for all reported therapies initiated post-study. Full details of the calculations performed to estimate the costs are given in Appendix 11. An estimate of one cycle was assumed given the absence of data regarding the time spent on post-study treatment, and in consideration of the poor prognosis of patients at this stage of disease.
Key: mCRC, metastatic colorectal cancer.	

5.7 Base-case results

5.7.1 Base-case incremental cost-effectiveness analysis results

The discounted base-case results for trifluridine/tipiracil versus BSC are shown in Table 72 at the list price for trifluridine/tipiracil, and in Table 73 with the commercial in confidence patient access scheme (PAS) price for trifluridine/tipiracil.

At the list price, trifluridine/tipiracil is associated with 0.27 life years gained (LYG), 0.17 incremental QALYs, and incremental costs of [redacted] per patient, compared with BSC. The incremental cost-effectiveness ratio (ICER) is [redacted] per additional QALY gained.

At the commercial in confidence PAS price, trifluridine/tipiracil is associated with 0.27 LYG, 0.17 incremental QALYs, and incremental costs of £7,574 per patient, compared with BSC. The ICER is £44,032 per additional QALY gained.

Table 72: Base-case results without patient access scheme

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER (£) incremental (QALYs)
BSC	[redacted]	0.42	0.66				
T/T	[redacted]	0.59	0.92	[redacted]	0.17	0.27	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; T/T, trifluridine/tipiracil.

Table 73: Base-case results with patient access scheme ([redacted]%)

Technologies	Total costs (£)	Total QALYs	Total LYG	Incremental costs (£)	Incremental QALYs	Incremental LYG	ICER (£) incremental (QALYs)
BSC	10,286	0.42	0.66				
T/T	16,386	0.59	0.92	7,574	0.17	0.27	44,032

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; T/T, trifluridine/tipiracil.

5.7.2 Clinical outcomes from the model

The clinical trial and model results for the median and mean OS and PFS of trifluridine/tipiracil and BSC patients are shown in Table 74.

As discussed in Section 5.3, modelled OS and PFS were extrapolated beyond the end of the trial to demonstrate the estimated long-term impacts of trifluridine/tipiracil and BSC for the treatment of patients in this setting. The mean OS and PFS estimates derived from the model use these extrapolated survival curves for the entire modelled time horizon.

The clinical trial results for mean OS and PFS were calculated in the model using the pooled trial data. At the end of the Kaplan-Meier curves, all patients were assumed to die, allowing the area under the curve to be calculated. Median OS and PFS were also taken from the model by using the Kaplan-Meier curves as published literature considering pooled data are not currently available.

Comparison between the modelled estimates and clinical trial results are limited by the length of follow-up, but given the completeness of the OS and PFS data, these estimates are similar.

Table 74: Summary of model results compared with clinical data

Outcome	Clinical trial results (pooled data)	Model result
Overall survival	*Median:* BSC: 5.4 months T/T: 7.3 months *Mean:* BSC: 6.8 months T/T: 9.1 months	*Median:* BSC: 5.3 months T/T: 7.4 months *Mean:* BSC: 7.9 months T/T: 11.1 months
Progression-free survival	*Median:* BSC: 1.7 months T/T: 1.9 months *Mean:* BSC: 1.9 months T/T: 3.7 months	*Median:* BSC: 1.6 months T/T: 2.6 months *Mean:* BSC: 1.9 months T/T: 3.7 months
Key: BSC, best supportive care; T/T, trifluridine/tipiracil.		

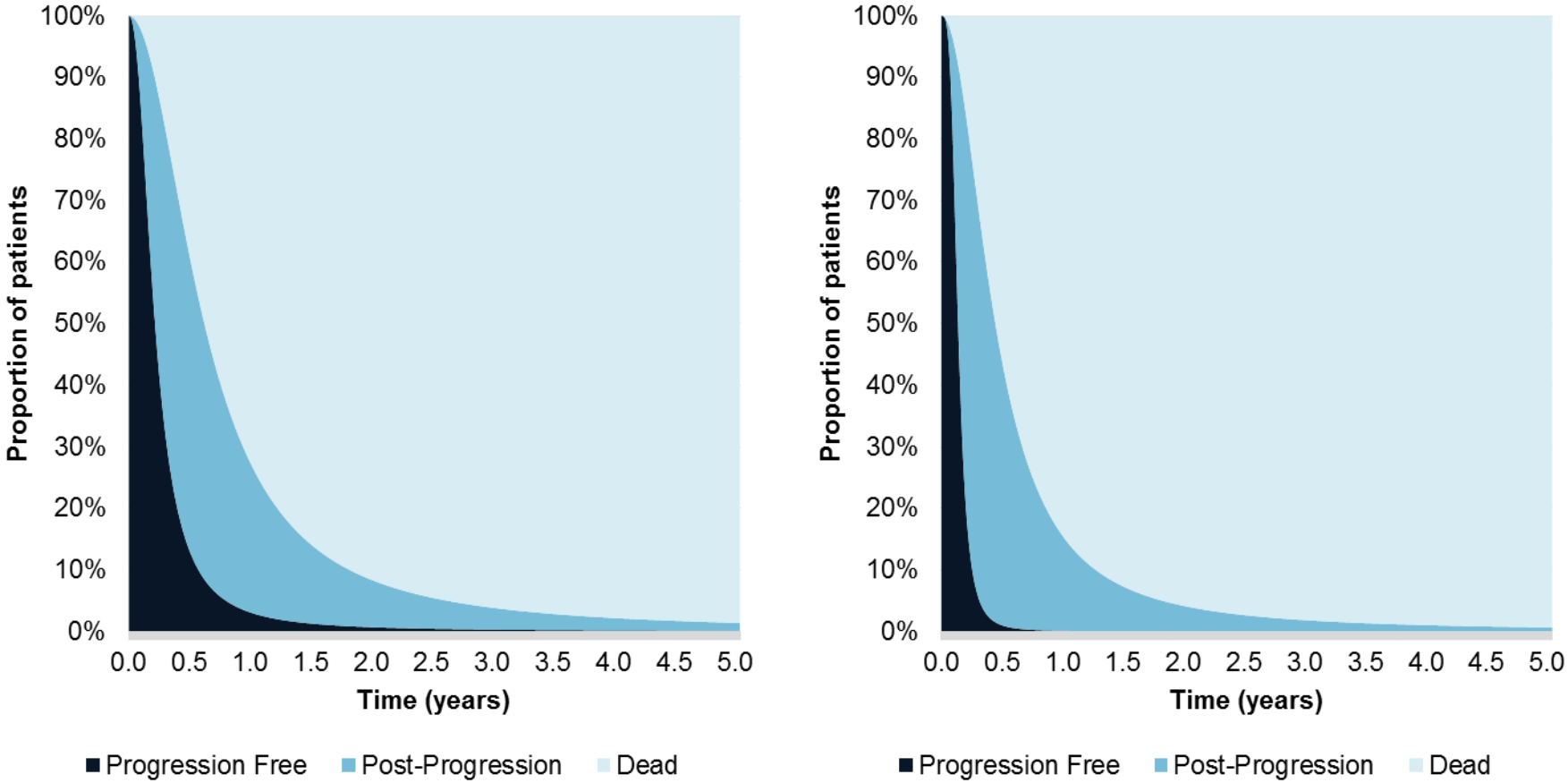
For OS, median modelled estimates are in line with those observed in the clinical trial. The mean estimates are slightly larger in the model results due to the extrapolation of survival data beyond the end of the trial.

For PFS, the median estimate for trifluridine/tipiracil is larger in the model due to the shape of the curve and how progression was measured in the RECOURSE trial. Radiological assessment of tumours were performed by investigators every 8 weeks.[2] The curve fit to PFS smooth's out the small differences in PFS over time due to these cut off points. Please refer to Figure 30 for the curve fit applied for PFS in the model base case.

As shown in Table 74, the mean estimates of PFS (while also accounting for extrapolation beyond the end of the trial) are in line with those observed in the clinical trial.

Five-year Markov traces for trifluridine/tipiracil and BSC are presented in Figure 36.

Figure 36: 5-year Markov traces for trifluridine/tipiracil (left) and best supportive care (right)



5.7.3 Disaggregated results of the base-case incremental cost-effectiveness analysis

The tables below report the disaggregated model results. QALYs, life years and costs are reported separately, in Table 75, Table 76 and [redacted], respectively.

Table 75: Summary of QALY gain by health state

Health state	QALY T/T	QALY BSC	Increment	Absolute increment	% absolute increment
Pre-progression	0.22	0.12	0.10	0.10	61%
Post-progression	0.37	0.30	0.07	0.07	39%
Total	0.59	0.42	0.17	0.17	100%
Key: BSC; best supportive care; QALY, quality-adjusted life year; T/T, trifluridine/tipiracil.					

Table 76: Summary of life year gain by health state

Health state	LY T/T	LY BSC	Increment	Absolute increment	% absolute increment
Pre-progression	0.30	0.16	0.15	0.15	55%
Post-progression	0.62	0.50	0.12	0.12	45%
Total	0.92	0.66	0.27	0.27	100%
Key: BSC; best supportive care; LY, life year; T/T, trifluridine/tipiracil.					

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 78: Summary of costs by health state and category – PAS price

Health state	Costs T/T (£)	Costs BSC (£)	Increment (£)	Absolute increment (£)	% absolute increment
Pre-progression	**8,325**	**869**	**7,456**	**7,456**	**100%**
Drug costs	6,550	0	6,550	6,550	88%
Monitoring	852	443	409	409	5%
Adverse events	923	426	497	497	7%
Post-progression	**2,860**	**2,672**	**188**	**188**	**100%**
Drug costs	1,511	1,519	-8	8	4%
Monitoring	1,348	1,152	196	196	96%
Total	**17,859**	**10,286**	**7,574**	**7,574**	**100%**
Drug costs	8,062	1,519	6,542	6,542	85%
Monitoring	2,200	1,595	605	605	8%
Adverse events	923	426	497	497	6%
End of life*	6,675	6,745	-71	71	1%

Key: BSC; best supportive care; T/T, trifluridine/tipiracil.
Notes: * End-of-life care costs apply for all patients irrespective of progression status.

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was carried out to explore the sensitivity in the deterministic base-case model results when all model parameters were varied simultaneously. Each parameter was varied according to its associated distribution 1,000 times, and mean model results were recorded. These mean model results were then used to inform a PSA scatter plot and a cost-effectiveness acceptability curve (CEAC).

The PSA scatter plots for the list price and PAS price are presented in [redacted] and Figure 38, respectively. The scatterplots demonstrate an even spread of points in regards to the deterministic model result, with the majority of uncertainty shown in the estimation of the QALY gain as expected. This is likely driven by the variability in the utility values chosen, due to the lack of information regarding the uncertainty in these estimates.

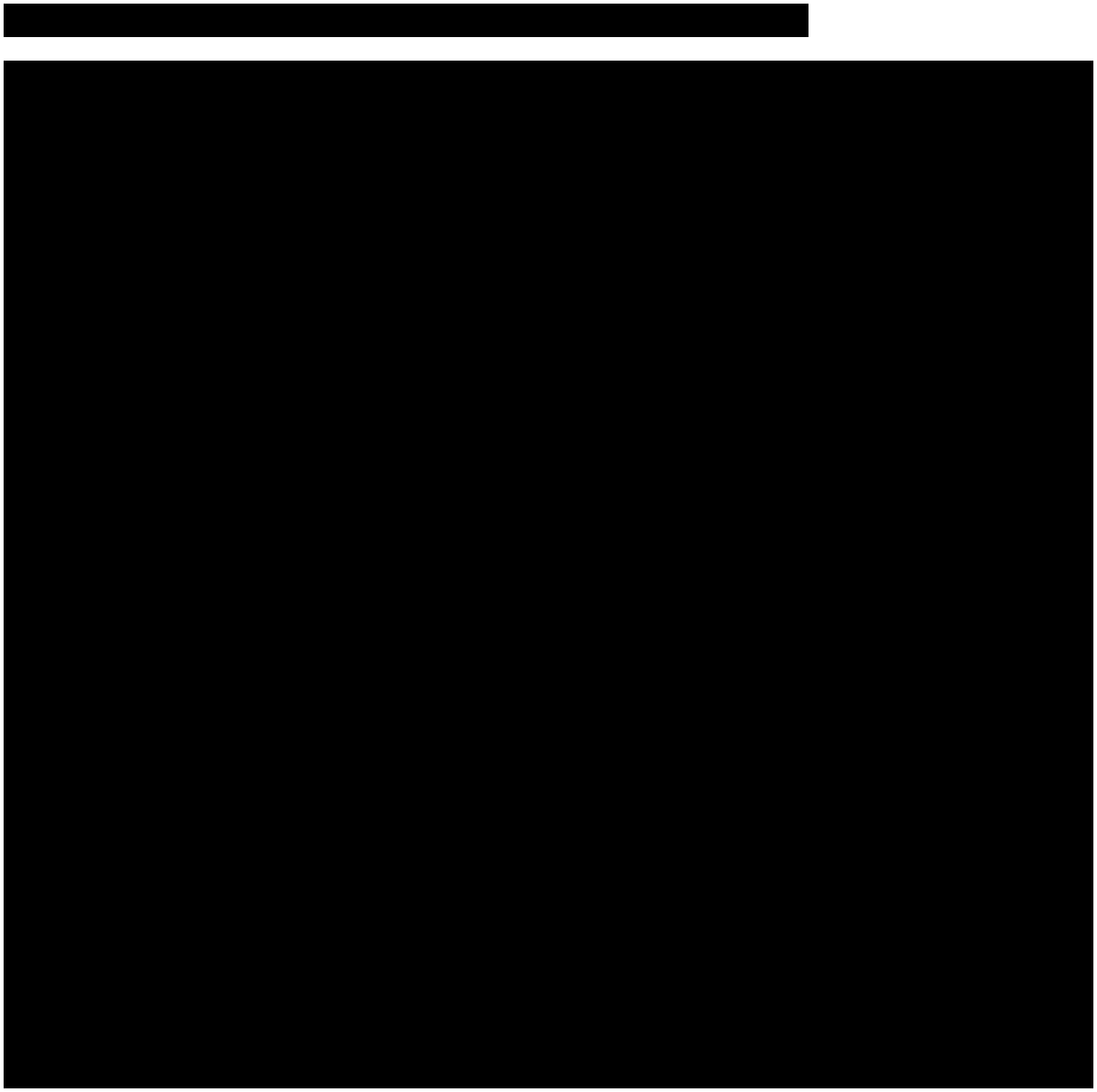
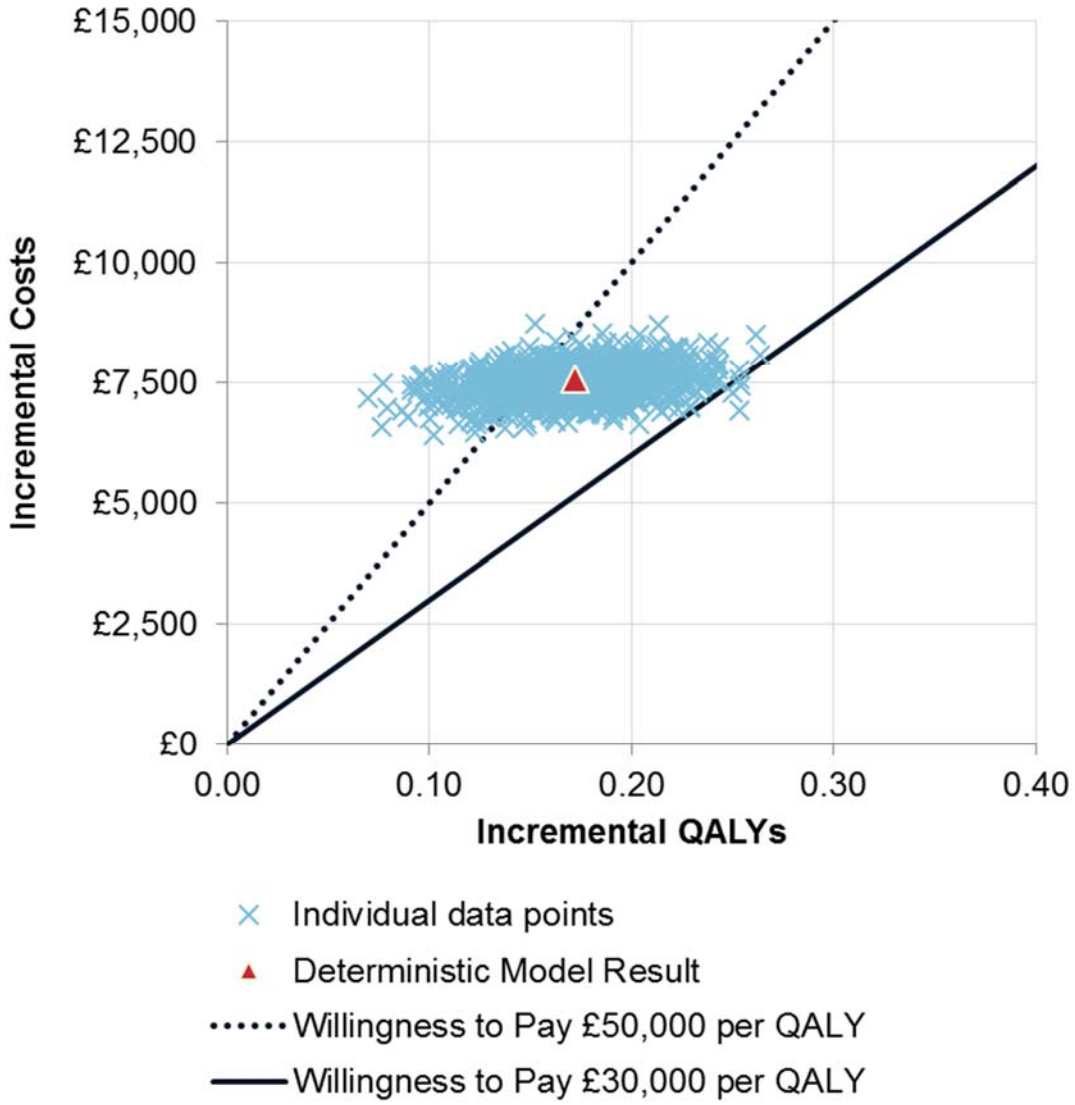


Figure 38: Probabilistic sensitivity analysis scatter plot – PAS price



Key: QALY, quality-adjusted life year.

The CEAC is presented for the list price and PAS price of trifluridine/tipiracil in [redacted] and Figure 40, respectively. At the list price, the probabilities of trifluridine/tipiracil being the most cost-effective treatment are 0% and 36% for willingness-to-pay (WTP) thresholds of £30,000 and £50,000, respectively, at the list price. At the PAS price, the probabilities of trifluridine/tipiracil being the most cost-effective treatment are 0% and 77% for WTP thresholds of £30,000 and £50,000, respectively.

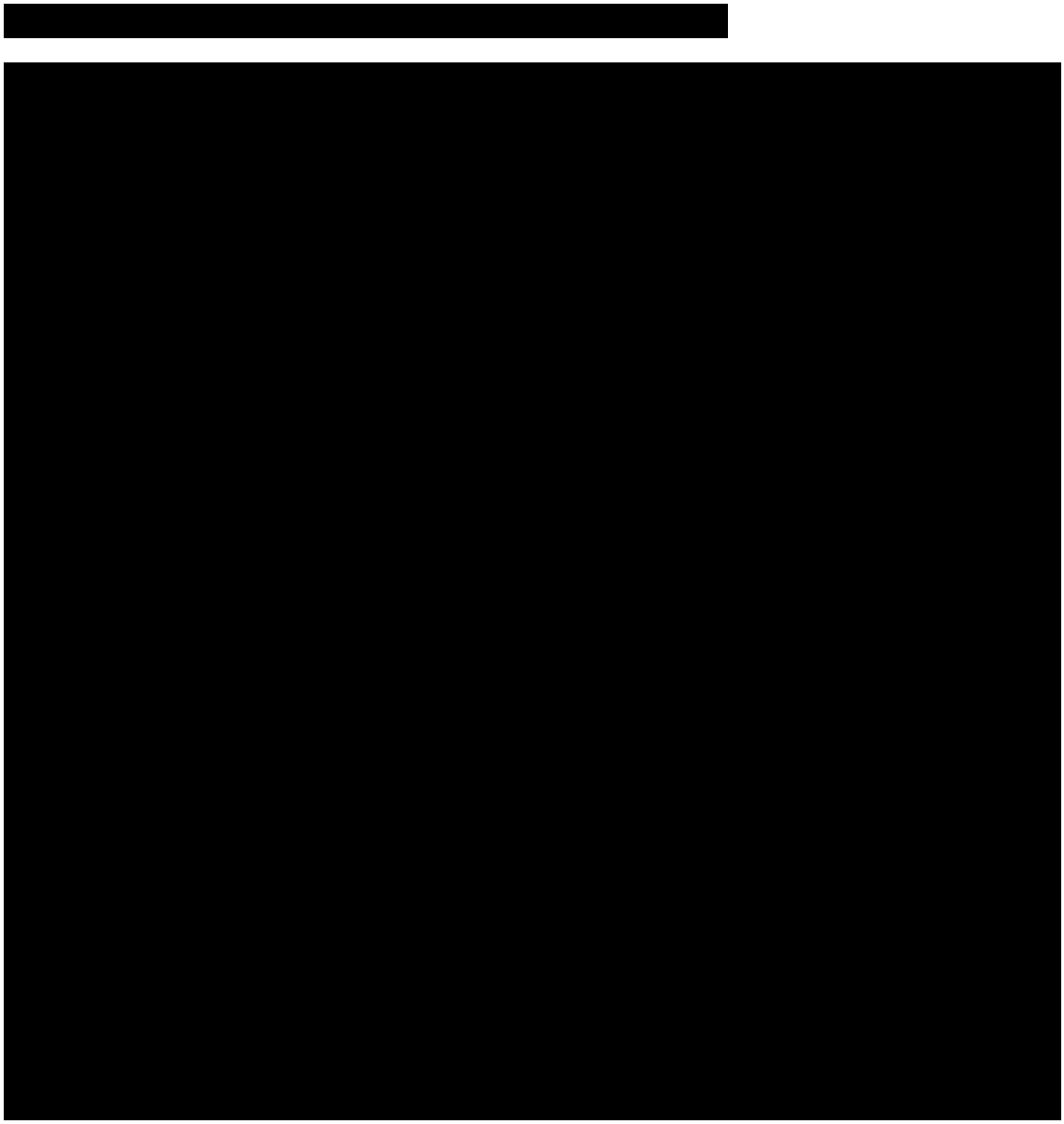
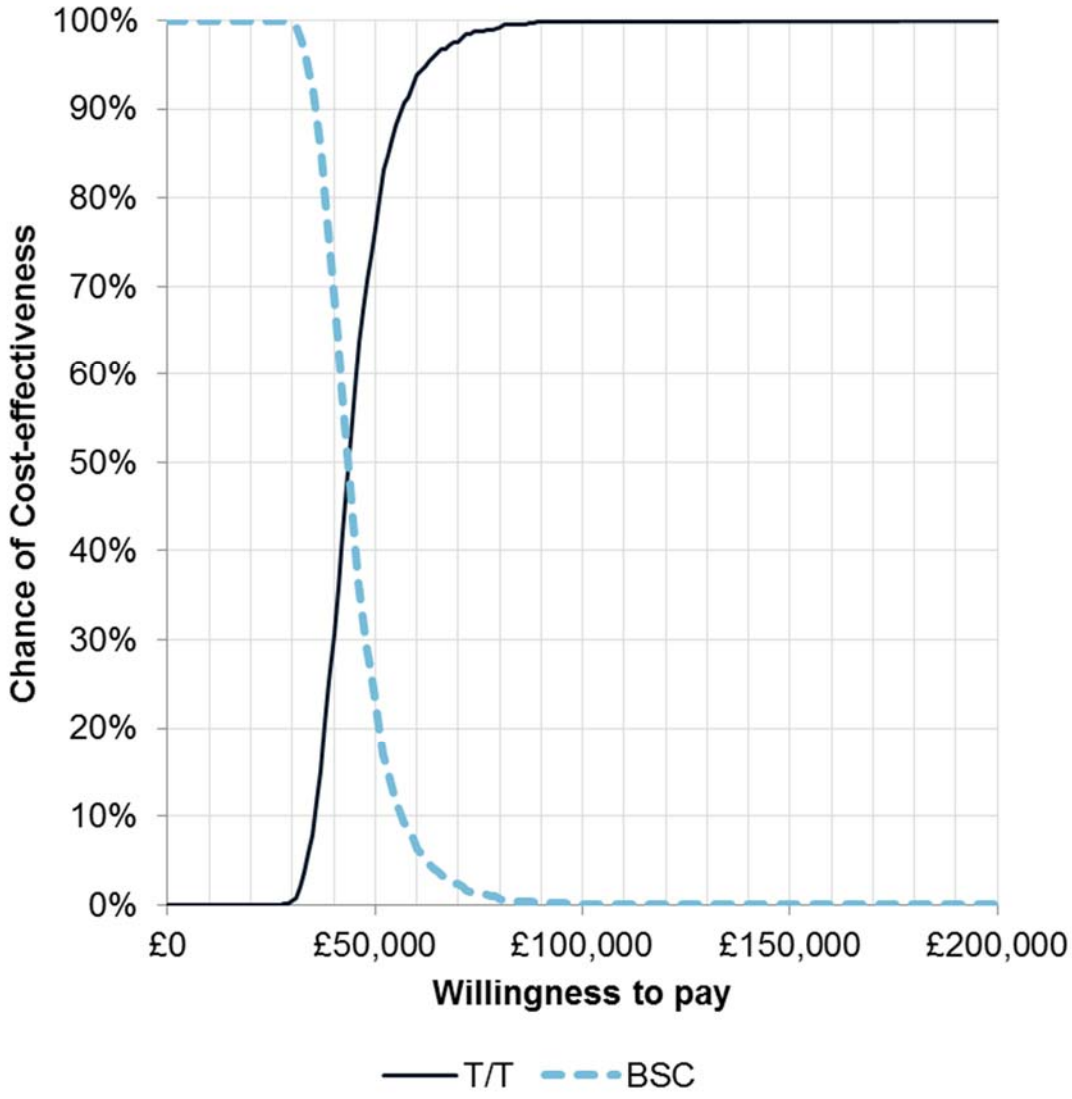


Figure 40: Cost-effectiveness acceptability curve – PAS price



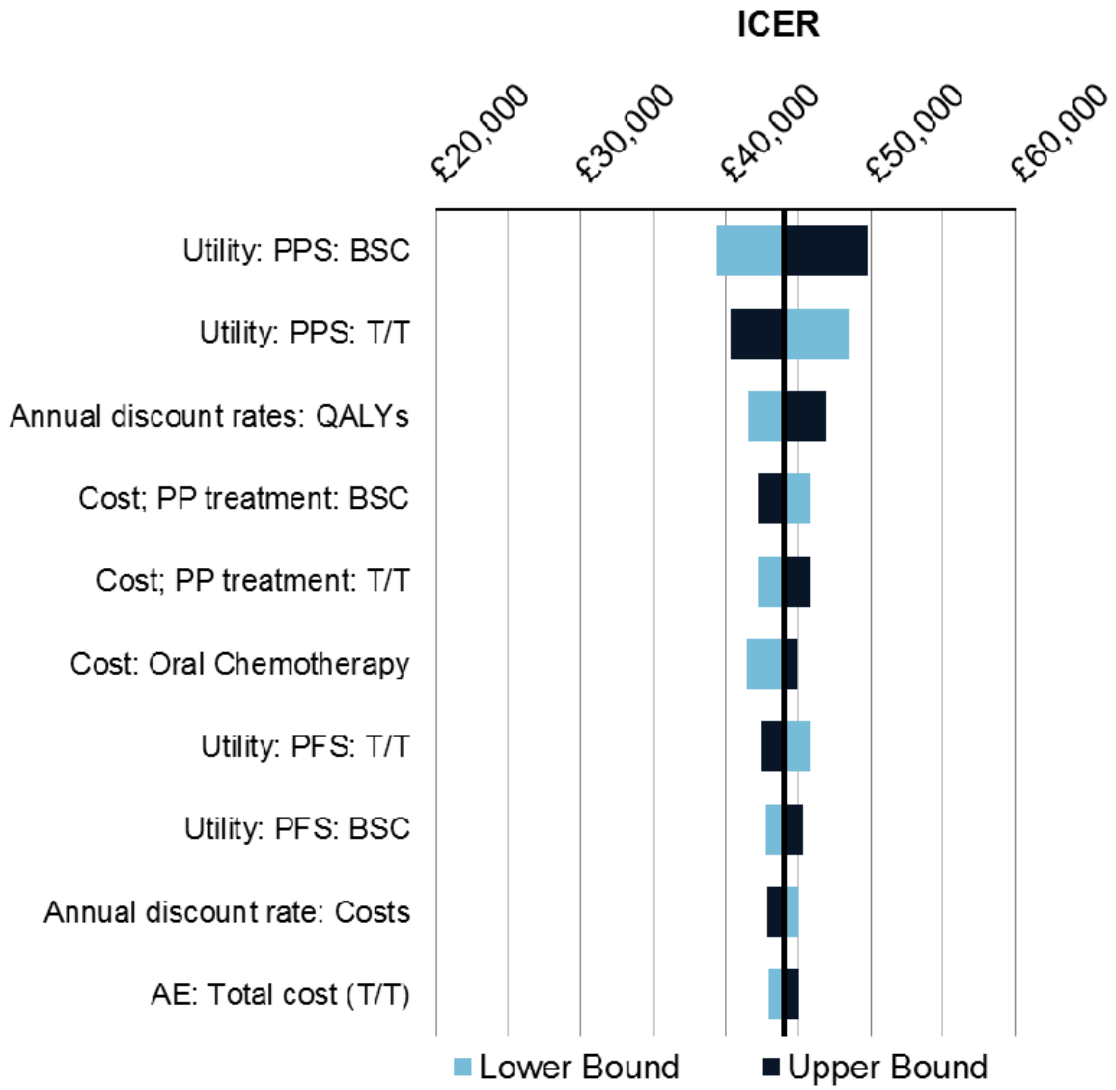
Key: BSC, best supportive care; T/T, trifluridine/tipiracil.

5.8.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted to explore the sensitivity in the deterministic base-case model results when one parameter is varied at a time. Each parameter was set to its lower and upper bound and the deterministic model results were recorded. The top ten influential parameters on the ICER are presented as a tornado diagram for the list price and PAS price in [redacted] and Figure 42, respectively.

[redacted]

Figure 42: One-way sensitivity analysis: Tornado diagram – PAS price



Key: AE, adverse event; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PFS, progression-free survival; PP, post-progression; PPS, post-progression survival; QALY, quality-adjusted life year; T/T, trifluridine/tipiracil.

As shown in the tornado diagram, the most influential parameters on the model result were utility values for pre- and post-progression health states, the annual discount rate for QALYs and the costs for post-progression treatment. The uncertainty surrounding the choice of utility values has been discussed previously, and is primarily due to the lack of available data to provide more robust estimates of the HRQL for patients in this setting. The variation in results due to the annual discount rate applied for QALYs further demonstrates the uncertainty surrounding the HRQL of these patients.

The uncertainty around the cost of post-progression treatment is relatively small, and is intrinsically linked to the fact that the costs are applied in isolation, and therefore, if varied simultaneously, this uncertainty would not be nearly as influential on model results.

5.8.3 Scenario analysis

Scenario analysis was performed to analyse the effect of varying a given model parameter on the base-case model results. The full list of scenarios considered for the list price and PAS price are presented in Table 81.

As part of scenario analysis, a comparison to regorafenib (Stivarga®; Bayer plc.) was undertaken. Regorafenib is the only other licensed product in the same disease stage as trifluridine/tipiracil, but is not recommended for use in the NHS, and its NICE appraisal was terminated due to non-submission by the company.

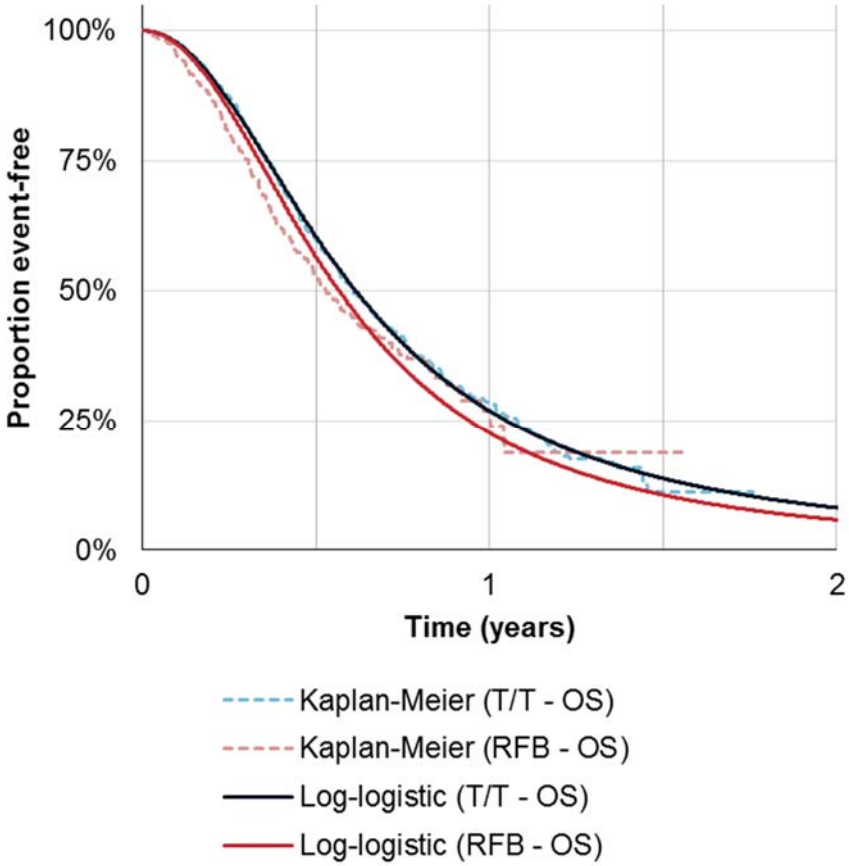
A naïve indirect Bucher comparison was undertaken to estimate the OS and PFS for patients on regorafenib, based on HRs reported from the CORRECT study of regorafenib versus BSC and from the RECOURSE study of trifluridine/tipiracil versus BSC.[2, 57] Both studies were placebo controlled, with neither allowing crossover, as such a naïve comparison is not expected to be biased.

The HRs taken from each trial are shown in Table 79, along with the derived HRs using the Bucher method of indirect comparison. The resultant OS and PFS curves are given in Figure 43 and Figure 44, respectively.

Table 79: Hazard ratios taken from the CORRECT and RECOURSE studies

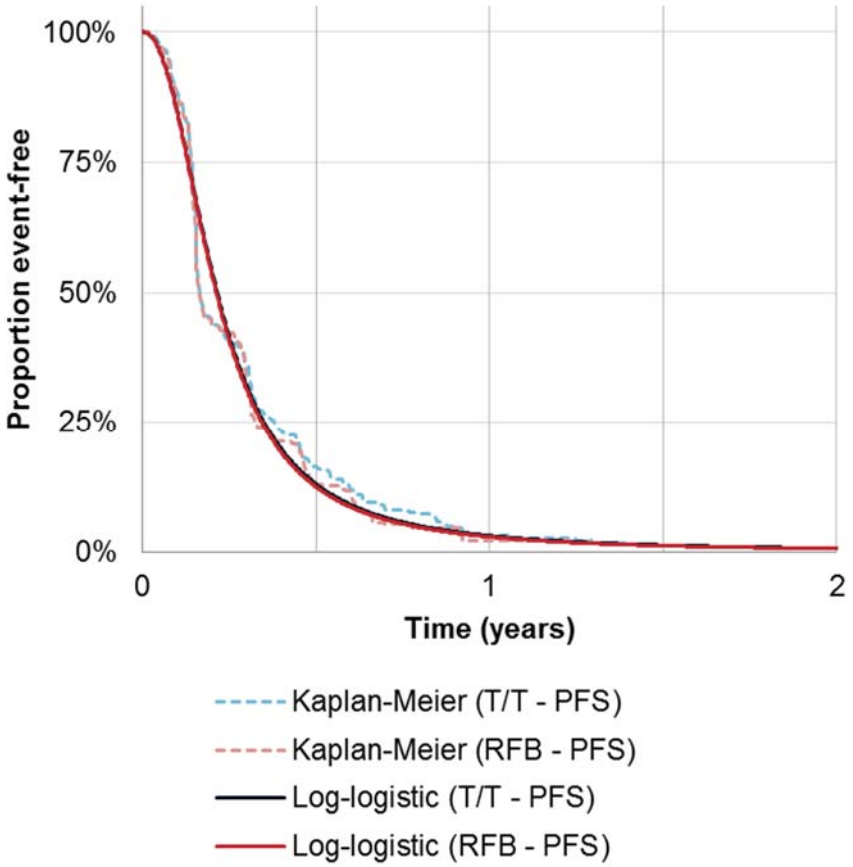
HR	Mean	95% CI (LB)	95% CI (UB)	p-value	SE	Reference
OS: T/T vs BSC	0.68	0.58	0.81	<0.001	0.09	Mayer et al. 2015[2]
PFS: T/T vs BSC	0.48	0.41	0.57	<0.001	0.08	
OS: RFB vs BSC	0.77	0.64	0.94	0.005	0.10	Grothey et al. 2013[57]
PFS: RFB vs BSC	0.49	0.42	0.58	<0.0001	0.08	
OS: RFB vs T/T	1.13	0.88	1.46	-	0.13	Calculation based on the Bucher method[66]
PFS: RFB vs T/T	1.02	0.81	1.29	-	0.12	
Key: BSC, best supportive care; CI, confidence interval; LB, lower bound; OS, overall survival; PFS, progression-free survival; RFB, regorafenib; SE, standard error; T/T, trifluridine/tipiracil; UB, upper bound.						

Figure 43: Overall survival – trifluridine/tipiracil versus regorafenib



Key: OS, overall survival; RFB, regorafenib; T/T, trifluridine/tipiracil.

Figure 44: Progression-free survival – trifluridine/tipiracil versus regorafenib



Key: PFS, progression-free survival; RFB, regorafenib; T/T, trifluridine/tipiracil.

Adverse event rates were also taken from the CORRECT study, with the costs of treating adverse events assumed to be the same as those for trifluridine/tipiracil and BSC. Additional adverse events were costed as shown in Table 80.

Table 80: Additional adverse events reported in the CORRECT study

AE	Actively treated		Cost of treatment		Reference (see notes for sources)	
	All grades	Grade ≥3	Grade ≤2	Grade ≥3	Grade ≤2	Grade ≥3
Oral mucositis	✓	✓	£158.43	£158.43	**a**	**a**
Hypertension		✓		£131.14		**b**
Rash		✓		£158.43		**a**
Constipation		✓		£158.43		**a**
Dry skin		✓		£158.43		**a**
Sensory neuropathy		✓		£158.43		**a**
Dyspnoea		✓		£158.43		**a**
Muscle pain		✓		£158.43		**a**
Headache		✓		£158.43		**a**
Hyperbilirubinemia		✓		£158.43		**a**
Proteinuria		✓		£158.43		**a**
Hypophosphatemia		✓		£158.43		**a**

Key: AE, adverse event.
Notes: a NHS Reference costs 14-15: Outpatient visit, general medicine[61]; **b** NHS Reference costs 14-15: Service code 320 Cardiology, Total cost.[61]

The cost of regorafenib was taken from the monthly index of medical specialities as £3,744 per 28 days (based on a pack size of 84 tablets and a dosing regimen of four pills per day on Days 1-21 of a 28 day cycle).[67] This is the main driver of the results in this sensitivity analysis as it is far in excess of the trifluridine/tipiracil list price (after the PAS is applied the difference becomes even more pronounced). With a far higher price and lower efficacy, in no plausible scenario is regorafenib cost effective compared to trifluridine/tipiracil.

All other model inputs were assumed to be comparable with those relating to trifluridine/tipiracil, given the similarities between the two oral chemotherapies.

Table 81: Scenario analysis results – list price

Input	Base case	Scenario	ICER (List price)	ICER (PAS price)
Base case			[redacted]	£44,032
Time horizon	10 years	2 years	[redacted]	£53,422
		4 years	[redacted]	£47,113
		6 years	[redacted]	£45,309
		8 years	[redacted]	£44,488
Patient population	Pooled	RECOURSE	[redacted]	£45,748
		Phase II	[redacted]	£37,523
Comparator	Best supportive care	Regorafenib	[redacted]	T/T Dominates
Subgroup	Updated OS	Original OS	[redacted]	£45,279
OS and PFS curve choice	Stratified log-logistic	Generalised Gamma	[redacted]	£43,528
		Log-logistic	[redacted]	£43,935
		Log-normal	[redacted]	£46,260
		Stratified Generalised Gamma	[redacted]	£47,460
		Stratified Log-normal	[redacted]	£44,460
Resource use	Total cost derived as per Section 5.5.	+20% of total cost	[redacted]	£44,704
		-20% of total cost	[redacted]	£42,647
Utility source	CORRECT study – utility associated with treatment	Cetuximab NICE submission	[redacted]	£45,509
		CORRECT study – assumed BSC utility for all patients	[redacted]	£44,702
Discounting (Costs, LYs, QALYs)	3.5%, 0%, 3.5%	0%, 0%, 0%	[redacted]	£42,523
		6%, 6%, 6%	[redacted]	£45,117
PP treatment	Equal costs by treatment arm	Unequal costs by treatment arm	[redacted]	£44,385

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PP, post-progression; QALY, quality-adjusted life year.

The results of the scenario analysis demonstrate similar levels of cost effectiveness to the results of both the list and PAS prices for trifluridine/tipiracil. The most influential scenarios on the model results were the time horizon over which the costs and benefits of treatment are considered, and the choice of distribution from which efficacy data were fit to and extrapolated. Only in one of these scenarios does the ICER with the PAS price exceed £50,000 per QALY.

The choice of time horizon will inherently affect model results as the full benefits of treatment with trifluridine/tipiracil will not be captured over a relatively small time horizon (e.g. 2 years) compared with a longer time horizon during which the lifetime of patients is considered.

The choice of distribution for OS and PFS will also affect model results, as these parameters directly influence transitions between the model health states, and are therefore linked with the associated costs and benefits. Discussion regarding the base-case choice of these distributions is provided in Section 5.3. Given the importance the choice of distribution has on the model results, the variation seen between alterative choices of distribution is not dramatically different.

ICERs from the scenario analyses ranged between [redacted] and [redacted] at the list price for trifluridine/tipiracil against BSC. At the PAS price for trifluridine/tipiracil, ICERs from the scenario analyses ranged between £30,197 and £53,422. Trifluridine/tipiracil was shown to be dominant against regorafenib at both the list price and the PAS price.

5.8.4 Summary of sensitivity analyses results

PSA demonstrated an even spread of points around the deterministic mean for both the list and PAS price of trifluridine/tipiracil, with the majority of uncertainty demonstrated in the QALY gain as opposed to the difference in costs. This is likely driven by the uncertainty surrounding the estimates of HRQL in the model.

At the list price, the probabilities of trifluridine/tipiracil being the most cost-effective treatment are 0% and 36% for WTP thresholds of £30,000 and £50,000, respectively. At the PAS price, the probabilities of trifluridine/tipiracil being the most cost-effective treatment are 0% and 77% for WTP thresholds of £30,000 and £50,000, respectively.

OWSA further demonstrated the impact of HRQL in the model.

Scenario analysis also reported similar levels of cost effectiveness across the scenarios considered. The most influential scenarios on the model results were the time horizon over which the costs and benefits of treatment are considered (explained by the full benefits and costs not being captured over a restricted time horizon of 2 years), and the choice of distribution from which efficacy data were fit to and extrapolated (due to the influence of these distributions having on the extrapolated OS).

Results from the scenario analyses ranged between [redacted] and [redacted] at the list price for trifluridine/tipiracil against BSC. At the PAS price for trifluridine/tipiracil, ICERs from the scenario analyses ranged between £30,197 and £53,422. Trifluridine/tipiracil was shown to be dominant against regorafenib at both the list price and the PAS price due to higher efficacy (0.11 LYG, 0.07 incremental QALYs), and lower costs [redacted] and -£7,764 at list price and the PAS price, respectively).

As expected, the model is mainly sensitive to features attributable to HRQL and survival, given the importance these parameters place on the transitions within the model and the valuation of survival spent in these health states. Survival data from the pooled trials are fairly complete, with only a small proportion of patients event-free at the end of the observed time period. However, limitations regarding the HRQL data are known, and therefore, uncertainty surrounding these parameters has been thoroughly tested through sensitivity analysis.

5.9 Subgroup analysis

Subgroup analysis is not considered in the de novo analysis, given the size of the patient population and that, in RECOURSE, trifluridine/tipiracil was associated with a clinically relevant prolongation in OS in all treatment subgroups.[2]

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

The de novo cost-effectiveness analysis was validated using a range of experts and methods, detailed in Table 82.

Table 82: Validation of the de novo cost-effectiveness analysis

Validation performed by	Nature of validation	Date	Aspects covered
Prof. Martin Hoyle	Full technical review	December 2015	Cost-effectiveness model and Section 5 of the submission.
Advisory board of health economic (and clinical) experts	Review	January 2016	Complete cost-effectiveness model and submission
BresMed	Quality-control check	January 2016	Cost-effectiveness model

5.11 Interpretation and conclusions of economic evidence

The economic evidence presented in this document considers the cost effectiveness of trifluridine/tipiracil 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 chemotherapy, an anti-VEGF biological therapy, and an anti-EGFR therapy.[7]

In the model base case, trifluridine/tipiracil was associated with an ICER of [redacted] the list price. This ICER consisted of incremental costs of [redacted] per patient for the list price of trifluridine/tipiracil, with a 0.27 LY gain and 0.17 incremental QALYs. Incremental costs considering the PAS price for trifluridine/tipiracil were £7,574 per patient with an ICER of £44,032. Sensitivity analysis demonstrated the robust nature of these estimates around all crucial model parameters.

Trifluridine/tipiracil has been shown to demonstrate substantial benefit in both pre-progression and post-progression health states, with an approximate extension to life of 3 months (0.27 LYs), approximately 2/3 of which is pre-progression. This, in combination with mean survival in mCRC patients at third-line treatment of approximately 6 months and a small patient population, suggests trifluridine/tipiracil qualifies as an end-of-life treatment with an impressive extension to life for patients with one of the worst survival profiles assessed by NICE.

6 Assessment of factors relevant to the NHS and other parties

6.1 Eligible patient population

In England, 34,322 patients were diagnosed with colorectal cancer in 2012.[8] Approximately, 19,600 patients will develop mCRC each year; see Table 9 for calculations.

One-year mortality in patients with mCRC is greater than 60%.[9] Mortality increases as patients proceed through the lines of treatment. Given the high mortality rates for patients at this stage of disease, it has been assumed that the number of patients with mCRC year on year remains constant.

Approximately 13% of patients with mCRC will be eligible for surgery.[35] Clinical experts suggested that of these, approximately 1,100 patients will have no further relapse following surgical intervention and have an effective cure.[4] This leaves approximately 18,500 patients who would be eligible to receive therapeutic options. Table 83 provides a breakdown of the estimated number of patients who receive therapy at each line of treatment. These estimates have been adapted from Hind et al. following expert opinion.[35]

Table 83: Estimate of patient numbers for metastatic colorectal cancer at different lines of treatment

Line	Disaggregation of patients	Number of patients
1st Line	No further therapy* (15%)	2,773
	First line therapy† (85%)	15,711
2nd line	No further therapy* (50%)	7,856
	Second line therapy† (50%)	7,856
3rd line onwards	No further therapy* (67%)	5,263
	Third line therapy onwards† (33%)	2,592

Key: mCRC, metastatic colorectal cancer.
Notes: Disaggregation of patients was were adapted from Hind et al. following expert opinion.[35]
* Patients have either died, are ineligible or have opted to stop active therapy.
† Either recommended treatment or clinical trial participation.

6.2 Projected uptake of trifluridine/tipiracil

Trifluridine/tipiracil is licensed 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-VEGF agents, and anti-EGFR agents.[7] Therefore, trifluridine/tipiracil will be available for patients who have received at least two lines of chemotherapy (i.e. third line or beyond). Table 83 shows that approximately 2,600 patients would be eligible at this line of treatment.

There are currently no NICE- or CDF-recommended treatment options for patients who have failed second-line treatment for mCRC. Discussion with clinical experts has identified that patients at this stage of disease who are well enough and who wish to continue active treatment may receive capecitabine, chemotherapy re-challenge or go into clinical trials. Table 84 sets out the projected uptake of trifluridine/tipiracil for the first five years of trifluridine/tipiracil availability, with 20% of patients expected to receive the treatment in the first year of availability, before reaching a steady state of approximately 40% of eligible patients being offered and electing to receive treatment with trifluridine/tipiracil.

Table 84: Expected uptake of trifluridine/tipiracil over Years 1-5

Year	Percentage	Number of patients
1	20%	518
2	30%	778
3	40%	1,037
4	40%	1,037
5	40%	1,037

6.3 Additional costs: Monitoring and management of adverse events

Full details are included in Section 5.5.

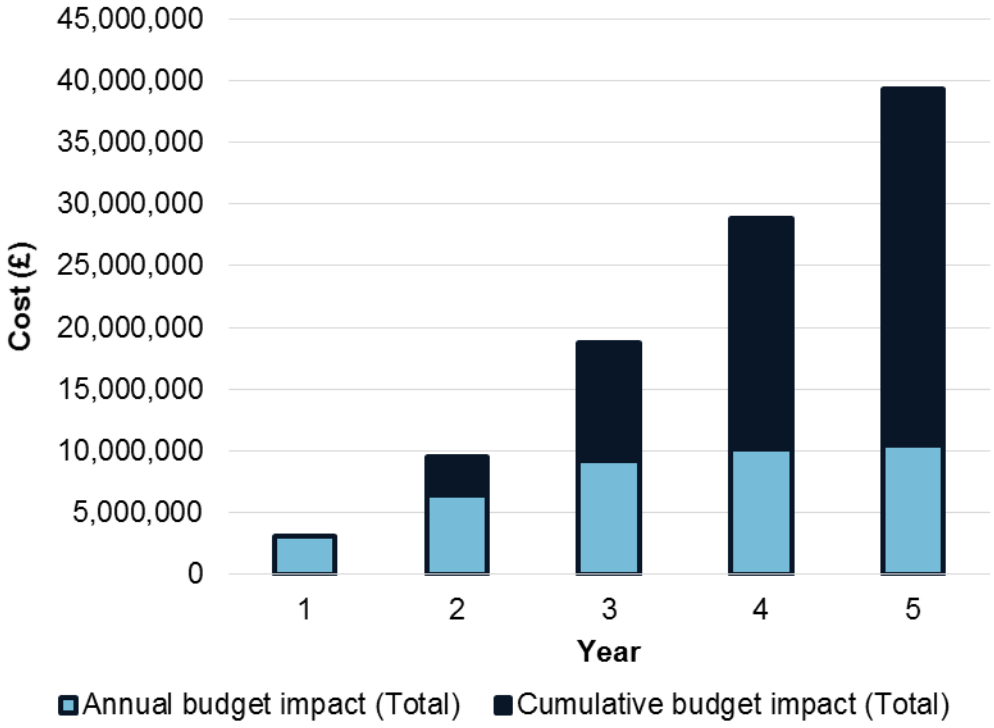
6.4 Estimated annual budget impact

Using these predicted patient figures, the budget impact is presented in Table 85 and [redacted] for the list price of trifluridine/tipiracil, and in Figure 46 and Table 86 for the PAS price. The budget impact presents results in terms of the total costs projected following implementation of trifluridine/tipiracil into the NHS. The presented results are incremental compared to BSC.

In the first year of availability, the total budget impact of trifluridine/tipiracil at the list price would be expected to be approximately [redacted], rising to [redacted] in Year 5. At the PAS price, the total budget impact of trifluridine/tipiracil in the first year of availability would be expected to be approximately £3.15 million, rising to £10.67 million in Year 5.

[redacted]

Figure 46: Budget impact results – PAS price



Key: PAS, patient access scheme.

Table 85: Budget impact results – list price

Year	Cost (£)						Patients				Budget impact (£)			
	T/T		BSC		Incremental		Incident		Total		Annual		Cumulative	
	Total	Drugs only	Total	Drugs only	Total	Drugs only	All Patients	Patients on T/T	Patients on T/T	Active patients	Total	Drugs only	Total	Drugs only
1	[redacted]	[redacted]	£9,085	£0	[redacted]	[redacted]	2,592	518	518	518	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	£10,062	£0	[redacted]	[redacted]	2,592	778	920	794	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	£10,291	£0	[redacted]	[redacted]	2,592	1,037	1,293	1,064	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	£10,378	£0	[redacted]	[redacted]	2,592	1,037	1,406	1,075	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	£10,424	£0	[redacted]	[redacted]	2,592	1,037	1,448	1,078	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; T/T, trifluridine/tipiracil.

Table 86: Budget impact results – PAS price

Year	Cost (£)						Patients				Budget impact (£)			
	T/T		BSC		Incremental		Incident		Total		Annual		Cumulative	
	Total	Drugs only	Total	Drugs only	Total	Drugs only	All Patients	Patients on T/T	Patients on T/T	Active patients	Total	Drugs only	Total	Drugs only
1	£15,163	£6,158	£9,085	£0	£6,078	£6,158	2,592	518	518	518	£3,148,337	£3,189,673	£3,148,337	£3,189,673
2	£17,183	£6,449	£10,062	£0	£7,121	£6,449	2,592	778	920	794	£6,465,953	£5,120,158	£9,614,289	£8,309,831
3	£17,720	£6,532	£10,291	£0	£7,428	£6,532	2,592	1,037	1,293	1,064	£9,401,427	£6,952,320	£19,015,716	£15,262,150
4	£17,942	£6,570	£10,378	£0	£7,563	£6,570	2,592	1,037	1,406	1,075	£10,302,300	£7,064,941	£29,318,017	£22,327,091
5	£18,057	£6,591	£10,424	£0	£7,634	£6,591	2,592	1,037	1,448	1,078	£10,668,729	£7,108,245	£39,986,745	£29,435,336

Key: BSC, best supportive care; T/T, trifluridine/tipiracil.

6.5 Limitations of the budget impact calculation

The main limitations of the budget impact calculation is that there are no published data detailing the number of patients with mCRC who receive treatment by line of therapy. Estimates for these numbers have been derived from expert opinion; nonetheless, they represent the best available data for patients at this line of therapy. Secondly, the uptake estimates provided are based on projections from clinical experts, and are not evidence based.

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Single Technology Appraisal (STA)

Trifluridine in combination with tipiracil hydrochloride for previously treated metastatic colorectal cancer [ID876]

Dear [redacted]

The Evidence Review Group, Kleijnen Systematic Reviews Ltd., and the technical team at NICE have now had an opportunity to take a look at the submission received on 26 February 2016 from Servier Laboratories. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter). The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **6pm** on **7th April 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Christian Griffiths, Technical Lead (christian.griffiths@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk)

Yours sincerely

Rosie Lovett PhD
Technical Adviser
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Section A: Clarification on effectiveness data

Information retrieval

A1. **Priority request:** The results of the literature searches to identify health-related quality of life (HRQoL) data reported in section 5.4.2 do not correspond with the results reported in the detailed search strategies produced in appendix 10.[1]

- Have the correct search strategies for identifying HRQoL studies been reported in appendix 10?
- Appendix 13, referred to on pages 148 and 150 of the company submission, is missing. Please provide this appendix.
- Please check whether the list of excluded studies (section 10.7, table 7) is correct.

A2. Please provide more details for the searches of conference proceedings, including the specific conference proceedings searched, the search strategies and search terms used, website addresses, and results.

Definitions

A3. **Priority requests:**

- Please provide a definition for best supportive care (BSC) used in the included trials.
- Please provide the guidance regarding BSC given to the centres involved in the included trials.
- Please explain whether the definition of BSC used in the RECOURSE trial is applicable to the UK setting.

A4. The supplementary tables for the main publication of the RECOURSE trial provide definitions of progression and stable disease.[2]

- Please clarify the definitions used in the included phase II RCT.[3]
- For both trials, please provide more details on the assessment methods, e.g. how many assessors, experience of assessors, training to ensure consistency between study centres.

Included trials

A5. **Priority request:** There appears to be a significant question as to the generalisability of RECOURSE to the UK population given a discrepancy in survival between the data presented in Section 3.4.1 and the survival observed in the trial. In particular,

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one-year survival for patients with metastatic colorectal cancer (mCRC) was presented as 40% and 33% for men and women, respectively, based on a UK data source.[4] This could be compared with the estimated 1-year survival in the placebo arm of 17.6% (table 25), which suggests that the survival in the trial is much lower. In fact, survival in the trial is conditional on having survived to 3rd line, which is about 3 years since diagnosis.[5] Therefore, the figure of 17.6% should actually be compared to survival to four years conditional on surviving three years from diagnosis. Assuming a constant annual mortality rate, this would be the same as the 1-year survival (from diagnosis) i.e. between 33% and 40% (the average across women and men). This is clearly very different to the 17.6% in the trial.

- Please explain this apparent discrepancy.
- The ERG was unable to assess whether this comparison was suitable. Please provide patient characteristics from all 3 sources (phase II trial,[3] RECOURSE[2] and cancer research UK[4]).
- Please explain how the RECOURSE trial can be applicable to the UK given this large discrepancy in survival.

A6. According to table 15 of the company submission, all people included in the phase II RCT were recruited in Japan whereas participants of RECOURSE were from Japan, Europe, USA and Australia.[2, 3]

- Please provide the number of RECOURSE participants by country.
- Please provide detailed baseline characteristics and results for patients in RECOURSE from Europe and the UK, respectively, i.e. separate Europe and the UK.
- Please justify how the included patients (from the phase II trial, RECOURSE, and the combined analysis) are representative for the UK setting.

A7. Information on clinicaltrials.gov for RECOURSE (NCT01607957) indicates the final data collection date for the primary outcome measure was February 2016. However, the main publication for the trial was submitted in January 2015.[2]

- Please confirm whether the final results for RECOURSE were presented in Mayer 2015 New England Journal of Medicine.[2]
- Section 4.4.2 of the company submission[6] suggests that updated analyses were conducted. Please indicate which (additional) endpoints were analysed and state which of these analyses were pre-specified and provide all of these results.

A8. Information on clinicaltrials.gov for TERRA (NCT01955837) indicates that the final data collection date for the primary outcome measure was February 2016.

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- Please confirm that no results are available or if they are, please provide them.

A9. Section 4.11 of the company submission provides details on two non-randomised studies.

- Please clarify how these studies were identified and selected for inclusion.
- Please submit an amended version of section 4.11 with the inclusion and exclusion criteria used as well as the flow chart.

Trial results

A10. Section 4.12 of the company submission[6] presents results on adverse events (AEs) observed in the two included trials. Table 43 (*"All adverse events within RECOURSE published data"*) shows that more serious AEs were observed in the placebo arm (33.6%) than the trifluridine and tipiracil arm (29.6%).

- Please provide breakdowns of the number of serious adverse events for trifluridine and tipiracil and for placebo (BSC) for the phase II trial and RECOURSE, respectively.
- Please provide any additional data which were not part of the "published data".

A11. Page 87 of the company submission presents results the median progression-free survival by KRAS type.[6]

- Were these analyses pre-specified?
- Please provide results for any subgroup analyses performed.

Statistical analysis

A12. **Priority request:** According to section 5.3 of the company submission [6], pooled progression-free survival and overall survival in the economic model were estimated using the updated RECOURSE (phase III) trial data[2] and phase II clinical trial data[3]. However, justification for pooling this and any explanation of how pooling was performed is lacking. Furthermore, other parameters, such as time on treatment, body surface area, dose reductions and adverse event rates are only based on RECOURSE data.

- Please justify why a pooled analysis is used, given that the phase II trial only consists of Japanese patients and hence using the RECOURSE trial only would be more representative for the UK setting.
- Please provide pooled estimates (based on the phase II trial[3] and RECOURSE[2]) for the following input parameters:

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- time on treatment,
- body surface area,
- dose reductions,
- adverse event rates.

- Please provide a detailed description of the methods used to pool the data from both trials for all above-mentioned parameters as well as progression-free survival and overall survival.

Section B: Clarification on cost-effectiveness data

Treatment effectiveness and adverse events

B1. **Priority request:** The NICE DSU technical support document for survival analysis[7] recommends that the decision of whether to stratify survival models should be based on log-cumulative hazard plots, quantile-quantile plots or suitable residual plots.

- Please provide the log-cumulative hazard plots and quantile-quantile plots for all survival curves representing progression-free survival and overall survival reported in the company submission.[6]

- It was unclear to the ERG how single Akaike Information Criterion (AIC) estimates were obtained for the stratified analyses. Stratified analyses result in two AIC estimates for each stratified analyses for trifluridine in combination with tipiracil and for BSC respectively. Please provide the AIC estimates separately for each stratified model (i.e. separately for the stratified models for trifluridine in combination with tipiracil and BSC) and explain how these AIC estimates were combined to obtain one AIC.

- On page 137 of the company submission[6], it is stated that a stratified model is preferred by the company *"Given that within both trials randomisation was not equal (2:1)"*. Please clarify why the unequal randomisation is an argument for selecting a stratified model.

B2. **Priority request:** In the RECOURSE trial[2], different magnitudes of effect of trifluridine in combination with tipiracil are observed in different pre-specified subgroups.

- Please provide subgroup analyses in the cost-effectiveness analysis for the following subgroups:
  - wild-type KRAS
  - mutant KRAS

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- Please provide the list of changed input parameters (progression-free survival, overall survival, time on treatment, body surface area, dose reductions, adverse event rates).

B3. Please provide the cost-effectiveness results of a sensitivity analysis containing the pooled estimates for time on treatment, body surface area, dose reductions and adverse event rates as asked in clarification question A13.

Health related quality of life

B4. **Priority request:** The impact of adverse events on health-related quality of life is not incorporated in the analysis despite the fact that patients receiving trifluridine in combination with tipiracil had more grade >2 adverse events than placebo in the RECOURSE trial. This is justified in the company submission by stating a lack of evidence. Evidence on the quality of life impact of these adverse events is available (see for instance TA307[8], table B29 of company submission[6]).

- Please incorporate the impact of adverse events on health related quality of life in the economic analysis.

B5. Chang 2015[9] and Siena 2013[10, 11] were identified in a systematic review as studies that may meet the requirements of the NICE reference case.

- Please justify why Siena et al. (CORRECT study)[10, 11] was used, and Chang[9] was not used.

B6. The model inputs for health state utilities are based on an average of utilities from the CORRECT study and TA176[12].

- Please justify why TA176[12] is an appropriate source for health state utilities, as 1) the health state utility used for pre-progression (0.73) retrieved from TA176[12] was based on strong assumptions and reported to be for 2nd line treatment while trifluridine in combination with tipiracil is indicated for third line treatment. Moreover, 2) for the health state utility used for post-progression (0.68) in TA176[12] it was reported that this value may not capture lower utility weights in the terminal stage and hence is unlikely to reflect 3rd line post-progression health related quality of life.

- Please justify why TA176[12] was used and not other NICE appraisals that may contain relevant information (e.g. TA118[13], TA212[14], TA307[8] and ID794[15]).

Resource use and costs

B7. **Priority request:** Table 57 in the company submission[6] provides an overview of adverse events observed in the RECOURSE trial[2] and table 67 of provides an overview of adverse events for which costs are incorporated in the model. Several

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adverse events are missing in this table (i.e. adverse events reported in table 57 but not in table 67).

- Please include all adverse events reported in table 57 in an updated version of table 67 (including the cost of treatment and references). For instance "Increase in total bilirubin" can be included using the costs of treatment for Hyperbilirubinemia reported in table 80 of the company submission.[6]

- Please provide the results of a scenario analysis including these updated adverse event costs in the cost-effectiveness analysis.

B8. In the economic model, time to treatment discontinuation was approximated using progression-free survival and dosing of trifluridine in combination with tipiracil was approximated using body surface area. Based on table 54 of the company submission[6], it seems that empirical data are available to estimate these parameters.

- Please provide time to treatment discontinuation and dosing for trifluridine in combination with tipiracil estimated using empirical data from the RECOURSE trial.[2]

- Please incorporate these empirical estimates for time to treatment discontinuation and trifluridine/tipiracil dosing in the economic model and provide the cost-effectiveness results.

- Please clarify how treatment delay was calculated for BSC (i.e. which treatment was used to calculate time to treatment initiation), reported in table 54 of the company submission.[6].

B9. Resource use was obtained from ID794[15] because the company considered ID794[15] to be 'particularly relevant'.

- Please justify why ID794[15] is an appropriate source for resource use, as this assessment considers a population in an earlier treatment line (1st line) and a specific subpopulation (RAS wild type).

- Please clarify why ID794[15] is preferred over other appraisals that may contain relevant information, e.g. TA118[13], TA176[12], TA212[14] and TA307[8].

B10. On page 157 of the company submission[6] it is explained that in pre-progression patients receiving BSC were assumed to have an outpatient consultation with an oncologist per treatment cycle.

- Please clarify what this assumption (both the outpatient consultation itself and its frequency) was based on and in the case of expert opinion provide details and a step-by-step description of the expert elicitation process.

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B11. Page 140 of the company submission[6] explains that *"treatment with trifluridine/tipiracil is continued until disease progression, clinical progression, the development of severe adverse events (AEs), withdrawal from the study, death, or a decision by the treating physician that discontinuation would be in the patient's best interest"*.

- Please confirm whether in the trials none of participants have continued treatment with trifluridine in combination with tipiracil after disease progression.
- If treatment continuation after disease progression did occur, please provide the rate of these occurrences and justify why this was not incorporated in the resource use.

B12. Page 157 of the company submission[6] states that medical resource use items were identified following consultation with clinical experts, due to the lack of published literature.

- Please report what steps were taken to systematically obtain evidence on resource use (publications, trial data, clinical guidelines, relevant STAs).
- Please provide details and a step-by-step description of the process used to obtain expert opinion (expert selection, elicitation method, etc).

B13. The costs of post-progression treatment were estimated based on the RECOURSE trial[2] and reported in Table 69 of the company submission[6].

- Please justify why equal post progression treatment costs were assumed for trifluridine in combination with tipiracil and BSC.

Model validation

B14. **Priority request:** External validation of model results is crucial to assess the validity of model outcomes. In section 5.3.3 of the company submission[6], survival estimates from the model are compared with other published data (e.g. cancer research UK)[4]. The cancer research UK data indicate that the survival 5 years after diagnosis of metastasis is 7-8%. This is compared with the estimated 2-year BSC survival in the model (4%) which is on average 5 years after diagnosis of metastatic disease (since time from diagnosis of metastatic disease to study initiation was, on average, 35.2 months[5]). Hence, the 2-year BSC survival of 4% is conditional on having survived approximately three years before trial inclusion (in contrast with the cancer research UK data).

- The ERG calculated the 2-years survival for stage 4 bowel cancer patients conditional on having already survived 3 years based on the cancer research UK data[4]. A constant mortality rate was assumed. The calculation resulted in a 2-years survival of approximately 35% for patients having already survived

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3 years. Please explain this discrepancy between the pooled 2-years survival estimates of patients participating in both trials provided in the company submission[6] (4%) and the estimate based on the cancer research UK data (~35%)[4].

- Please provide a comparison of the mean progression-free survival estimate as provided in table 74 of the company submission[6] with external sources such as cancer research UK and Jonker et al.[16] or other suitable sources (and justify why these sources are suitable for such a comparison by providing patients characteristics).

B15. Section 5.10 of the company submission[6] contains different efforts undertaken by the company to validate the cost-effectiveness model.

- Please describe which steps have been undertaken to assess the face validity and the internal validity of the cost-effectiveness model.

B16. Presumably, since the systematic review did not identify a cost-effectiveness analysis of trifluridine in combination with tipiracil compared with BSC (section 5.1 of the company submission), the company did not perform any cross validation of its results with another cost-effectiveness analysis. However, one study from Goldstein et al.[17], which was identified in the systematic review (and excluded), assesses the cost-effectiveness of regorafenib versus BSC as third-line treatment for mCRC. Furthermore, ID794[15] reports mean treatment and survival times for mCRC patients beginning third-line treatment (from a study of Jonker et al.[16]).

- Please compare the study by Goldstein et al.[17] with the present assessment and, separately, compare ID 794[15] with the present assessment:
  - Regarding input parameters, model structure and assumptions.
  - Regarding outcomes for the BSC arm of both studies.

General

B17. **Priority request:** According to the NICE Methods Guide[18], probabilistic methods provide the best estimates of mean costs and outcomes in non-linear decision models.

- Please provide the probabilistic results for all analyses presented in tables 72-78 and table 81.

B18. The scenario analyses for body surface area, described in section 5.3.5 of the company submission are missing in table 81.[6]

- Please provide the probabilistic results for these scenario analyses.

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B19. In the probabilistic sensitivity analyses, the minimum and maximum of multiple parameters was assumed to be +/- 20% of the mean (table 70).[6]

- Please use the empirical data if possible to estimate the variance for input parameters (e.g. for treatment delay per patient per cycle and post-progression costs) and provide the estimated standard errors.

- Please justify why the minimum and maximum was not estimated based on expert opinion as was done for the estimated value of the resource use parameters (instead of using the arbitrary +/- 20% of the mean).

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References

[1] Servier Laboratories. *Colorectal cancer (metastatic) - trifluridine with tipiracil hydrochloride, after standard therapy [ID876]: Appendices. Single technology appraisal (STA)*: Servier Laboratories, 2016

[2] Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 2015;372(20):1909-19.

[3] 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.

[4] Cancer Research UK (CRUK). Statistics and outlook for bowel cancer. (Updated: 26 August 2015) [Internet]. London: Cancer Research UK (CRUK), 2015 [accessed 10.3.16]. Available from: http://www.cancerresearchuk.org/about-cancer/type/bowel-cancer/treatment/statistics-and-outlook-for-bowel-cancer

[5] Servier Laboratories. *Analysis of RECOURSE trial data. Data on File*: Servier Laboratories, 2016

[6] Servier Laboratories. *Colorectal cancer (metastatic) - trifluridine with tipiracil hydrochloride, after standard therapy [ID876]: Company evidence submission to National Institute of Health and Care Excellence. Single technology appraisal (STA)*: Servier Laboratories, 2016

[7] Latimer N. *NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Report by the Decision Support Unit [Internet]*. Sheffield: School of Health and Related Research (ScHARR), 2013 [accessed 10.3.16] Available from: http://www.nicedsu.org.uk/

[8] Sanofi UK. *Aflibercept (Zaltrap®) for the treatment of metastatic colorectal cancer (mCRC) previously treated with an oxaliplatin containing regimen. Submitted by Sanofi UK 14 February 2013. Single technology appraisal (STA)*: Sanofi UK, 2013 Available from: https://www.nice.org.uk/guidance/TA307/documents/colorectal-cancer-metastatic-aflibercept-evaluation-report2

[9] Chang J, Ngai C, Odom D, Radder C, Kappeler C, Xu R-H, et al. Effects of regorafenib (REG) therapy on health-related quality of life (HRQoL) in patients with metastatic colorectal cancer (mCRC) in the phase III CONCUR trial. *J Clin Oncol* 2015;33(15 Suppl 1).

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[10] Siena S, Grothey A, Sobrero A, Falcone A, Ychou M, Lenz HJ, et al. Effects of regorafenib therapy on health-related quality of life in patients with metastatic colorectal cancer in the phase III CORRECT study. *Eur J Cancer* 2013;49(27):S482.

[11] 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.

[12] Merck Serono Ltd. *Single technology appraisal submission: erbitux (cetuximab) for the first-line treatment of metastatic colorectal cancer*: Merck Serono Ltd, 2008 Available from: https://www.nice.org.uk/guidance/TA176/documents/colorectal-cancer-first-line-cetuximab-merckserono2

[13] Roche. *Avastin (bevacizumab): NICE submission. Achieving clinical excellence in the treatment of metastatic colorectal cancer. Roche submission to the National Institute for Health and Clinical Excellence 26th August 2005*: Roche, 2005 Available from: https://www.nice.org.uk/guidance/TA118/documents/roche4

[14] Roche. *Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer. Roche submission to the National Institute for Health and Clinical Excellence 23rd July 2009. Single technology appraisal (STA)*: Roche, 2009 Available from: https://www.nice.org.uk/guidance/TA212/documents/manufacturer-submission3

[15] National Institute for Health and Care Excellence. *Colorectal cancer (metastatic) - cetuximab (review TA176) and panitumumab (part review TA240) (1st line). ID794 [Internet]*. London: National Institute for Health and Care Excellence, 2016 [accessed 11.3.16] Available from: https://www.nice.org.uk/guidance/indevelopment/gid-tag470

[16] Jonker DJ, C. K, Harbison C, O'Callaghan CJ, Tu D, Simes RJ, et al. High epiregulin (EREG) gene expression plus K-ras wild-type (WT) status as predictors of cetuximab benefit in the treatment of advanced colorectal cancer (ACRC): results from NCIC CTG CO.17-A phase III trial of cetuximab versus best supportive care (BSC). *J Clin Oncol* 2009;27(15 Suppl):4016.

[17] Goldstein DA, Ahmad BB, Chen Q, Ayer T, Howard DH, Lipscomb J, et al. Cost-effectiveness analysis of regorafenib for metastatic colorectal cancer. *J Clin Oncol* 2015;33(32):3727-32.

[18] National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013 [Internet]*. London: NICE, 2013 [accessed 3.3.16]. 93p. Available from: http://publications.nice.org.uk/pmg9

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Single Technology Appraisal (STA)

Trifluridine in combination with tipiracil hydrochloride for previously treated metastatic colorectal cancer [ID876]

Dear [redacted],

The Evidence Review Group, Kleijnen Systematic Reviews Ltd., and the technical team at NICE have now had an opportunity to take a look at the submission received on 26 February 2016 from Servier Laboratories. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter). The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **6pm** on **7th April 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Christian Griffiths, Technical Lead (christian.griffiths@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (jeremy.powell@nice.org.uk)

Yours sincerely

Rosie Lovett PhD
Technical Adviser
Centre for Health Technology Evaluation
Encl. checklist for in confidence information

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Servier responses to the questions are provided in blue within this document.

Section A: Clarification on effectiveness data

Information retrieval

A1. **Priority request:** The results of the literature searches to identify health-related quality of life (HRQoL) data reported in section 5.4.2 do not correspond with the results reported in the detailed search strategies produced in appendix 10.[1]

- Have the correct search strategies for identifying HRQoL studies been reported in appendix 10?

The Embase and MEDLINE search strategies presented in Appendix 10 of the company evidence submission had mixed up captions, however, the search strategies themselves were correct. In Appendix 10 Section 10.3 the first table caption on page 140 should be 'Embase 1980 to 2015 Week 43; Searched on 26th October' and the second table caption on page 142 should be '2015 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present; Searched on 26th October 2015'

- Appendix 13, referred to on pages 148 and 150 of the company submission, is missing. Please provide this appendix.

Appendix 13 is a typographical error. The information for these searches is in Appendix 10

- Please check whether the list of excluded studies (section 10.7, table 7) is correct.

We have checked the list of excluded studies from the utility review and can confirm that it is correct.

A2. Please provide more details for the searches of conference proceedings, including the specific conference proceedings searched, the search strategies and search terms used, website addresses, and results.

A summary of the hand searching for the utility review, which includes all of the requested information is detailed in table 1.

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Table 1: Summary of hand searching methodology for the utility review

Conference	Date searched	Source	Additional methodology details	Search terms	Number of hits	Number downloaded
ASCO						
ASCO Annual Meeting 2015	02/11/15	Online library: http://meetinglibrary.asco.org/abstracts	Library was searched according to meeting and using the keyword search facility	Metastatic colorectal cancer	220	1
				Advanced colorectal cancer	94	0
ASCO Annual Meeting 2014	02/11/15	Online library: http://meetinglibrary.asco.org/abstracts	Library was searched according to meeting and using the keyword search facility	Metastatic colorectal cancer	187	0
				Advanced colorectal cancer	114	0
ASCO Annual Meeting 2013	02/11/15	Online library: http://meetinglibrary.asco.org/abstracts	Library was searched according to meeting and using the keyword search facility	Metastatic colorectal cancer	218	0
				Advanced colorectal cancer	111	0
ESMO						
European Cancer Congress 2015 (Vienna, Austria)	03/11/2015	Abstract book: http://scientific.sparx-ip.net/ecco2015/	Searched using built in search menu facility	Metastatic colorectal cancer	86	0
				Advanced colorectal cancer	11	0
ESMO World Congress on GI Cancer 2015 (Barcelona, Spain)	03/11/2015	Annals of Oncology Volume 26 suppl 4 June 2015 (abstract book): http://annonc.oxfordjournals.org/content/26/suppl_4/local/complete-issue.pdf	Searched using CTRL+F search facility	Metastatic colorectal cancer	NA	0
				Advanced colorectal cancer	NA	0
ESMO Congress 2014 (Madrid, Spain)	03/11/2015	Annals of Oncology Volume 25 suppl 4 September 2014 (online): http://annonc.oxfordjournals.org/content/25/suppl_4.toc	Searched using the 'Search this issue' facility	Metastatic colorectal cancer	1,547	0
				Advanced colorectal cancer	1,544	0
ESMO World Congress on GI Cancer 2014 (Barcelona, Spain)	03/11/2015	Website searched, abstracts not available: http://www.esmo.org/Conferences/Past-	Not searched	NA	NA	NA
				NA	NA	NA

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		Conferences/World-GI-2014-Gastrointestinal-Cancer				
European Cancer Congress 2013 (Amsterdam, Netherlands)	03/11/2015	Online library: http://2013.europeancancercongress.org/Scientific-Programme/Abstract-search.aspx	Library searched using 'Abstract keywords' search facility	Metastatic colorectal cancer	25	1
				Advanced colorectal cancer	1	0
ESMO World Congress on GI Cancer 2013 (Barcelona, Spain)	03/11/2015	Annals of Oncology Volume 24 suppl 4 June 2013 (online): http://annonc.oxfordjournals.org/content/24/suppl_4.toc	Searched using the 'Search this issue' facility	Metastatic colorectal cancer	368	0
				Advanced colorectal cancer	368	0
ISPOR						
20th Annual International Meeting 2015 (Philadelphia, US)	03/11/2015	Website searched, abstracts unavailable: http://www.ispor.org/Event/Index/2015Philadelphia	Not searched	NA	NA	NA
				NA	NA	NA
19th Annual International Meeting 2014 (Montreal, Canada)	05/11/2015	Value in Health, Volume 17:3 (May 2014) (abstract book): http://www.ispor.org/publications/value/VIH_17-3_final.pdf	Searched using CTRL+F search facility	Metastatic colorectal cancer	NA	0
				Advanced colorectal cancer	0	0
18th Annual International Meeting 2013 (New Orleans, US)	05/11/2015	Value in Health, Volume 16:3 (May 2013) (abstract book): http://www.ispor.org/publications/value/JVAL_16-3_FINAL.pdf	Searched using CTRL+F search facility	Metastatic colorectal cancer	NA	0
				Advanced colorectal cancer	0	0
18th Annual European Congress 2015 (Milan, Italy)	05/11/2015	Website searched, abstracts unavailable: http://www.ispor.org/Event/Index/2015Milan	Not searched	NA	NA	NA
				NA	NA	NA
17th Annual European Congress 2014 (Amsterdam, Netherlands)	05/11/2015	Website searched, abstracts unavailable: http://www.ispor.org/Event/Index/2014Amsterdam	Not searched	NA	NA	NA
				NA	NA	NA
16th Annual European Congress 2013	05/11/2015	Value in Health, Volume 16:7 (November	Searched using CTRL+F search facility	Metastatic colorectal cancer	Not available	0

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(Dublin, Ireland)		2013) (abstract book): http://www.ispor.org/publications/value/JVAL_16-7_final.pdf		Advanced colorectal cancer	0	0
Key: ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; GI, gastrointestinal; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; US, United States.						

Definitions

A3. **Priority requests:**

- Please provide a definition for best supportive care (BSC) used in the included trials.

There is currently no internationally accepted definition of BSC for clinical trials (Ahmed, 2004, Cherny, 2009).[2, 3] The European Organisation for the Research and Treatment of Cancer (EORTC) defines supportive care as follows:

> *"Supportive care for cancer patients is the multi-professional attention to the individual's overall physical, psychosocial, spiritual and cultural needs, and should be available at all stages of the illness, for patients of all ages, and regardless of the current intention of any anti-cancer treatment."* [2]

The National Cancer Institute (NCI) defines supportive care as:

> *"Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of supportive care is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment. Also called comfort care, palliative care, and symptom management."* [4]

Details of best supportive care provided in the trials is detailed below.

- Please provide the guidance regarding BSC given to the centres involved in the included trials.

Phase II

All necessary support was provided to patients, with the exception of concomitant use of other anti-cancer drugs or other investigational drugs.

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All necessary support was provided to patients which included permitted concomitant medications and therapies and study medication. All patients received the best supportive care available but were not to receive other investigational antitumour agents or antineoplastic chemotherapy, hormonal therapy, or immunotherapy.

Palliative radiotherapy was not permitted while the patient was receiving study treatment.

If used concomitantly with study medication, antiviral drugs that are human thymidine kinase substrates (e.g. stavudine, zidovudine, telbivudine) were to be used with caution because such drugs may theoretically compete with the effector of trifluridine/tipiracil, i.e. trifluridine, for activation via thymidine kinases.

- Please explain whether the definition of BSC used in the RECOURSE trial is applicable to the UK setting.

Yes. Patients in both trial arms were provided with all appropriate support for their condition with the exception of the medications and/or treatment (e.g. palliative radiotherapy etc.) that were excluded in the trial protocol.

A4. The supplementary tables for the main publication of the RECOURSE trial provide definitions of progression and stable disease.[5]

- Please clarify the definitions used in the included phase II RCT.[6]

Progression

The definition of progression free survival is provided in the company evidence submission (Table 15 page 53)

Stable disease

Is defined as follows, the response has not reached complete response (CR) or partial response (PR) in radiologic assessments over at least six weeks since the start of study drug administration and it has been confirmed that progressed disease (PD) has not occurred.

- For both trials, please provide more details on the assessment methods, e.g. how many assessors, experience of assessors, training to ensure consistency between study centres.

Servier confirm that both trials were conducted in accordance with good clinical practice (GCP). In order to be selected as a study centre the centres had to demonstrate the following: Adherence to GCP, experience in managing clinical trials, resources and expertise to undertake the investigations defined in the trial protocol, appropriate numbers of patients. The training provided to each centre was consistent across all study centres.

Phase II

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The trial was conducted in accordance with GCP.

To ensure consistency across study centres all secondary efficacy endpoints were subject to independent radiologic image assessment as defined below:

The determination of the antitumour effect was to be performed in the following protocol in accordance with RECIST Ver. 1.0. At the independent image assessment site (CRO), they were to make a determination regarding the antitumor effect in accordance with RECIST Ver. 1.0 as well as make an evaluation with RECIST Ver. 1.1 as an indicator for reference. Definitions of RECIST Ver. 1.0 and Ver. 1.1 were established in the separate document 'Procedure for agency entrusted with image evaluation'.

RECOURSE

The protocol was written with reference to Clinical Trial Protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines E6 – GCP, Section 4:

> *"On-site tumour assessments will be performed by the Investigator/local radiologist according to RECIST criteria (version 1.1, 2009). Results of these assessments including response for target and non-target lesions and appearance of new lesions will be the basis for the continuation or discontinuation of study medication. Response definitions are provided in Section 8.0."*

In the protocol measurable and target lesions are very well described and an imaging manual was provided to the sites for consistency. There was also an audit plan in the protocol which is detailed in section 12.4.5 Sponsor's Audits and Regulatory Inspections

> *"For the purpose of ensuring compliance with the protocol, GCP and applicable regulatory requirements, the Investigator will permit auditing by the Sponsor or its representative and inspections by regulatory authorities.*
>
> *The Investigator agrees to allow the auditors and inspectors to have direct access to the study records for review. The people performing these activities will not disclose any personal identity or personal medical information assessed.*
>
> *The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data and documents pertaining to the clinical trial. As soon as the Investigator is notified of a planned inspection by the regulatory authorities or IRB/IEC, the Investigator will inform the Sponsor. Any results arising from such inspections will be immediately communicated by the Investigator to the Sponsor. The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during audits and or inspections."*

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Included trials

A5. **Priority request:** There appears to be a significant question as to the generalisability of RECOURSE to the UK population given a discrepancy in survival between the data presented in Section 3.4.1 and the survival observed in the trial. In particular, one-year survival for patients with metastatic colorectal cancer (mCRC) was presented as 40% and 33% for men and women, respectively, based on a UK data source.[7] This could be compared with the estimated 1-year survival in the placebo arm of 17.6% (table 25), which suggests that the survival in the trial is much lower. In fact, survival in the trial is conditional on having survived to 3rd line, which is about 3 years since diagnosis.[8] Therefore, the figure of 17.6% should actually be compared to survival to four years conditional on surviving three years from diagnosis. Assuming a constant annual mortality rate, this would be the same as the 1-year survival (from diagnosis) i.e. between 33% and 40% (the average across women and men). This is clearly very different to the 17.6% in the trial.

- Please explain this apparent discrepancy.

Servier do not believe there is a discrepancy in the data presented. The Cancer Research UK (CRUK) data were presented to give a general overview of the one-year survival of patients with CRC by stage of disease. However, the data and in particular those for mCRC (stage IV) are limited by the fact that they apply to all patients with mCRC irrespective of time since diagnosis of metastatic disease, number of lines of chemotherapy received etc. Therefore the CRUK data are not reflective of the population defined by the decision problem for this appraisal.

The decision problem defines a patient population diagnosed with mCRC who would have received two or more previous lines of chemotherapy (i.e. they have received NICE recommended standard therapies for mCRC and their disease has progressed or when they received the therapy they were found to be intolerant to it). Patients at this line of therapy have much lower survival than those receiving first or second line therapy. Unfortunately, CRUK and other sources do not report mCRC mortality by the line of treatment – this can only be determined from clinical trials.

In the case of disease progression after two lines of therapy for mCRC, the survival is approximately 4-6 months with best supportive care alone.[9-11] Therefore the survival observed in the phase II and RECOURSE trials is consistent with the published evidence for patients relevant to the decision problem for this appraisal.

- The ERG was unable to assess whether this comparison was suitable. Please provide patient characteristics from all 3 sources (phase II trial,[6] RECOURSE[5] and cancer research UK[7]).

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CRUK

All patients with CRC diagnosed during 2006-2010 in the former Anglia Cancer Network, irrespective of time since diagnosis, number of lines of treatment received etc. As described above, these patients are not consistent with the population defined in the decision problem.

Phase II

Eligible patients were 20 years or older; had histologically or cytologically confirmed unresectable metastatic colorectal adenocarcinoma; had a previous treatment history of two or more regimens of standard chemotherapy; and were refractory or intolerant to a fluoropyrimidine, irinotecan, and oxaliplatin.

RECOURSE

Eligible patients were ≥18 years old, had biopsy documented adenocarcinoma of the colon or rectum, had received ≥2 prior regimens of standard chemotherapies, which could have included; adjuvant chemotherapy if a tumour had recurred within 6 months after the last administration of this therapy, tumour progression within 3 months after the last administration of chemotherapy, clinically significant AEs from standard chemotherapies that precluded the re-administration of those therapies. Patients were also required to have received chemotherapy with each of the following agents: fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, cetuximab or panitumumab if *KRAS* wild-type.

- Please explain how the RECOURSE trial can be applicable to the UK given this large discrepancy in survival.

As explained above, there is no discrepancy in the data, the survival rates are similar to other trials in mCRC in patients receiving treatment at third line or later.[9-11]

A6. According to table 15 of the company submission, all people included in the phase II RCT were recruited in Japan whereas participants of RECOURSE were from Japan, Europe, USA and Australia.[5, 6]

- Please provide the number of RECOURSE participants by country.

Table 2: RECOURSE participants by country

Country	Number of centres	Number of patients
United states	21	99
Japan	20	266
Spain	11	112
Italy	9	108
Germany	8	22
Belgium	6	64

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France	6	50
United Kingdom	5	9
Austria	4	20
Ireland	3	8
Sweden	2	6
Czech Republic	1	4
Australia	5	32

- Please provide detailed baseline characteristics and results for patients in RECOURSE from Europe and the UK, respectively, i.e. separate Europe and the UK.

The UK subpopulation only comprises 9 patients (7 patients in trifluridine/tipiracil arm and 2 patients in Placebo arm), therefore a statistical analysis to compare baseline characteristics and efficacy between the EU and UK patients is unlikely to be helpful and therefore not relevant. The sample size is not big enough to draw reliable statistical conclusions.

- Please justify how the included patients (from the phase II trial, RECOURSE, and the combined analysis) are representative for the UK setting.

The company evidence submission pages 89 – 95 provides details of the pre-specified subgroup analyses of OS that were undertaken. In the multivariate analysis of OS none of the factors (one of which was geographic region) demonstrated any interaction with treatment when treatment was added into the model (treatment interaction p-values were >0.20 for all factors). Therefore there was no evidence of heterogeneity of treatment effect for OS.

A prespecified geographic regional subgroup analysis (pages 93-95) was undertaken on the RECOURSE population and demonstrated that the OS and PFS benefits observed in each geographic region were similar to the overall RECOURSE population.

As there is no evidence of a difference in efficacy based on ethnicity, the included patients are generalisable to the UK setting.

A7. Information on clinicaltrials.gov for RECOURSE (NCT01607957) indicates the final data collection date for the primary outcome measure was February 2016. However, the main publication for the trial was submitted in January 2015.[5]

- Please confirm whether the final results for RECOURSE were presented in Mayer 2015 New England Journal of Medicine.[5]

RECOURSE was an event driven trial. The power calculation determined that at least 571 events (deaths) would be required for the primary analysis. A total of 574 deaths were included in the primary analysis of OS based on a cut-off date of 24 January 2014 (4 patients died on the calendar day of the 571st event). The publication by Mayer *et al.* (2015) reports the trial results based on 574 deaths and the cut-off date of January 2014.[12]

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- Section 4.4.2 of the company submission[13] suggests that updated analyses were conducted. Please indicate which (additional) endpoints were analysed and state which of these analyses were pre-specified and provide all of these results.

It is common practice in oncology trials to update the survival data when a greater proportion of the population have died. The updated analysis based on a data cut-off of 08 October 2014 was conducted for the primary endpoint (overall survival), these data present 712 events (deaths) representing 89% of the study population (i.e. 138 additional events compared to those presented in Mayer et al (2015)) . This was a post hoc analysis requested by European Medicines Agency (EMA) during the Committee for Medicinal Products for Human Use (CHMP) review.

Full details of the results of this analysis are provided in the company evidence submission (pages 77-78).

A8. Information on clinicaltrials.gov for TERRA (NCT01955837) indicates that the final data collection date for the primary outcome measure was February 2016.

- Please confirm that no results are available or if they are, please provide them.

No data are currently available for this trial, the clinical study report (CSR) is expected in July 2016. The first communications for the TERRA study are planned for the European Society of Medical Oncology (ESMO) conference in Copenhagen in October 2016.

A9. Section 4.11 of the company submission provides details on two non-randomised studies.

- Please clarify how these studies were identified and selected for inclusion.

These studies were not identified via a specific search, however, Servier were aware that they had been presented and as they are relevant to the decision problem it was decided to present them in Section 4.11 of the company evidence submission.

- Please submit an amended version of section 4.11 with the inclusion and exclusion criteria used as well as the flow chart.

As stated in section 4.11 due to the nature of the studies and the data currently available it is not possible to provide further details at this time. All available data are included in the two references that accompanied the company evidence submission.

Trial results

A10. Section 4.12 of the company submission[13] presents results on adverse events (AEs) observed in the two included trials. Table 43 (*"All adverse events within RECOURSE*

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published data") shows that more serious AEs were observed in the placebo arm (33.6%) than the trifluridine and tipiracil arm (29.6%).

- Please provide breakdowns of the number of serious adverse events for trifluridine and tipiracil and for placebo (BSC) for the phase II trial and RECOURSE, respectively.

A breakdown of the number of serious adverse events (Fatal AE and Serious AE) for the RECOURSE and phase II trials are provided in the respective CSRs as follows:

1. RECOURSE Fatal AE (Table 14.3.1.11 pages 822-824)
2. RECOURSE Serious AE (Table 14.3.1.7 pages 806-813)
3. Phase II - List of Patients Who Died due to an Adverse Event (Table 12.3.1.1-1 page 281)
4. Phase II – List of Serious Adverse Events (table 12.3.1.2-1 page 283)

- Please provide any additional data which were not part of the "published data".

These data comprise all the information that is available.

A11. Page 87 of the company submission presents results the median progression-free survival by KRAS type.[13]

- Were these analyses pre-specified?

Yes, the analyses by *KRAS* type were pre-specified – full details can be found in section 9.7.9.2 pages 59 and 60 of the RECOURSE CSR.

- Please provide results for any subgroup analyses performed.

The subgroup analysis by *KRAS* status is provided in the company evidence submission (Phase II pages 86 - 87, RECOURSE pages 88-90). Further information can also be found in the RECOURSE CSR (Table 14.2.2.1 pages 474-477) and elsewhere within this response.

Statistical analysis

A12. **Priority request:** According to section 5.3 of the company submission [13], pooled progression-free survival and overall survival in the economic model were estimated using the updated RECOURSE (phase III) trial data[5] and phase II clinical trial data[6]. However, justification for pooling this and any explanation of how pooling was performed is lacking. Furthermore, other parameters, such as time on treatment, body surface area, dose reductions and adverse event rates are only based on RECOURSE data.

- Please justify why a pooled analysis is used, given that the phase II trial only consists of Japanese patients and hence using the RECOURSE trial only would be more representative for the UK setting.

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The findings of RECOURSE are supported by a Phase II trial in a similar patient population of mCRC patients which was the pivotal trial used for registration purposes in Japan. Both trials were conducted in a patient population that is relevant to the decision problem for this appraisal and are consistent with the proposed marketing authorisation. The meta-analysis presented in Section 4.9 of the company evidence submission demonstrates that the treatment effect of trifluridine/tipiracil is consistent across both trials for both OS and PFS.

A number of patients in the Phase II trial had not received bevacizumab or cetuximab (22% and 37%, respectively), which have recently been delisted from the CDF (along with panitumumab) and are therefore not available for treatment at third line or later in England. The phase II data therefore provide insight into the efficacy of trifluridine/tipiracil in patients who have received all NICE recommended, available chemotherapy, but who have not necessarily received biological agents and demonstrate that efficacy is maintained.

Furthermore as described in the response to A6, there is no evidence of a difference in efficacy based on ethnicity. The mean OS presented on page 127 of the company evidence submission shows that the results for the pooled analysis are similar to RECOURSE, 3.2 months and 3.0 months respectively.

The economic model submitted alongside the company evidence submission presents data for all scenarios i.e. Pooled analysis, RECOURSE, phase II etc.

- Please provide pooled estimates (based on the phase II trial[6] and RECOURSE[5]) for the following input parameters:
    - time on treatment,
    - body surface area,
    - dose reductions,
    - adverse event rates.

Time on treatment

Time on treatment (or time to treatment discontinuation (TTD)) parameter estimates for the pooled patient population are presented in Appendix A. A Kaplan-Meier estimate of TTD is presented in Figure 1 below for the pooled population.

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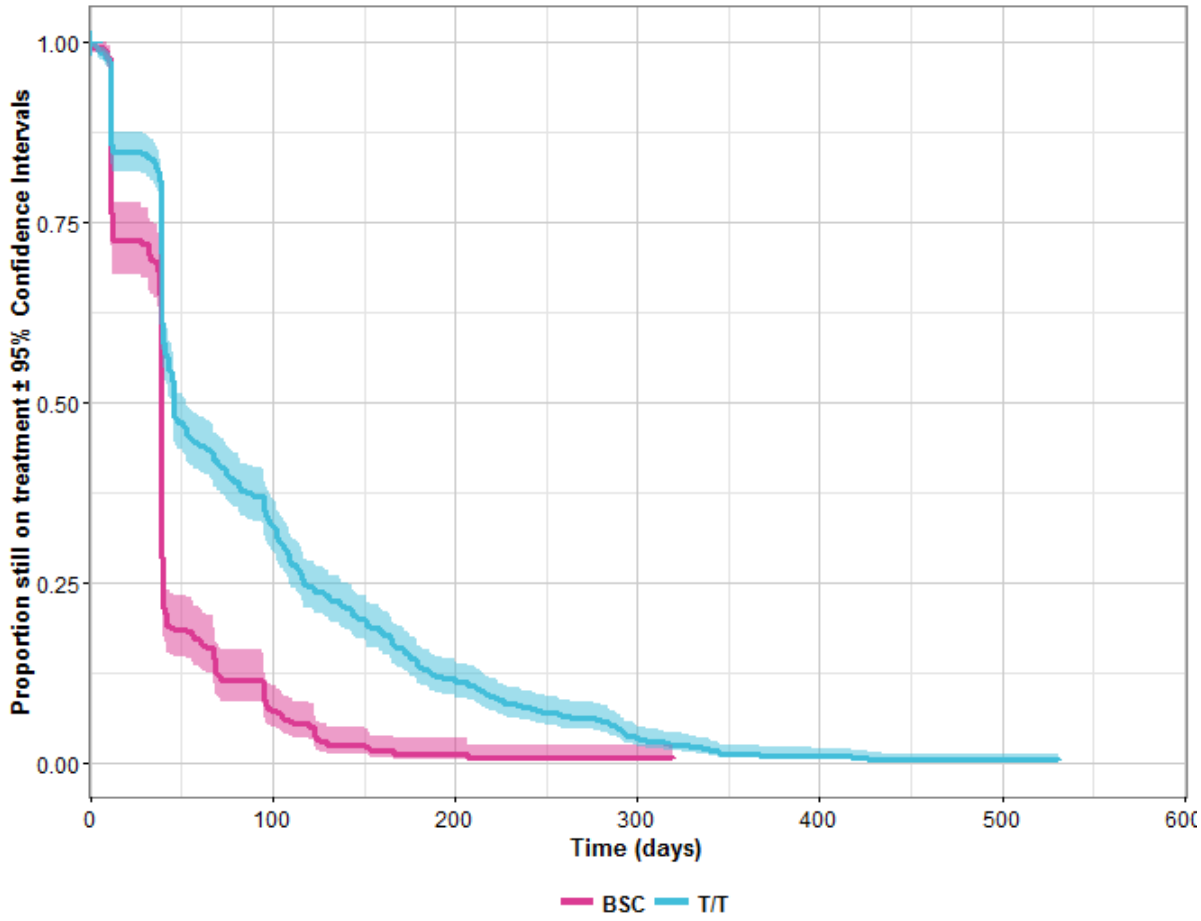
Figure 1: TTD estimate for the pooled patient population



For the comparison of estimated TTD used in the *de novo* economic model to PFS and OS within the model, please see the response to B8.

Body surface area

Log-normal parameter estimates for the distribution of patient BSA for all patient populations are presented in Appendix A. These have been appropriately implemented into the model, and may be overridden for the purposes of comparison to the use of RECOURSE-only patients.

Due to time constraints, only the log-normal distribution for patient populations different to that of RECOURSE-only may be selected (i.e. raw data for subgroups other than RECOURSE-only is not a selectable option, and will instead return the same result as using the log-normal distribution).

Dose reductions

Estimates of dose reductions per cycle were originally sourced from the following section within the CSR for the RECOURSE trial:

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> "*A total of 73 (13.7%)* [trifluridine/tipiracil] *patients had dose reductions: 53 (9.9%) patients had a single dose reduction, 18 (3.4%) patients had 2 reductions, and 2 (0.4%) patients had 3 reductions.*"

Equivalent patient-level data for the Phase II trial were used to calculate the percentage of patient experiencing dose reductions after the first three cycles of treatment, for the pooled and Phase II patient populations, as shown in Table 3.

Table 3: Percentage of patient experiencing a dose reduction – all populations

Reduction after…	RECOURSE	Phase II	Pooled
Cycle 1	9.9% (53/534)	14.3% (16/112)	10.7% (69/646)
Cycle 2	3.4% (18/534)	4.5% (5/112)	3.6% (23/646)
Cycle 3	0.4% (2/534)	0.9% (1/112)*	0.5% (3/646)
Notes: * This patient received 4 dose reductions, but has been assumed to receive three in line with the current model structure.			

Adverse event rates

Adverse event rates have now been included based upon the most frequently observed adverse events (defined as occurring with a frequency of at least 3% in the safety population) in the Phase II trial, as reported in the publication by Yoshino *et al.* (2009).[6] The rates presented in this publication have been selected for inclusion using the same criteria as per the adverse events from the RECOURSE study, which were taken from the publication by Mayer *et al.* (2015).[5]

The rates used in the *de novo* economic model are presented in Table 4. The rates considered are those for which a cost is applied in the model for the associated grade. Grade <3 adverse events that are not costed in the model are not presented in Table 4. Commonly occurring Grade ≥3 adverse events that are not costed in the model are presented in the table along with the reason they have been excluded.

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Table 4: Adverse event rates from the Phase II study

Grade 1 or 2 adverse events	Trifluridine/tipiracil	Placebo	Excluded?
Diarrhea	43/113 (38%)	12/57 (21%)	
Febrile neutropenia	5/113 (4%)	0	
Vomiting	38/113 (34%)	14/57 (25%)	
Grade 3 or 4 adverse events	**Trifluridine/tipiracil**	**Placebo**	**Excluded?**
Neutropenia	57/113 (50%)	0	
Leucopenia	32/113 (28%)	0	
Anaemia	19/113 (17%)	3/57 (5%)	
Lymphopenia	11/113 (10%)	2/57 (4%)	Yes[a]
Thrombocytopenia	5/113 (4%)	0	
Fatigue	7/113 (6%)	2/57 (4%)	
Diarrhea	7/113 (6%)	0	
Nausea	5/113 (4%)	0	
Anorexia	5/113 (4%)	2/57 (4%)	Yes[b]
Febrile neutropenia	5/113 (4%)	0	
Vomiting	4/113 (4%)	0	

Reasons for exclusion:
a: <1% of patients in both arms of the RECOURSE trial experienced Grade ≥3 lymphopenia
b: Anorexia is not explicitly reported in the RECOURSE trial – the most similar adverse events would be Grade ≥3 "Weight Decreased" or "Decreased Appetite". "Decreased Appetite" is already included within the model, and "Weight Decreased" only occurred in 1 trifluridine/tipiracil patient (and 0 placebo patients).

Within the *de novo* economic model, these adverse event rates have been included by considering a weighted average of affected adverse events of the percentages presented in Table 4 for the Phase II trial, and the figures reported for the Phase III trial. Adverse events not reported in the Phase II trial most commonly observed adverse events have been unchanged (i.e. rate from RECOURSE assumed).

For the Phase II trial alone, the included adverse events presented in Table 4 have been used, with all other adverse event rates set to zero.

- Please provide a detailed description of the methods used to pool the data from both trials for all above-mentioned parameters as well as progression-free survival and overall survival.

Pooled data for the above were combined as follows:

Overall survival and progression-free survival: Full patient cohort considered, analysis ran on complete dataset.

Time to treatment discontinuation: TTD data were combined using the same methodology as per OS and PFS.

Body surface area: Full patient cohort considered, analysis ran on complete dataset.

Dose reductions: Weighted average by number of trifluridine/tipiracil patients – please see Table 3.

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Adverse event rates: For the pooled population, adverse event rates for those reported in the Phase II study publication by Yoshino *et al.* (2009)[6] were weighted according to the difference in rates and patient numbers across RECOURSE and the Phase II study. Adverse event rates not reported in the Phase II study publication by Yoshino *et al.* (2009)[6] were left as per the RECOURSE study (i.e. unadjusted).

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Section B: Clarification on cost-effectiveness data

Treatment effectiveness and adverse events

B1. **Priority request:** The NICE DSU technical support document for survival analysis[14] recommends that the decision of whether to stratify survival models should be based on log-cumulative hazard plots, quantile-quantile plots or suitable residual plots.

- Please provide the log-cumulative hazard plots and quantile-quantile plots for all survival curves representing progression-free survival and overall survival reported in the company submission.[13]

Log-cumulative hazard plots have been produced for the following patient populations using both the updated and original OS data cut points where applicable:

- Figure 2: OS for the pooled population ("Updated OS" left; "Original OS" right)
- Figure 3: OS for the RECOURSE population ("Updated OS" left; "Original OS" right)
- Figure 4: OS for the Phase II population
- Figure 5: OS for the pooled population
- Figure 6: OS for the RECOURSE population
- Figure 7: OS for the Phase II population

Figure 2: Log-cumulative hazard plot for OS – Pooled population

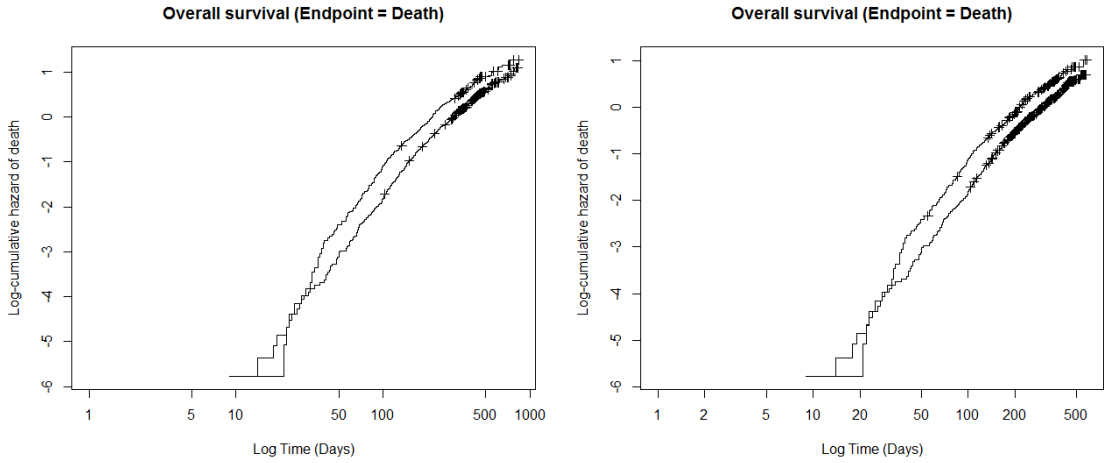

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Figure 3: Log-cumulative hazard plot for OS – RECOURSE population

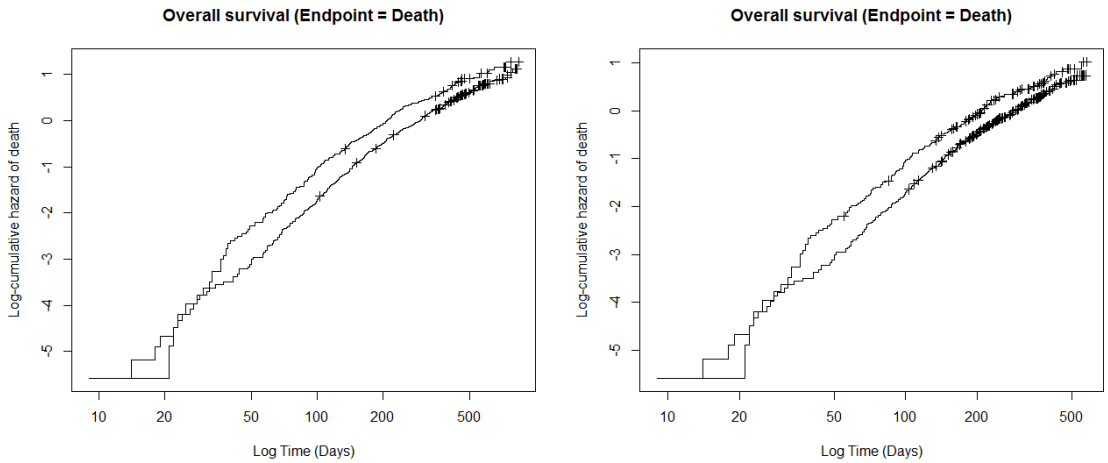

Figure 4: Log-cumulative hazard plot for OS – Phase II population

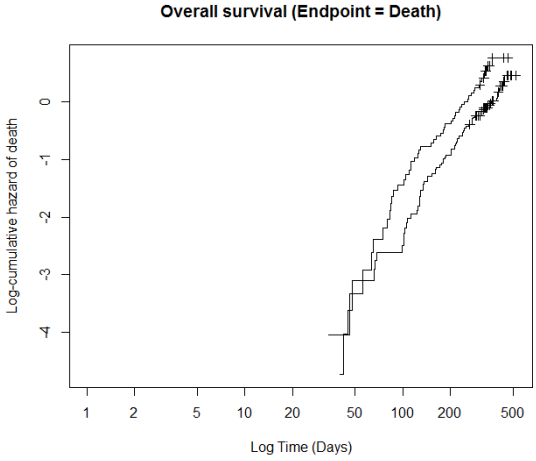

Figure 5: Log-cumulative hazard plot for PFS – Pooled population

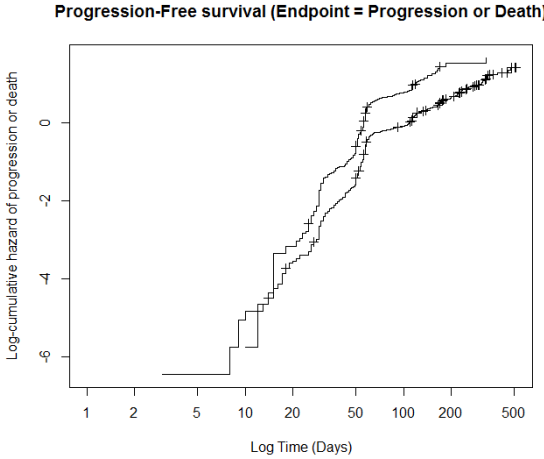

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Figure 6: Log-cumulative hazard plot for PFS – RECOURSE population

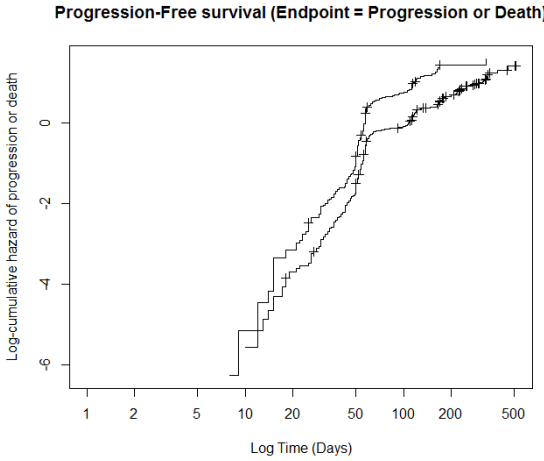
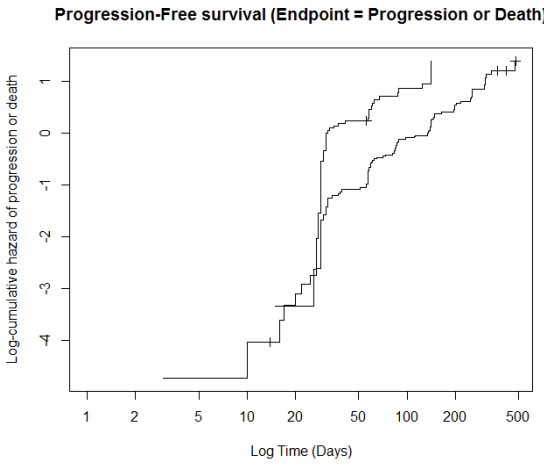


Figure 7: Log-cumulative hazard plot for PFS – Phase II population



The log-cumulative hazard plots appear as relatively straight lines (taking into account the protocol-driven large drops in the PFS curves), but are not necessarily parallel as they appear to converge towards the tails.

- It was unclear to the ERG how single Akaike Information Criterion (AIC) estimates were obtained for the stratified analyses. Stratified analyses result in two AIC estimates for each stratified analyses for trifluridine in combination with tipiracil and for BSC respectively. Please provide the AIC estimates separately for each stratified model (i.e. separately for the stratified models for trifluridine in combination with tipiracil and BSC) and explain how these AIC estimates were combined to obtain one AIC.

AIC scores were obtained for the stratified models using the same methodology as per the unstratified models. Please see below the R code used to produce the AIC scores for the stratified log-logistic model:

Requires the "`survival`" package

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```
loglogistic_stratified <- aftreg(S~strata(Treatment), dist="loglogistic",
model=TRUE, x=TRUE, y=TRUE, data=Dataset)

loglogistic_stratified$df <- 4

AIC.loglogistic_stratified <- cbind(extractAIC(loglogistic_stratified))
```

For more complex models not considered by the "aftreg" function (i.e. Generalised Gamma and Gompertz models), the AIC score was manually calculated using the following formula:

```
AIC = -2 x Maximum log likelihood + 2 x degrees of freedom
```

The maximum log likelihood for stratified models comprises of the sum of the component maximum log likelihoods for each treatment arm.

- On page 137 of the company submission[13], it is stated that a stratified model is preferred by the company *"Given that within both trials randomisation was not equal (2:1)"*. Please clarify why the unequal randomisation is an argument for selecting a stratified model.

Unequal randomisation (in this case 2:1) implies that unstratified parametric survival models will inherently utilise a relatively larger proportion of patients in the larger patient group (in this case, patients receiving trifluridine/tipiracil) compared with the smaller patients group (in this case, patients receiving placebo) in the estimate of the associated parametric curve parameters.

B2. **Priority request:** In the RECOURSE trial[5], different magnitudes of effect of trifluridine in combination with tipiracil are observed in different pre-specified subgroups.

- Please provide subgroup analyses in the cost-effectiveness analysis for the following subgroups:
  - wild-type KRAS
  - mutant KRAS

Subgroup analysis by KRAS mutation type was not originally included within the cost-effectiveness analysis as the forest plots from the RECOURSE and Phase II studies demonstrated benefit in both wild-type and mutant KRAS patients, and the mutation type with the most benefit was unclear, as shown in Figure 8.

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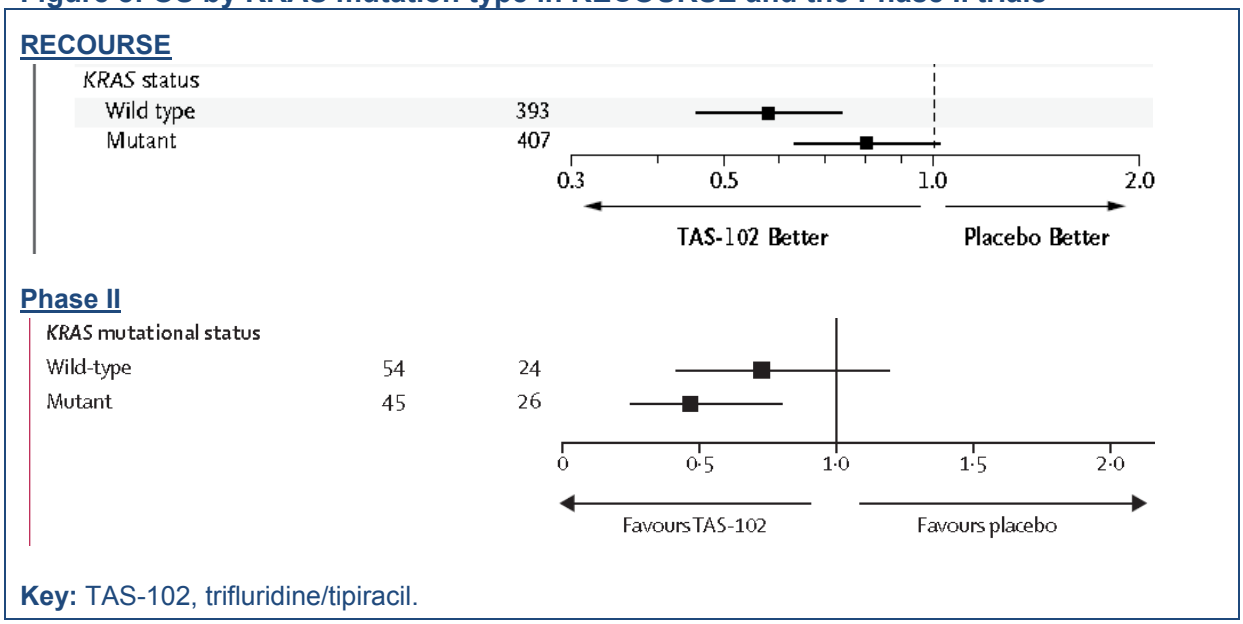
Figure 8: OS by KRAS mutation type in RECOURSE and the Phase II trials



Key: TAS-102, trifluridine/tipiracil.

However, subgroup analysis is possible by KRAS mutation for all patient populations (i.e. pooled, RECOURSE and Phase II populations).

Results of these subgroup analyses are presented (as requested) as a scenario analysis in response to B17.

- Please provide the list of changed input parameters (progression-free survival, overall survival, time on treatment, body surface area, dose reductions, adverse event rates).

The OS and PFS curves have be re-run for *KRAS* mutation subgroup. Estimated TTD curves have also been ran for all patient populations, including *KRAS* mutation subgroup. BSA has also been recalculated for *KRAS* mutation subgroup, as well as for each patient population (i.e. pooled, RECOURSE and Phase II populations).

Dose reductions and adverse event rates have not been recalculated as dose reductions were only reported for the entire patient population (not separated by *KRAS* mutation subgroup), and adverse event rates have not been included following the response to question B4.

Revised curve fit parameters (for the pooled population as per the model base case) and log-normal parameters for the distribution of patient BSA are presented in Appendix A. Parameters for all patient populations are available in the updated *de* novo economic model, and used for *KRAS* mutation subgroup-specific analyses.

B3. Please provide the cost-effectiveness results of a sensitivity analysis containing the pooled estimates for time on treatment, body surface area, dose reductions and adverse event rates as asked in clarification question A13.

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As discussed in the responses to A12 and B2, pooled estimates for TTD, BSA and adverse event rates are available for all subgroups, but pooled estimates for dose reductions are not available for populations other than the RECOURSE study. Cost-effectiveness results using pooled estimates for these parameters are provided within the response to B18.

Health related quality of life

B4. **Priority request:** The impact of adverse events on health-related quality of life is not incorporated in the analysis despite the fact that patients receiving trifluridine in combination with tipiracil had more grade >2 adverse events than placebo in the RECOURSE trial. This is justified in the company submission by stating a lack of evidence. Evidence on the quality of life impact of these adverse events is available (see for instance TA307[15], table B29 of company submission[13]).

- Please incorporate the impact of adverse events on health related quality of life in the economic analysis.

As no directly measured utilities were available from either the RECOURSE or Phase II clinical studies of trifluridine/tipiracil versus placebo, estimates from the CORRECT study (Grothey *et al.* (2013)[11]) and the cetuximab NICE manufacturer submission (TA176[16]) data have been combined to give estimated utilities for the health states of pre-progression (on active treatment), pre-progression (no active treatment), and post-progression.

Whilst adverse event rates are available from all relevant clinical studies, in order to adjust the utilities for adverse events, information would be needed on the impact of each adverse event on the data sources used (this would include the magnitude of impact, and the duration). The source utilities could then be adjusted to give the utility of pre-progression patients who were on active treatment, with no adverse events, before being readjusted for the adverse event profile seen in the trifluridine/tipiracil clinical studies.

In practice however, this is not possible, as we do not have access to the patient-level data from either of the required two studies. The utility values we have used are taken from patients who were undergoing treatment with active therapy, and thus a portion would be experiencing adverse events at the point of measurement. It was therefore assumed that patients treated with trifluridine/tipiracil would have a disutility from adverse events similar to this, as to use assumptions to adjust these existing utilities would introduce a bias of unknown magnitude and direction.

Based on clinical opinion, the values we have used represent a 'worst case' for utility values whilst on treatment with trifluridine/tipiracil, as clinicians highlighted that trifluridine/tipiracil was better tolerated than other drugs at this treatment line, particularly regorafenib.

B5. Chang 2015[17] and Siena 2013[11, 18] were identified in a systematic review as studies that may meet the requirements of the NICE reference case.

- Please justify why Siena et al. (CORRECT study)[11, 18] was used, and Chang[17] was not used.

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Siena *et al.* (2013)[10] and Chang *et al.* (2015)[17] were not used in the *de* novo economic model. Both studies were identified via the systematic literature review, but did not provide health-state specific utility values for use in the model. In addition both publications were only abstracts and did not present utility values by progression status.

Consequently, health state utility values were derived from both TA176[16] and the CORRECT study using the publication by Grothey *et al.* (2013)[11], as the latter study reported utility values for health states of pre-progression (on active treatment), pre-progression (no active treatment), and post-progression.

B6. The model inputs for health state utilities are based on an average of utilities from the CORRECT study and TA176[16].

- Please justify why TA176[16] is an appropriate source for health state utilities, as 1) the health state utility used for pre-progression (0.73) retrieved from TA176[16] was based on strong assumptions and reported to be for 2nd line treatment while trifluridine in combination with tipiracil is indicated for third line treatment. Moreover, 2) for the health state utility used for post-progression (0.68) in TA176[16] it was reported that this value may not capture lower utility weights in the terminal stage and hence is unlikely to reflect 3rd line post-progression health related quality of life.

TA176[16] was selected as an appropriate source for an upper bound of health state utilities, given that the utility used for patients in pre-progression was taken from patients on second-line treatment. The lower bound estimate was taken from the CORRECT study publication by Grothey *et al.* (2013)[11], and as previously discussed the toxicity profile of regorafenib is different to that of trifluridine/tipiracil.

The toxicity profile of regorafenib may be deemed worse than the “acceptable toxicity profile” of trifluridine/tipiracil given the increased incidence of Grade ≥3 hypertension and hand-foot syndrome associated with regorafenib treatment.[19-21] Therefore, it was concluded that both sources provide suitable bounds for the estimation of health state utility values in the *de novo* economic model, and as such the average was taken in the model base case.

- Please justify why TA176[16] was used and not other NICE appraisals that may contain relevant information (e.g. TA118[22], TA212[23], TA307[15] and ID794[19]).

Below are the associated reasons why TA176[16] was selected for use over the other possible candidates:

- TA118[22]: The manufacturers submission from this appraisal used health state utility values of 0.80 for pre-progression and 0.50 for post-progression. Consequently, these health state utility values were deemed inappropriate for consideration given that 0.80 is too high for patients in this late stage of disease.
- TA212[23]: The manufacturers submission from this appraisal used the same health state utility values as TA176[16].

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- TA307[15]: The manufacturers submission from this appraisal marked health state utility values as commercial in confidence, and therefore we were unable to apply these in our model.
- ID794[19]: The manufacturers submission from this appraisal used health state utility values of 0.769 for pre-progression and 0.663 for post-progression, with alternate values of 0.762 for pre-progression and 0.641 for post-progression. These utility values were deemed inappropriate for use given that the pre-progression utility value from TA176[16] (0.73) is already considered to be an upper bound.

In summary, we chose to utilise the appraisal which was previously referenced in another similar appraisal (TA212[23]) which provided reasonable estimates of health state utility values for patients in this late stage of disease.

Resource use and costs

B7. **Priority request:** Table 57 in the company submission[13] provides an overview of adverse events observed in the RECOURSE trial[5] and table 67 of provides an overview of adverse events for which costs are incorporated in the model. Several adverse events are missing in this table (i.e. adverse events reported in table 57 but not in table 67).

- Please include all adverse events reported in table 57 in an updated version of table 67 (including the cost of treatment and references). For instance "Increase in total bilirubin" can be included using the costs of treatment for Hyperbilirubinemia reported in table 80 of the company submission.[13]

The cost of hyperbilirubinemia within the model was assumed to be captured by the NHS Reference costs 14-15: Outpatient visit, general medicine cost (£158.43).[24] Equivalently, all other additional adverse events have also been assumed to be captured by this cost, due to the lack of other appropriate costs within the NHS Reference costs 14-15 database to apply to these adverse events.

As metastatic cancer of the liver is a known cause of abnormally elevated blood liver enzyme levels, we have assumed that the cost of treatment is only applied for patients with severe cases (Grade ≥3). We would expect that mild increases in these levels will be dealt with via non-medical interventions (such as dose reductions, clinician advice at follow up visits etc.) based upon the following:

> "*The decision about the need for further diagnostic evaluation* [following the occurrence of elevated liver enzymes] *and/or the most appropriate evaluation can best be made on the basis of the specific clinical scenario of the individual patient. Those with significant (> 5-fold) elevations of ALT* (alanine aminotransferase) *or AST* (aspartate aminotransferase)*… should clearly undergo an expeditious evaluation.*" [25]

An updated version of Table 67 including these additional adverse events is presented in Table 5.

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Table 5: Adverse events included in the model

Adverse event	Actively treated		Cost of treatment		Reference (see notes for sources)	
	All grades	Grade ≥3	Grade ≤2	Grade ≥3	Grade ≤2	Grade ≥3
Nausea		✓		£158.43		**a**
Vomiting	✓	✓	£158.43	£158.43	**a**	**a**
Decreased appetite		✓		£158.43		**a**
Fatigue		✓		£158.43		**a**
Diarrhoea	✓	✓	£158.43	£158.43	**a**	**a**
Abdominal pain		✓		£139.52		**b**
Fever	✓	✓	£158.43	£158.43	**a**	**a**
Asthenia		✓		£158.43		**a**
Febrile neutropenia	✓	✓	£2,583.98	£2,583.98	**c**	**c**
Stomatitis		✓		£158.43		**a**
Hand-foot syndrome		✓		£158.43		**a**
Cardiac ischaemia	✓	✓	£158.43	£158.43	**a**	**a**
Neutropenia		✓		£1,227.95		**d**
Leucopenia		✓		£158.43		**a**
Anaemia		✓		£799.00		**e**
Thrombocytopenia		✓		£643.48		**f**
Increase in alanine aminotransferase level		✓		£158.43		**a**
Increase in aspartate aminotransferase level		✓		£158.43		**a**
Increase in total bilirubin		✓		£158.43		**a**
Increase alkaline phosphatase level		✓		£158.43		**a**
Increase in creatine level		✓		£158.43		**a**

Key: DSU, Decision Support Unit; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.
Notes: a NHS Reference costs 14-15: Outpatient visit, general medicine; **b** NHS Reference costs 14-15: Outpatient visit, pain management[2424]; **c** NICE DSU report; **d** NHS Reference costs 14-15: Average non-elective inpatient stay; **e** PENTAG ERG Report for cetuximab; **f** NHS Reference costs 14-15: Weighted cost of thrombocytopenia based on complications and comorbidities score. (Full references supplied in original company submission document)

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- Please provide the results of a scenario analysis including these updated adverse event costs in the cost-effectiveness analysis.

The difference in results including these updated adverse event costs is presented as a scenario analysis in response to B17.

B8. In the economic model, time to treatment discontinuation was approximated using progression-free survival and dosing of trifluridine in combination with tipiracil was approximated using body surface area. Based on table 54 of the company submission[13], it seems that empirical data are available to estimate these parameters.

- Please provide time to treatment discontinuation and dosing for trifluridine in combination with tipiracil estimated using empirical data from the RECOURSE trial.[5]

Table 54 from the company submission contains the total number of cycles of treatment received by each patient group, the number of cycles in which a treatment delay was experienced along with the average delay in treatment initiation for cycles in which a delay was experienced. These data only tell us an estimated number of cycles initiated, and do not provide an empirical estimate of time to treatment discontinuation.

Time on treatment was not explicitly reported in either of the clinical trials from which efficacy data were derived, and therefore specific TTD outcomes are not available for use within the economic model.[13] However, data are available regarding the start and end time of treatment for patients within both studies, from which an estimate of TTD may be derived. Please note however that this estimate should be considered with the following caveats:

- All remaining patients have been assumed to experience the event of treatment discontinuation at the end time of treatment (i.e. no patients have been censored at this time, due to available data).
- TTD was calculated simply as:

$$End\ date - Start\ date$$

For incorporation into the *de novo* economic model, the following assumptions were made:

- A stratified Generalised Gamma curve fit was applied, as this provided the best AIC score. Other curve fits are available for use within the model. The top 6 AIC scores are presented in Table 6 below.

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Table 6: Goodness of fit statistics: Time to treatment discontinuation

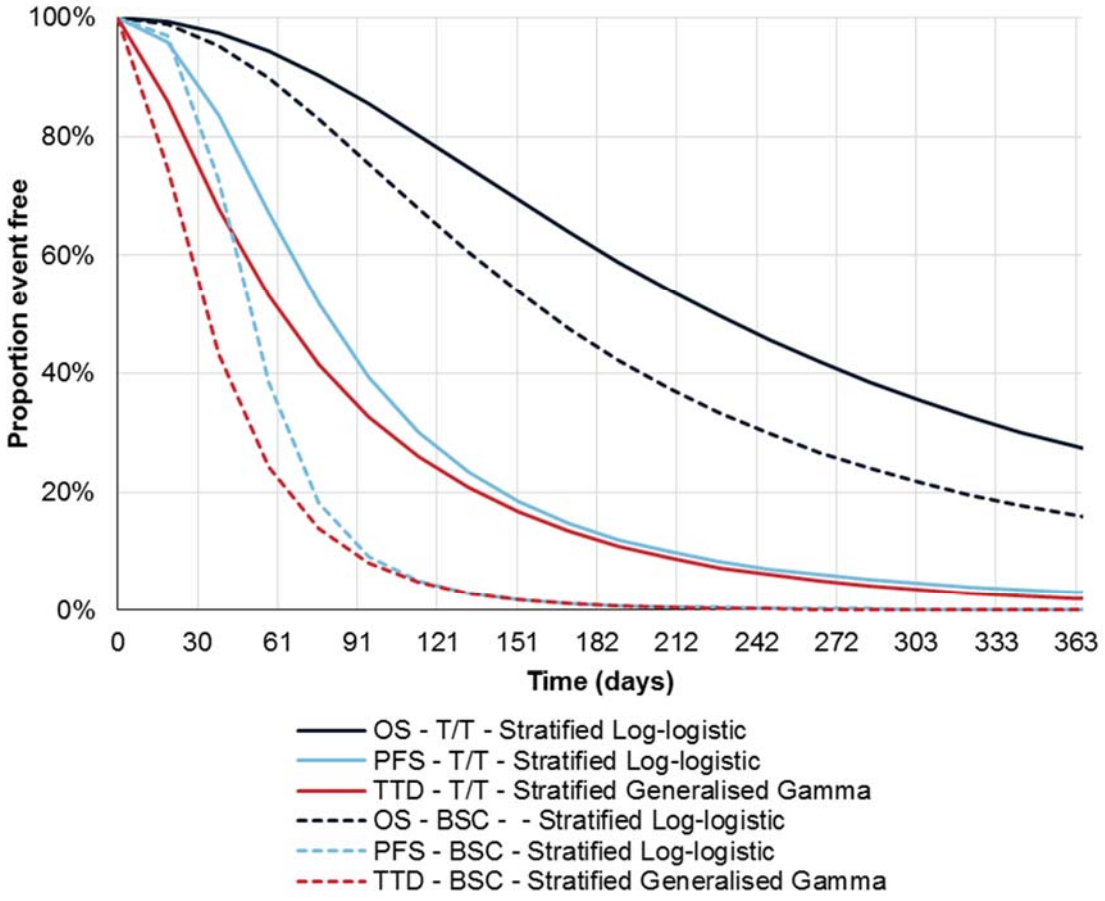
Model	AIC
Stratified Generalised Gamma	10040.75
Generalised Gamma	10056.67
Stratified log-logistic	10062.89
Stratified log-normal	10063.83
Log-logistic	10079.76
Log-normal	10083.59

Key: AIC, Akaike information criterion.

- If the TTD curve produces estimates larger than the PFS curve, the value from the PFS curve is assumed.
- TTD is not used for BSC patients, as no active treatment cost is applied.
- Within the patient flow, a treatment cycle length of 28 days has been assumed (i.e. no average delay in treatment initiation is).
- Patients receive monitoring and their utility is based upon progression status, and not whether patients are still on treatment.

OS, PFS and TTD estimates for up to 1 year in the model are presented in Figure 9. The solid lines demonstrate outcomes for patients receiving trifluridine/tipiracil, and the dashed lines demonstrate outcomes for patients receiving BSC.

Figure 9: Estimation of OS, PFS and TTD used in the economic model



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As demonstrated with the curves above, TTD is similar to PFS and therefore we would consider either method (adjustment of PFS to estimate TTD, or estimation of TTD using empirical data) to provide similar cost-effectiveness results. The difference in results using either method is presented as a scenario analysis in response to B17.

For the dosing of trifluridine/tipiracil, empirical estimates of BSA were used. A log-normal fit was supplied for the purposes of variation, with results also presented in response to B17.

- Please incorporate these empirical estimates for time to treatment discontinuation and trifluridine/tipiracil dosing in the economic model and provide the cost-effectiveness results.

Please see the above.

- Please clarify how treatment delay was calculated for BSC (i.e. which treatment was used to calculate time to treatment initiation), reported in table 54 of the company submission.[13]

Treatment delay for patients on BSC was calculated using the same methodology as for trifluridine/tipiracil patients, with the treatment used as placebo in the RECOURSE trial.

B9. Resource use was obtained from ID794[19] because the company considered ID794[19] to be 'particularly relevant'.

- Please justify why ID794[19] is an appropriate source for resource use, as this assessment considers a population in an earlier treatment line (1st line) and a specific subpopulation (RAS wild type).

Resource use data were initially considered from ID794 to inform the economic model, as utility data from this study were deemed applicable (please see the response to B6). Following the advisory board held in January 2016, resource use estimates within the model were replaced with those more suited to clinical practice at this later stage of disease. Consequently, the statement of "ID794 is particularly relevant, with the assessment report becoming available in August 2015; we have therefore utilised the resource costs identified within this document" is incorrect as although data from this assessment were initially considered for use within the economic model, more appropriate estimates of resource use from the advisory board process were used instead.

- Please clarify why ID794[19] is preferred over other appraisals that may contain relevant information, e.g. TA118[22], TA176[16], TA212[23] and TA307[15].

See response above

B10. On page 157 of the company submission[13] it is explained that in pre-progression patients receiving BSC were assumed to have an outpatient consultation with an oncologist per treatment cycle.

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- Please clarify what this assumption (both the outpatient consultation itself and its frequency) was based on and in the case of expert opinion provide details and a step-by-step description of the expert elicitation process.

At the advisory board held in January 2016, it was deemed appropriate that patients receiving trifluridine/tipiracil would be expected to incur the cost of an outpatient chemotherapy day case appointment once per treatment cycle. For patients receiving BSC, similar resource use was expected as these patients still require complete blood cell (CBC) tests, assessment of disease progression status etc. As patient receiving BSC are not receiving active chemotherapy, the cost of such a visit was deemed inappropriate for application, and therefore the cost of an outpatient oncologist consultation and CBC test was applied instead.

For details regarding the expert elicitation process, please see the response to B12.

B11. Page 140 of the company submission[13] explains that *"treatment with trifluridine/tipiracil is continued until disease progression, clinical progression, the development of severe adverse events (AEs), withdrawal from the study, death, or a decision by the treating physician that discontinuation would be in the patient's best interest"*.

- Please confirm whether in the trials none of participants have continued treatment with trifluridine in combination with tipiracil after disease progression.

Servier confirm that all patients were withdrawn from study treatment after disease progression.

- If treatment continuation after disease progression did occur, please provide the rate of these occurrences and justify why this was not incorporated in the resource use.

N/A

B12. Page 157 of the company submission[13] states that medical resource use items were identified following consultation with clinical experts, due to the lack of published literature.

- Please report what steps were taken to systematically obtain evidence on resource use (publications, trial data, clinical guidelines, relevant STAs).

A review NICE technology appraisals and the associated assessment reports in mCRC was undertaken. These data were presented at and advisory boards and face to face meetings described below.

- Please provide details and a step-by-step description of the process used to obtain expert opinion (expert selection, elicitation method, etc).

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The evidence for resource use for patients receiving chemotherapy or BSC for mCRC at third line or later was obtained from clinical experts, these included medical and clinical oncologists, Palliative care consultants (primary and secondary care) and health economists.

The information was elicited through discussion at two advisory board meetings and a number of face to face meetings. The evidence from all these engagements was subsequently compiled and the information was used to inform this section of the cost effectiveness model.

The estimates in the model were validated as described in the response to question B15.

B13. The costs of post-progression treatment were estimated based on the RECOURSE trial[5] and reported in Table 69 of the company submission[13].

- Please justify why equal post progression treatment costs were assumed for trifluridine in combination with tipiracil and BSC.

The cost of post-progression treatment was assumed to be the same for both groups of patients based upon the following:

- Clinical expert opinion at the advisory board held in January 2016 suggested that the costs would be approximately equal following progression given that patients would be expected to be eligible for the same treatment following progression and that patient prognosis following progression at this late stage of disease is similarly poor across treatment groups.
- Analysis of the data demonstrated that costs between trifluridine/tipiracil versus BSC patients were approximately equal (£1,549 versus £1,487).

Consequently, the cost applied in the model was assumed to be the same across treatment arms at pre-progression. The application of separate costs by treatment arm are explored in scenario analysis, with results presented in Table 81 of the company submission document. These results demonstrated a difference in the ICER with the PAS included of £353 (pooled population) (£44,032 versus £44,385).

Model validation

B14. **Priority request:** External validation of model results is crucial to assess the validity of model outcomes. In section 5.3.3 of the company submission[13], survival estimates from the model are compared with other published data (e.g. cancer research UK)[7]. The cancer research UK data indicate that the survival 5 years after diagnosis of metastasis is 7-8%. This is compared with the estimated 2-year BSC survival in the model (4%) which is on average 5 years after diagnosis of metastatic disease (since time from diagnosis of metastatic disease to study initiation was, on average, 35.2 months[8]). Hence, the 2-year BSC survival of 4% is conditional on having survived approximately three years before trial inclusion (in contrast with the cancer research UK data).

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- The ERG calculated the 2-years survival for stage 4 bowel cancer patients conditional on having already survived 3 years based on the cancer research UK data[7]. A constant mortality rate was assumed. The calculation resulted in a 2-years survival of approximately 35% for patients having already survived 3 years. Please explain this discrepancy between the pooled 2-years survival estimates of patients participating in both trials provided in the company submission[13] (4%) and the estimate based on the cancer research UK data (~35%)[7].

The use of Cancer Research UK (CRUK) data was initially considered to be appropriate for comparison with data from RECOURSE and the Phase II trial, based on the disease area. As discussed in response to A5, we agree with the ERG that these data are not reflective of the population defined by the decision problem for this appraisal.

- Please provide a comparison of the mean progression-free survival estimate as provided in table 74 of the company submission[13] with external sources such as cancer research UK and Jonker et al.[26] or other suitable sources (and justify why these sources are suitable for such a comparison by providing patients characteristics).

As described above, the use of Cancer Research UK (CRUK) data would no longer be considered appropriate for comparison following the revision of the calculation of mCRC patients 5 years after diagnosis. Consequently, it would be inappropriate to compare outcomes for patients in these datasets. Additionally, CRUK data does not provide information regarding progression-free survival, as only estimates of mortality, incidence and prevalence etc. are given.

The Jonker *et al.* (2009) source is a meeting abstract for the 2009 American Society of Clinical Oncology, in which cetuximab is used for the treatment of mCRC patients with high epiregulin (EREG) gene expression plus KRAS wild-type status. Our analysis does not consider patients in this "combimarker" subgroup, and therefore results are unlikely to be comparable.

As an alternative, the company submission considered a comparison to patients treatment with regorafenib within the CORRECT study.[13, 11] As previously discussed within the company submission, regorafenib is the only treatment currently avaialble with a similar indication to trifluridine/tipiracil but is not currently recommended by NICE. [13] However, BSC patients within both the CORRECT and RECOURSE studies demonstrated similar estimates for PFS. Below are the superimposed figures below which demonstrate the approximate overlap of PFS outcomes for BSC patients within both trials (both trials considered similar assessments of progression and therefore exhibit drops at similar times).

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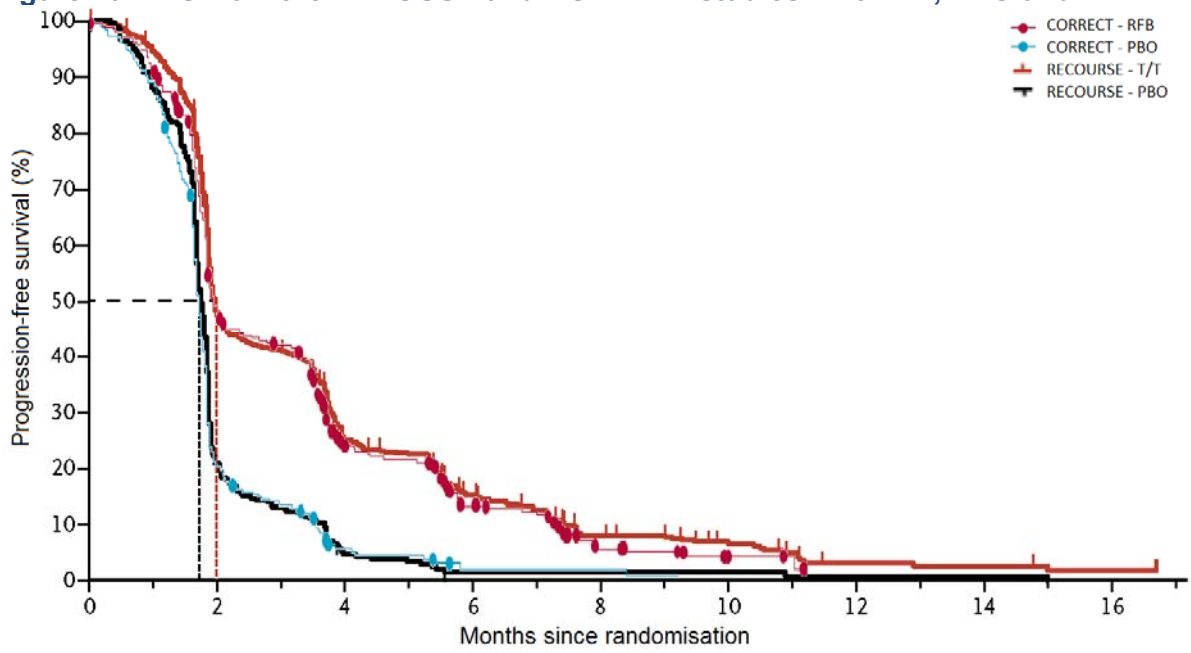
Figure 10: PFS from the RECOUSE and CORRECT studies – For T/T, PBO and RFB



Key: RFB, regorafenib; PBO, placebo, T/T, trifluridine/tipiracil.

B15. Section 5.10 of the company submission[13] contains different efforts undertaken by the company to validate the cost-effectiveness model.

- Please describe which steps have been undertaken to assess the face validity and the internal validity of the cost-effectiveness model.

The actions undertaken to evaluate the cost effectiveness model are outlined in the evidence submission Section 5.10.

Professor Martin Hoyle (Director of PenTAG) was the primary consultant on model validation. Professor Hoyle was the ERG lead for TA242 in mCRC for treatment after first line chemotherapy and developed the ERG cost effectiveness model for this appraisal. In addition, he is also part of the ERG group for ID794 in mCRC. Therefore, Professor Hoyle is an appropriate expert for validation given his academic expertise and his experience in NICE appraisals in mCRC.

Professor Hoyle was provided with the complete model and conducted a systematic assessment. As part of this assessment he undertook the following: validation of model inputs, parameters, results and sensitivity analyses. In addition he checked the economic model by constructing an independent simplified model. His response is as follows

> *"The results from the simplified model are very close to those from the main model which is reassuring, as it means that there are either no logical errors in the main model, or only one or more errors which have little effect on cost-effectiveness".*

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Overall his assessment was that the model was accurate and appropriate to the NICE decision problem.

The model also fully reviewed by health economic and clinical experts at an advisory board. The findings of the group were that the model was appropriate to the NICE decision problem.

B16. Presumably, since the systematic review did not identify a cost-effectiveness analysis of trifluridine in combination with tipiracil compared with BSC (section 5.1 of the company submission), the company did not perform any cross validation of its results with another cost-effectiveness analysis. However, one study from Goldstein et al.[27], which was identified in the systematic review (and excluded), assesses the cost-effectiveness of regorafenib versus BSC as third-line treatment for mCRC. Furthermore, ID794[19] reports mean treatment and survival times for mCRC patients beginning third-line treatment (from a study of Jonker et al.[26]).

- Please compare the study by Goldstein et al.[27] with the present assessment and, separately, compare ID 794[19] with the present assessment:
  - Regarding input parameters, model structure and assumptions.
  - Regarding outcomes for the BSC arm of both studies.

B16: Comparison of Goldstein et al with our assessment.

- Model structure

Both assessments use the same model structure, the only difference in the Goldstein *et al.* (2015) model was that the post-progression health state was split into two 'supportive care' health states. Patients who entered the model could either start on third line treatment or proceed directly to 'supportive care', and then could also progress to 'supportive care' after third line treatment. In our model all patients started in the pre-progression health state.

Both assessments used results from the appropriate trial data to determine the probability of transitioning between health states. Goldstein *et al.* (2015) used parametric survival curves based on the CORRECT study.

- Utility estimates

Health utility was not collected in either of the phase II or RECOURSE trial hence out estimates came from published literature, including the CORRECT study. Goldstein *et al.* (2015) used the quality of life data collected in the CORRECT trial.

- Adverse events

The choice of adverse events for the Goldstein *et al.* (2015) model was slightly different to our model due to the different toxicity profile of regorafenib. However, the method of selecting the adverse events for both models were similar as both considered events which had significant differences between the two arms of the studies or were deemed important. Goldstein *et al.* (2015) made assumptions for management of adverse events based on

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published guidelines. Our adverse event assumptions on whether or not the event was actively treated was based on expert opinion from clinical and medical oncologists. The Goldstein *et al.* (2015) model was designed for patients with mCRC from a US payer perspective therefore costs cannot be compared.

- Outcomes of the BSC arm

Goldstein showed that the patients on BSC had a loss of 6 weeks of life (0.13 LYs) and a loss of 2 quality adjusted life-weeks (0.04 QALYs) compared with regorafenib, but exact LYs for the BSC arm are not reported. The Goldstein BSC arm had 40% less patients with an adverse event grade 3 or 4 and in our assessment the BSC arm had 17.7% less adverse event grade 3 or higher.

- Resource Use

Resource use was not reported in Goldstein *et al*. (2015) publication and therefore cannot be compared.

B16: Comparison of ID 794 with our assessment.

- Resource use and end of life

Both the ID 794 assessment and our assessment split the resource use costs by pre and post progression. ID 794 also split costs depending on successful liver resections - this was not relevant to our study as liver resection is not considered. Both assessments used medical expert opinion to estimate the resource use occurrences.

Given the different stages of the studies (ID794 considered 1st, 2nd and 3rd line progression where as our study looked at third line onwards) there were slight differences in the resource use applied. ID 794 considered outpatient consultations, blood tests, CT scans and MRI scans for 1st and 2nd line pre progression patients. Post successful resection pre-progression patients also considered outpatient consultations, blood tests, CT scans and additionally colonoscopy.

In our assessment pre-progression patients were considered to incur the cost of an oral chemotherapy day case visit, which would include all routine tests and clinician appointments, as well as a home consultation. Pre-progression patients on BSC would have an outpatient consultation instead of chemotherapy day case appointment.

For post-progression ID 794 used the cost of best supportive care per month instead of looking at individual costs components. This cost was based on a Finnish study and incorporated the end of life costs instead of having this as a separate component. Our assessment considered GP home consultation, community nurse, home health visitor, district nurse and GP surgery visit for post progression patients. A separate end of life cost was also applied which included health, social and informal care based on the study by Round et al. (2015).

- Adverse events

Both studies considered similar adverse events. Seven out of the 15 events reported in ID 794 were also reported in our assessment. Adverse events were included in ID 794 if they

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were Grade ≥3, whereas we only included those which commonly occurred. Both approaches will capture the costs of the most relevant adverse events.

Our model considers 14 additional adverse events which were not considered in ID 794. Of the events reported in both assessments, most of the costs used were from the same NHS reference. We also based our cost of Anaemia from the ID 794 study. The only cost which differed was for neutropenia, which we based on the NHS reference costs 14/15 average non-elective inpatient stay cost of £1,228, whereas ID794 used the NHS reference cost 13/14 spell based average inpatient stay cost of £2,160.

- Model structure

The model structure used in both assessments is very similar and both are based on previous cancer models. Transitions throughout the model are either caused by progression or death, however we do not consider the health state post resection as we only consider patients from third line onwards, whilst ID794 looks at 1st, 2nd and 3rd line.

- Outcomes of the BSC arm

It is not appropriate to compare the outcomes of the BSC arms in both studies as they consider patients at different stages of the disease.

General

B17. **Priority request:** According to the NICE Methods Guide[24], probabilistic methods provide the best estimates of mean costs and outcomes in non-linear decision models.

- Please provide the probabilistic results for all analyses presented in tables 72-78 and table 81.

In response to this question, and in response to other questions which refer to updated results, please find the appropriate updated result required in Table 7 below.

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Table 7: Updated results directory

Result	Link
Deterministic model results	
Updated Table 72 *(Updated results – list price)*	Table 11
Updated Table 73 *(Updated results – PAS price)*	Table 12
Updated Table 74 *(Model versus clinical trial results)*	Not provided[a]
Updated Table 75 *(QALY breakdown)*	
Updated Table 76 *(LY breakdown)*	
Updated Table 77 *(Updated cost breakdown – list price)*	Table 13
Updated Table 78 *(Updated cost breakdown – PAS price)*	Table 14
Updated Table 81 *(Updated scenario analysis)*	Table 15
Probabilistic model results	
Updated results – list price	Table 16
Updated results – PAS price	Table 17
Updated PSA plots *(PSA scatterplots and CEACs for both the list price and the PAS price)*	Figure 11, Figure 12, Figure 13, Figure 14
Model versus clinical trial results	Table 18
QALY breakdown	Table 19
LY breakdown	Table 20
Updated cost breakdown – list price	Table 21
Updated cost breakdown – PAS price	Table 22
Updated scenario analysis	Table 23

Key: CEAC, cost-effectiveness acceptability curve; LY, life year; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.
Notes: a: Tables 74, 75 and 76 remain unchanged from the original company submission document, as these tables rely on overall survival, progression-free survival and utility data (all unchanged).

B18. The scenario analyses for body surface area, described in section 5.3.5 of the company submission are missing in table 81.[13]

- Please provide the probabilistic results for these scenario analyses.

Scenarios regarding the distribution of patient BSA are included within the updated set of scenario analyses presented in response to B17. As previously discussed, due to time constraints the non-parameterised estimates of BSA have not been included for population other than RECOURSE alone. Furthermore, as probabilistic sensitivity analysis was requested, these parameters would remain unchanged, and therefore we would consider the log-normal fit to be most appropriate for assessing the uncertainty associated with BSA.

B19. In the probabilistic sensitivity analyses, the minimum and maximum of multiple parameters was assumed to be +/- 20% of the mean (table 70).[13]

- Please use the empirical data if possible to estimate the variance for input parameters (e.g. for treatment delay per patient per cycle and post-progression costs) and provide the estimated standard errors.

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The variance around estimates where empirical data would be inappropriate for use have +/- 20% of the mean bounds applied. This was decided based upon the uncertainty in the initial estimates, from which it was decided that precise estimates of uncertainty would be inappropriate – i.e. given that the average cost for post-progression treatment is already uncertain, producing a standard error for this cost would be inappropriate.

In lieu of producing specific measures of uncertainty, larger bounds were utilised to account for larger amounts of uncertainty. For the example of post-progression treatment costs, Table 10 below shows the derived standard error based bounds compared with using +/- 20% of the mean. The calculations used to compute these were taken from a publication by Hozo *et al.* (2005).[28] The median was estimated by using the formula:

$$Median \cong \frac{4 * Mean - Min - Max}{2}$$

From which, the variance of the sample was estimated by:

$$Variance \cong \frac{1}{12}\left(\frac{(Min - 2 * Median + Max)^2}{4} + (Max - Min)^2\right)$$

Therefore, estimates of the standard error of the sample were computed.

Table 8: Possible bounds for post-progression treatment cost

Parameter	+/- 20% of the mean			Derived standard error		
	All	T/T	BSC	All	T/T	BSC
Mean	£1,528	£1,549	£1,487	£1,528	£1,549	£1,487
Minimum value	*Not applicable*			£0	£0	£0
Maximum value				£3,744	£3,744	£3,744
Number of patients	335	222	113	335	222	113
Estimated median	*Not applicable*			£1,184	£1,226	£1,103
Estimated variance				£1,460,111	£1,460,109	£1,460,114
Estimated SD				£1,208	£1,208	£1,208
Estimated SE				£66	£81	£114
Lower bound	£1,222	£1,239	£1,190	£1,399	£1,390	£1,265
Upper bound	£1,834	£1,859	£1,785	£1,657	£1,708	£1,710
Key: BSC, best supportive care; SD, standard deviation; SE, standard error; T/T, trifluridine/tipiracil						

Consequently, as the bounds produced by the standard error estimate are smaller than the bounds produced by using +/- 20% of the mean, the uncertainty around the cost of post-progression treatment is appropriately captured with current estimates. However, an alternative setting is now included within the model to use these bounds for the cost of post-progression treatment.

For the delay in treatment initiation per patient per cycle, this was calculated using the following formula:

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$$\frac{(n\ of\ delayed\ cycles * average\ delay) + (n\ of\ non - delayed\ cycles * 0)}{Total\ n\ of\ cycles}$$

Consequently, deriving the standard error associated with the final values for BSC and trifluridine/tipiracil patients of 1.40 and 2.72 days, respectively was deemed inappropriate for demonstrating the uncertainty in the derived result. Given the time constraint with which to address these clarification questions (and run many probabilistic scenarios) we have not been able to provide these estimates, though do not anticipate that deriving such measures of uncertainty to have a noteworthy impact on the (probabilistic) model results,

Furthermore, we would consider using +/- 20% of the mean to sufficiently estimate the uncertainty around the delay in treatment initiation per patient per cycle, and sufficient uncertainty is therefore captured with current estimates (reflected in the above calculations of a standard error for the cost of post-progression treatment).

- Please justify why the minimum and maximum was not estimated based on expert opinion as was done for the estimated value of the resource use parameters (instead of using the arbitrary +/- 20% of the mean).

Clinical expert opinion was used to derive estimates for resource use, model structure, the clinical pathway of patients, but the uncertainty surrounding each estimate was not addressed within the consultation. A +/- 20% of the mean estimate for the lower and upper bounds of parameters was applied in absence of data regarding the uncertainty of these estimates.

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Appendices

Appendix A

Changed input parameters: Response to B2

OS, PFS and TTD

The parameters used for the OS, PFS and TTD curves are presented in Table 9 for the base case considered in the *de novo* economic model (pooled population, KRAS wild type and KRAS mutant type).

Table 9: OS, PFS and TTD curve fit parameters

	EXPO	EXVA	GGAM	GOMP	LLOG	LNOR	WEIB
OS – T/T	0.00	6.18	5.54	0.00	5.42	5.41	5.77
		0.04	0.81	0.00	0.72	0.86	0.36
			0.34				
OS - BSC	0.00	5.95	5.10	0.00	5.09	5.08	5.45
		-0.08	0.83	0.00	0.74	0.83	0.29
			0.04				
PFS – T/T	0.01	5.31	4.32	0.00	4.36	4.40	4.78
		-0.14	0.78	0.01	0.81	0.78	0.27
			0.21				
PFS - BSC	0.02	4.70	3.87	0.00	3.91	3.92	5.45
		-0.16	0.53	0.01	1.27	0.53	0.49
			0.16				
TTD – T/T	0.01	5.14	4.27	0.00	4.07	4.04	4.54
		-0.28	0.97	0.01	0.54	1.02	0.10
			0.46				
TTD - BSC	0.02	4.47	3.57	0.00	3.51	3.46	3.86
		-0.34	0.80	0.02	0.80	0.81	0.23
			0.27				

Key: BSC; best supportive care, EXPO; exponential, EXVA; extreme value, GGAM; Generalised Gamma, GOMP; Gompertz, LLOG; log-logistic, LNOR; log-normal, OS; overall survival, PFS; progression-free survival, T/T; trifluridine/tipiracil, TTD; time to treatment discontinuation, WEIB; Weibull.

BSA

The parameters used to estimate the log-normal distribution of BSA are presented in Table 10 for the base case considered in the *de novo* economic model (pooled population, KRAS wild type and KRAS mutant type).

Table 10: Body surface area log-normal fit parameters

Parameter	Value	Standard error
All patients – Pooled		
Mean	0.549332	0.004286
Standard deviation	0.133207	0.00303

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Appendix B

Updated results: Response to B17 and updated results for other questions

Updated results

The updated model results consider (with associated settings as they appear in the model):

- Pooled patient population, all KRAS mutation type, "Updated OS" (original company submission),

Patient population	Pooled
KRAS mutation subgroup	All patients
Scenario	Updated OS

- Revised estimate of TTD (in response to B8),

Use revised TTD estimate?	Yes

- Pooled estimates for BSA, adverse events and dose reductions (in response to B3),

Use RECOURSE BSA only?	No
Use RECOURSE AE rates only?	No
Patients experiencing a dose reduction after cycle 1	10.7%
Patients experiencing a dose reduction after cycle 2	4.5%
Patients experiencing a dose reduction after cycle 3	0.9%

- Additional costs for adverse events not included in the previous model base case (in response to B7),

Include additional AE costs?	Yes

- Equal estimates for post-progression treatment costs (in response to B13).

Cost of post-progression treatment is equal for all treatments	Yes

The updated model results does not consider revised estimates of uncertainty for model parameters (please see the response to B19).

Use derived standard errors?	No

Full results are presented in the tables and figures in the pages below. A directory for these results is given in Table 7.

Compared with the base case results presented in the company submission, the ICER including the PAS has decreased from £44,032 to £42,674, with similar results holding at list price [redacted] versus [redacted]. Both sets of results demonstrate similar levels of the cost-effectiveness of trifluridine/tipiracil versus BSC.

Table 11: Updated results without patient access scheme - Deterministic

Technologies	Total			Incremental			
	Costs (£)	QALYs	LYG	Costs (£)	QALYs	LYG	ICER (£)
BSC	[redacted]	0.42	0.66				
T/T	[redacted]	0.59	0.92	[redacted]	0.17	0.27	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; T/T, trifluridine/tipiracil.

Table 12: Updated results with patient access scheme ([redacted]) - Deterministic

Technologies	Total			Incremental			
	Costs (£)	QALYs	LYG	Costs (£)	QALYs	LYG	ICER (£)
BSC	10,116	0.42	0.66				
T/T	17,456	0.59	0.92	7,340	0.17	0.27	42,674

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; T/T, trifluridine/tipiracil.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table 14: Summary of costs by health state and category – PAS price - Deterministic

Health state	Costs T/T (£)	Costs BSC (£)	Increment (£)	Absolute increment (£)	% absolute increment
Pre-progression	**7,790**	**641**	**7,149**	**7,149**	**100%**
Drug costs	5,829	0	5,829	5,829	82%
Monitoring	926	460	466	466	7%
Adverse events	1,035	181	854	854	12%
Post-progression	**2,991**	**2,730**	**261**	**261**	**100%**
Drug costs	1,511	1,519	-8	8	3%
Monitoring	1,480	1,211	269	269	97%
Total	**17,456**	**10,116**	**7,340**	**7,340**	**100%**
Drug costs	7,340	1,519	5,821	5,821	78%
Monitoring	2,406	1,671	736	736	10%
Adverse events	1,035	181	854	854	11%
End of life*	6,675	6,745	-71	71	1%

Key: BSC; best supportive care; T/T, trifluridine/tipiracil.
Notes: * End-of-life care costs apply for all patients irrespective of progression status.

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Table 15: Scenario analysis results - Deterministic

Input	Base case	Scenario	ICER (List price)	ICER (PAS price)
Updated			[redacted]	£42,674
Time horizon	10 years	2 years	[redacted]	£52,657
		4 years	[redacted]	£45,888
		6 years	[redacted]	£43,992
		8 years	[redacted]	£43,140
Patient population	Pooled	RECOURSE	[redacted]	£45,775
		Phase II	[redacted]	£31,569
Comparator	BSC	RFB	[redacted]	T/T Dominates
Subgroup	Updated OS	Original OS	[redacted]	£43,875
OS and PFS curve choice	Stratified log-logistic	Generalised Gamma	[redacted]	£48,975
		Log-logistic	[redacted]	£45,392
		Log-normal	[redacted]	£46,872
		Stratified Generalised Gamma	[redacted]	£52,149
		Stratified Log-normal	[redacted]	£43,097
Resource use	Total cost	+20% of total cost	[redacted]	£43,493
		-20% of total cost	[redacted]	£41,854
Utility source	Pooled sources	Cetuximab NICE submission	[redacted]	£41,332
		CORRECT study	[redacted]	£44,106
		CORRECT study – BSC utility used for all patients	[redacted]	£43,323
Discounting (Costs, LYs, QALYs)	3.5%, 0%, 3.5%	0%, 0%, 0%	[redacted]	£41,092
		6%, 6%, 6%	[redacted]	£43,813
PP treatment cost by treatment arm	Equal costs	Unequal costs	[redacted]	£43,027
KRAS status	All patients	Wild type	[redacted]	£40,910
		Mutant type	[redacted]	£45,759
BSA from RECOURSE	Not used	Used	[redacted]	£43,350
Revised TTD estimate	Used	Not used	[redacted]	£45,348
Derived SE for PP treatment cost	Not used	Used	[redacted]	£42,674
RECOURSE only AEs	Not used	Used	[redacted]	£42,476
Additional AEs	Used	Not used	[redacted]	£42,760

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PP, post-progression; QALY, quality-adjusted life year.

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Table 16: Updated results without patient access scheme - Probabilistic

Technologies	Total			Incremental			
	Costs (£)	QALYs	LYG	Costs (£)	QALYs	LYG	ICER (£)
BSC	[redacted]	0.42	0.66				
T/T	[redacted]	0.59	0.92	[redacted]	0.17	0.26	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; T/T, trifluridine/tipiracil.

Table 17: Updated results with patient access scheme ([redacted]) - Probabilistic

Technologies	Total			Incremental			
	Costs (£)	QALYs	LYG	Costs (£)	QALYs	LYG	ICER (£)
BSC	10,205	0.42	0.66				
T/T	17,424	0.59	0.92	7,219	0.17	0.26	44,057

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; T/T, trifluridine/tipiracil.

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[redacted]

[redacted]

Figure 13: Probabilistic sensitivity analysis scatter plot – PAS price

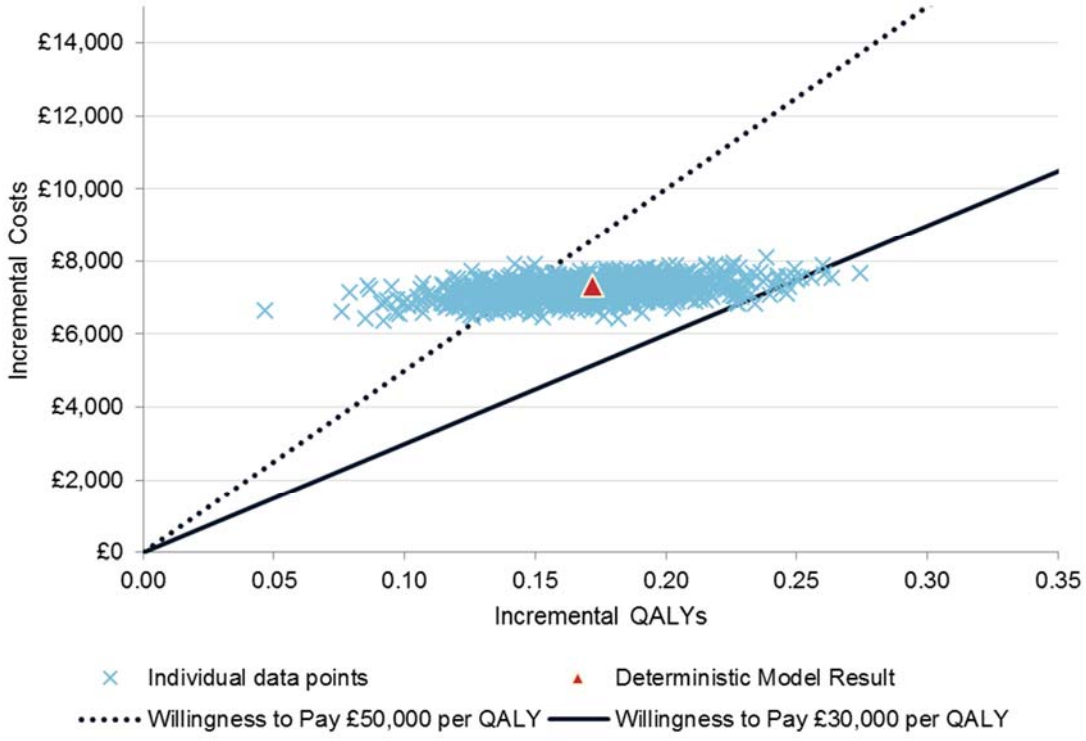

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Figure 14: Cost-effectiveness acceptability curve – PAS price

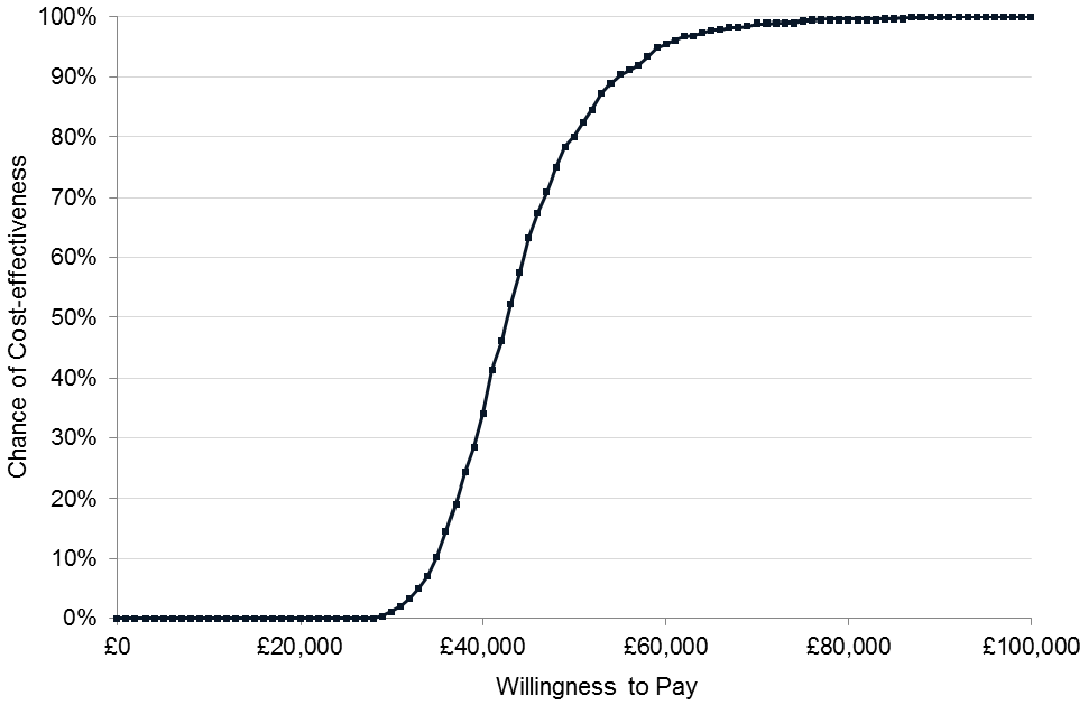

Table 18: Summary of model results compared with clinical data - Probabilistic

Outcome	Clinical trial results (pooled data)	Model result
Overall survival	*Median:* BSC: 5.4 months; T/T: 7.3 months *Mean:* BSC: 6.8 months; T/T: 9.1 months	*Median:* BSC: 5.3 months; T/T: 7.3 months *Mean:* BSC: 7.9 months; T/T: 11.1 months
Progression-free survival	*Median:* BSC: 1.7 months; T/T: 1.9 months *Mean:* BSC: 1.9 months; T/T: 3.7 months	*Median:* BSC: 1.7 months; T/T: 2.6 months *Mean:* BSC: 1.9 months; T/T: 3.7 months
Key: BSC, best supportive care; T/T, trifluridine/tipiracil.		

Table 19: Summary of QALY gain by health state - Probabilistic

Health state	QALY T/T	QALY BSC	Increment	Absolute increment	% absolute increment
Pre-progression	0.22	0.12	0.10	0.10	61%
Post-progression	0.37	0.31	0.06	0.06	39%
Total	0.59	0.42	0.16	0.16	100%
Key: BSC; best supportive care; QALY, quality-adjusted life year; T/T, trifluridine/tipiracil.					

Table 20: Summary of LY gain by health state - Probabilistic

Health state	LY T/T	LY BSC	Increment	Absolute increment	% absolute increment
Pre-progression	0.31	0.16	0.15	0.15	56%
Post-progression	0.62	0.50	0.12	0.12	44%
Total	0.93	0.66	0.27	0.27	100%
Key: BSC; best supportive care; LY, life year; T/T, trifluridine/tipiracil.					

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Table 22: Summary of costs by health state and category – PAS price - Probabilistic

Health state	Costs T/T (£)	Costs BSC (£)	Increment (£)	Absolute increment (£)	% absolute increment
Pre-progression	**7,685**	**641**	**7,044**	**7,044**	**100%**
Drug costs	5,829	0	5,829	5,829	83%
Monitoring	819	460	359	359	5%
Adverse events	1,037	181	856	856	12%
Post-progression	**2,987**	**2,742**	**246**	**246**	**100%**
Drug costs	1,507	1,523	-16	16	6%
Monitoring	1,480	1,218	262	262	94%
Total	**17,424**	**10,205**	**7,219**	**7,219**	**100%**
Drug costs	7,336	1,523	5,813	5,813	79%
Monitoring	2,299	1,679	621	621	8%
Adverse events	1,037	181	856	856	12%
End of life*	6,751	6,822	-71	71	1%

Key: BSC; best supportive care; T/T, trifluridine/tipiracil.
Notes: * End-of-life care costs apply for all patients irrespective of progression status.

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Table 23: Scenario analysis results - Probabilistic

Input	Base case	Scenario	ICER (List price)	ICER (PAS price)
Updated			[redacted]	£44,057
Time horizon	10 years	2 years	[redacted]	£56,629
		4 years	[redacted]	£49,674
		6 years	[redacted]	£47,019
		8 years	[redacted]	£45,686
Patient population	Pooled	RECOURSE	[redacted]	£49,661
		Phase II	[redacted]	£38,128
Comparator	BSC	RFB	[redacted]	83% T/T dominates
Subgroup	Updated OS	Original OS	[redacted]	£47,369
OS and PFS curve choice	Stratified log-logistic	Generalised Gamma	[redacted]	£52,234
		Log-logistic	[redacted]	£48,644
		Log-normal	[redacted]	£49,618
		Stratified Generalised Gamma	[redacted]	£57,576
		Stratified Log-normal	[redacted]	£45,848
Resource use	Total cost	+20% of total cost	[redacted]	£46,491
		-20% of total cost	[redacted]	£45,381
Utility source	Pooled sources	Cetuximab NICE submission	[redacted]	£46,487
		CORRECT study	[redacted]	£47,972
		CORRECT study – BSC utility used for all patients	[redacted]	£45,590
Discounting (Costs, LYs, QALYs)	3.5%, 0%, 3.5%	0%, 0%, 0%	[redacted]	£44,779
		6%, 6%, 6%	[redacted]	£46,999
PP treatment cost by treatment arm	Equal costs	Unequal costs	[redacted]	£48,181
KRAS status	All patients	Wild type	[redacted]	£45,919
		Mutant type	[redacted]	£51,881
BSA from RECOURSE	Not used	Used	[redacted]	£47,216
Revised TTD estimate	Used	Not used	[redacted]	£45,623
Derived SE for PP treatment cost	Not used	Used	[redacted]	£47,216
RECOURSE only AEs	Not used	Used	[redacted]	£47,216
Additional AEs	Used	Not used	[redacted]	£45,623

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PP, post-progression; QALY, quality-adjusted life year.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Trifluridine in combination with tipiracil hydrochloride for previously treated metastatic colorectal cancer [ID876]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Beating Bowel Cancer

Your position in the organisation: [redacted]

Brief description of the organisation: Beating Bowel Cancer is the support and campaigning charity for everyone affected by bowel cancer. The organisation employs 41 people and we rely entirely on voluntary donations and gifts in Wills to fund our important work.

We provide practical and emotional help – on the phone, digitally and face to face. We run the UK's only nurse-led, specialist bowel cancer helpline

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

At present bowel cancer remains a taboo subject - due to the nature of the disease and the part of the body which is affected, so people are reluctant to talk freely about their condition. This in turn leads to patients and relatives/carers not knowing where to go and who to ask for help; increasing their sense of isolation. The treatment for bowel cancer frequently involves major surgery which is physically debilitating and can dramatically affect the individual's quality of life both in the short and long term. Surgery is also often complemented with radiotherapy and chemotherapy, both of which can be lengthy treatments, leading to fatigue as well as many other physical side-effects.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Cure

No stoma

No loss of fertility

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Recent guidelines on standardising treatment for bowel cancer have done much to improve the inequalities of treatment across the country, however there remains unacceptable variations in the standard of treatment concerning: access to primary care (G.P.s), urgent referral to the hospital, access to clinical nurse specialist input, outcomes from surgical treatment, access to innovative treatments and clinical trials, access to supportive care such as cancer support centres. Recent changes to the Cancer Drugs Fund have had a direct and detrimental effect on metastatic bowel cancer patients, denying many of them access to targeted therapies which could help prolong their life.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- those patients in whom standard treatment has failed
- It can improve overall survival in a patient group where curative treatment is no longer the intent
- It offers an option to patients who have become resistant to fluoropyrimidines
- Control of symptoms
- It seems to be well tolerated with no more side effects than patients currently experience on standard treatments

- As a treatment that is administered orally, the medication does not require the insertion of intravenous access lines
- Potential benefit in conjunction with other known drug treatments for metastatic bowel cancer

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Many of the benefits that patients or carers expect to gain are as those listed above in section 4. However, for many patients, symptom control, hope and additional life expectancy would be the main gains

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

As there are such limited treatment options for metastatic bowel cancer patients, this new treatment would be a welcome addition

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

Not known

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- More treatment and hospital visits
- Unknown side-effects?

Please list any concerns patients or carers have about current NHS treatments in England.

Availability – more drug treatments available to Private Patients, reduced access (for NHS patients) to therapies which are available in mainland Europe and other parts of the world.

Regional differences in access to treatment

Please list any concerns patients or carers have about the treatment being appraised.

Not aware of any

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

Not aware of any

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Stage IV bowel cancer patients who have not responded to standard treatments

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Patients who cannot tolerate the treatment either due to allergic reaction or poor tolerance

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

This treatment is not currently available as part of routine NHS care

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

The issue of overall survival is an important outcome for patients

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Not aware of any

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not aware of any

9. Other issues

Do you consider the treatment to be innovative?

Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

There are very few treatments options for this condition, therefore any new treatments that give choice to this group of patients is innovative

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Improve patient choice
- Improve availability of treatments (either alone or in combination)
- Consider quality of life and palliation of symptoms as an important aspect of treatment
- Not to deny hope and the possibility of successful treatment improving patients options
-

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Trifluridine with tipiracil hydrochloride for treating metastatic colorectal cancer after standard therapy [ID876]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:Richard Adams

Name of your organisation

Velindre Cancer Centre, Velindre NHS Trust ,

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There is currently no funded alternative therapy in this setting in England or Wales, thus the phase III trial representing Lonsurf versus best supportive care is relevant to the national setting. Alternative drugs do exist but have not met with a favourable NICE appraisal. The three alternative drugs in this setting all appear to have a less favourable toxicity profile. The most valid alternative is only relevant to the 50% of patients whose tumour does not harbour a RAS mutation. Lonsurf has additional advantage over these drugs as it is administered orally and may be taken in the patients own home.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

It is interesting to note from the trial data that those patients who had not received prior bevacizumab therapy as a component of their care gain an apparent greater PFS advantage if administered Lonsurf. This is relevant to the practice in England and Wales, where bevacizumab has received a negative NICE appraisal and has been removed from the Cancer drug fund listing. No novel biomarkers have yet been identified to predict benefit from this drug.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

This drug should be prescribed under the direct supervision of a qualified clinical or medical oncologist

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Available temporarily on a patient access scheme in the UK pending licensing and marketing availability

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

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Single Technology Appraisal (STA)

European Society of Medical Oncology (ESMO) guidelines are in development and are likely to include Lonsurf as an option for last line therapy

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Lonsurf is easy to use, it is an oral medication, which is appreciated by most patients, many of whom will have received the oral therapy "capecitabine" in earlier settings. As an oral therapy patient education is required but there is a lesser impact on hard pushed chemotherapy chair time, specialist nurse in put and pharmacy time. Clinical assessment prior to each cycle of therapy is essential; however this is 4 weekly and outpatient based. Toxicities may result in acute admission to hospital as with other chemotherapy treatments in this disease.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

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These rules are pretty much as defined by any other systemic anticancer therapy in this arena.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

It is widely accepted that trial patient cohorts are generally fitter and younger than the average from cohorts seen in clinical practice. However, it is also acknowledged that clinicians are able to gauge the appropriate administration of this drug for the appropriate population of patients seen in clinical practice. Further research will be able to gauge the utility of Lonsurf in an older and frailer population. The phase III trial unfortunately did not asses quality of life paramaters, however in the cohorts of patients treated on the patient access schemes, it is broadly felt that there is minimal detriment to the majority of patients in terms of quality of life, indeed feedback from patients personally and from colleagues in the same scenario is that most appreciate the ability to have access to a further line of therapy, which is relatively non toxic and with limited effect on quality of life overall.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Neutropenia results in delays in therapy, a small proportion of patients develop neutropenic sepsis which will result in an acute hospital admission. There have been no significant effects on cardiac function, which have been seen with the standard fluoropyrimidine based drugs.

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Single Technology Appraisal (STA)

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; **No**
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; **Negative appraisal may result in a discrepancy in administration if Lonsurf is then accepted by the cancer drugs fund, with inequality of availability between wales and England.**
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities **NO**

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Discussions with the Cancer drug Fund appraisal group

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.
Experience gained through the UK patient access scheme

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Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Additional training of chemotherapy specialist nurses and pharmacy would be required, however, this training is neither complex or long

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Single Technology Appraisal (STA)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Trifluridine with tipiracil hydrochloride for treating metastatic colorectal cancer after standard therapy [ID876]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Mark Saunders

Name of your organisation: The Christie, Manchester, UK

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **I am the medical chair of the charity Beating Bowel Cancer**
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: Nil

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The only available treatments for patients that have failed conventional chemotherapies are regorafenib and cetuximab / panitumumab (in wtRAS pts). Both of these drugs are not funded by CDF/NICE in this situation. There is therefore no funded treatment for patients in this situation. TAS102 would therefore fill a valuable "hole" in our management of this condition.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

TAS102 would be available in its licenced indications for patients with either wt or mutated RAS. This is an advantage of this drug compared to cetuximab or panitumumab that may only benefit pts with wtRAS (50%).

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

It is an oral drug and therefore could be given in all oncology units that are already experienced in giving oral chemotherapies (such as capecitabine) for patients with CRC. It does not need to be given in a specialist unit.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

It is not presently available. I have experience in giving this drug as part of the "named patient access scheme". We presently have more than 30 patients on this drug at the Christie. I am also the UK CI for a new trial with this drug for patients with MCRC that have not received chemo for advanced disease yet.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

There are no clinical guidelines for this drug since it isn't presently available outside the indications I have stated above. If it does become available, then it would be used in its licenced indication for patients that have failed conventional chemo for MCRC. This will probably be in the 3rd or 4th line of

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Single Technology Appraisal (STA)

treatment (represents about 10-30% of patients with MCRC that were able to receive 1st line chemotherapy for MCRC)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

It is easy to administer (oral) in all CRC chemotherapy units
It is "well tolerated" compared to other CRC chemotherapies
Unlike capecitabine it is better tolerated by patients with cardiac co-morbidity and does not cause "hand-foot-syndrome (HFS)".
No special precautions need to be taken other than the normal precautions available in all chemotherapy units.
It can be given to all patients whatever their RAS status
There are no other funded treatments in this situation (it is a "niche" product presently)

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

No additional testing is required (ie no need for RAS testing)
It is given in monthly cycles and I would expect that 2 or 3 monthly cycles are given before the patients response is evaluated with a repeat CT scan to compare to the baseline scan. This is very routine practice.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

I think they do. However, outside trials patients may be older, less fit and less well-supported compared to trial patients. This is common however for all new drugs that are introduced after gaining positive results in a clinical trial. The company would have to ensure that clinicians / units are well informed of the side-effects and their management. From my experience it is well tolerated but it can cause pancytopaenia. It is important that units are advised strongly of this and it is emphasised it is still a cytotoxic agent and should only be given to patients that are fit enough and have the appropriate blood parameters and support. Good patient info and diaries for example are important to consider.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice

Please see above

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I do not think there are any equality and diversity issues with this drug / appraisal

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I have nothing to add here

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that

have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

I do not think it would be hard to implement since CRC oncologist are very familiar with the use of another oral drug - capecitabine. However, TAS102 has not been trialled extensively in England and Wales. Therefore, as I have stated above, I think it is important for the company to ensure that clinicians are well informed of the side-effects of this agent and the actions required to treat such issues. As stated above, the main problem may be with neutropaenia nd thrombocytopaenia. However, this is common for many agents and CRC oncologists will know how to treat such side-effects. It is important to make sure that clinicians only give it to patients of good performance status and do not give it to elderly frail patients. This sounds "common sense" but this has to be reinforced if the drug is introduced due to simplicity of administering an oral agent to patients desperate for treatment.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Trifluridine with tipiracil hydrochloride for treating metastatic colorectal cancer after standard therapy [ID876]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. *About you*

Your name: Helena Hanratty
Name of your nominating organisation: Beating Bowel Cancer
Do you know if your nominating organisation has submitted a statement?

☑ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☑ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes ☑ No

- a carer of a patient with the condition?

☐ Yes ☑ No

- a patient organisation employee or volunteer?

☑ Yes ☐ No

Do you have experience of the treatment being appraised?

☐ Yes ☑ No

If you wrote the organisation submission and do not have anything to add, tick here ☑ (If you tick this box, the rest of this form will be deleted after submission.)

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Trifluridine in combination with tipiracil hydrochloride for previously treated metastatic colorectal cancer

Produced by	Kleijnen Systematic Reviews (KSR) Ltd., United Kingdom (UK) in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University, The Netherlands (NL)
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None.

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[redacted]

Rider on responsibility for report
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Contributions of authors
Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Bram Ramaekers acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Anoukh van Giessen, Xavier Pouwels and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter and Shona Lang acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse event
AiC	Academic in confidence
AIC	Akaike information criterion
ARR	Absolute risk reduction
ASCO	American Society of Clinical Oncology
BRAF	Serine/threonine-protein kinase B-Raf
BSA	Body surface area
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness Analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CER	Cost-effectiveness ratio
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in confidence
CR	Complete response
CRC	Colorectal cancer
CRD	Centre for Reviews and Dissemination
CRO	Contract research organisation
CRUK	Cancer Research UK
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
CHMP	Committee for Medicinal Products for Human Use
CTCAE	Common Terminology Criteria for Adverse Events
DARE	Database of Abstracts of Reviews of Effects
DCR	Disease control rate
DSU	Decision Support Unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EED	Economic Evaluation Database
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
EREG	Epiregulin
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
F	Female
FDA	Food and Drug Administration
FOBt	Faecal occult blood test
FOLFIRI	Chemotherapy combining folinic acid, fluorouracil and irinotecan
GP	General practitioner
HR	Hazard ratio
HRQoL	Health-related Quality of Life
HTA	Health Technology Assessment
HUI3	Health Utilities Index Mark III
ICER	Incremental Cost-effectiveness Ratio
ICTRP	International Clinical Trials Registry Platform
IRC	Independent review committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research

ITT	Intention-to-treat
IWRS	Interactive voice/web response system
JCOG	Japan Clinical Oncology Group
JSCO	Japan Society of Clinical Oncology
KRAS	Kirsten rat sarcoma viral oncogene homolog
KSR	Kleijnen Systematic Reviews
LY	Life year
LYG	Life years gained
M	Male
mCRC	Metastatic colorectal cancer
mg	Milligram
MRU	Medical resource utilisation
NA	Not applicable
NCIN	National Cancer Intelligence Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NL	The Netherlands
NR	Not reported
NS	Not specified
ORR	Overall response rate
OS	Overall survival
PAN	Panitumumab
PAS	Patient Access Scheme
PBO	Placebo
PD	Progressive disease
PenTAG	Peninsula Technology Assessment Group
PFS	Progression-free survival
PP	Post-progression
PPS	Post-progression survival
PR	Partial response
Pre-P	Pre-progression
PS	Performance status
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted Life Year
QQ	Quantile-quantile
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumours
RFB	Regorafenib
SAE	Serious Adverse Events
SD	Stable disease
SD	Standard deviation
SE	Standard error
SIGN	Scottish Intercollegiate Guidelines Network
STA	Single Technology Appraisal
TA	Technology Appraisal
TPase	Thymidine phophorylase
T/T	Trifluridine/tipiracil
TTD	Time to treatment discontinuation
TTF	Time to treatment failure
UK	United Kingdom
VEGF	Vascular endothelial growth factor
WHO	World Health Organisation
WTP	Willingness-to-pay

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1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The patient population described in the final scope is *"adults with metastatic colorectal cancer whose disease has progressed after standard therapies or for whom standard therapies are unsuitable"*. The final scope defined *"fixed dose combination of trifluridine and tipiracil hydrochloride"* as intervention and *"best supportive care"* as the comparator of interest. Outcomes of interest included *"overall survival, progression-free survival, response rates, adverse effects of treatment and health-related quality of life"*. The company did not offer any special considerations, including issues related to equity or equality. [redacted]

The decision problem in the company submission (CS) is in line with the final scope issued by the National Institute for Health and Care Excellence (NICE). Furthermore, the Evidence Review Group (ERG) noted that on 25 February 2016, a positive summary of opinion was issued by the European Medicines Agency (EMA). However, health-related quality of life (HRQoL) data were not collected in either of the two clinical trials presented in the CS.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS includes a systematic review of the available evidence for trifluridine/tipiracil (T/T) compared to best supportive care (BSC) for patients with advanced/metastatic colorectal cancer (mCRC) receiving treatment at the third line or beyond.

This review identified two randomised trials (phase II trial and RECOURSE). Both of these trials compared T/T to placebo with both treatment groups in the trials receiving BSC. The phase II trial included 172 participants from Japan while RECOURSE was a multinational trial including 800 participants. RECOURSE included 394 participants from Europe (nine from the United Kingdom (UK)). The company conducted analyses demonstrating that the effect of T/T did not vary according to geographical location and as a result, the trials were pooled.

Based on the pooled clinical trial results, there was an increase in median overall survival (OS) of 1.9 months (T/T: 7.3 months, BSC: 5.4 months). The pooled mean increase in OS was 2.3 months (T/T: 9.1 months, BSC: 6.8 months). Confidence intervals were not reported for the pooled analyses.

Regarding median progression-free survival (PFS), the pooled results showed an increase of 0.2 months (T/T: 1.9 months, BSC: 1.7 months). The mean PFS increase was 1.8 months (T/T: 3.7 months, BSC: 1.9 months). In the phase II trial no participant in either group had a complete response and one in the T/T group had a partial response. In RECOURSE one patient in the BSC group (placebo + BSC) had a complete response and eight in the T/T group had a partial response. A greater proportion of T/ T patients in both trials had stable disease (42.9% vs. 10.5% in the phase II trial and 42.4% vs. 15.9% in RECOURSE).

Two non-randomised trials were presented in the CS. The justification for including these was that the population was relevant to the decision problem. One study was a retrospective review of the outcomes of 55 patients with mCRC treated with T/T at a Japanese clinic. The other was a post-marketing surveillance survey presenting 370 AEs observed in 219 patients and was only reported as a poster.

No indirect or mixed treatment comparisons were presented in the CS.

The CS provides evidence from various sources to support that the submission fulfils end of life criteria. The first criterion of a short life expectancy includes the RECOURSE trial where survival was 7.7 months in the best supportive care arm. Evidence for the second criterion (an extension to life of at least three months compared to current National Health Service (NHS) treatment) is taken from the survival modelling calculations for the pooled estimate OS for both included trials (incremental survival: 3.2 months) and for RECOURSE alone (incremental survival: 3.0 months). The third criterion of a small patient population is taken from a survey of the number of patients in the UK with mCRC who would be treated at third line or beyond and from the company's estimates based on a previous technology assessment (approx. 2,600 patients) as well as expert opinion (2,490 patients).

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

The CS includes a systematic review of the available evidence for T/T compared to BSC for patients with mCRC receiving treatment at the third line or beyond. The literature searches reported in the CS were well documented and easily reproducible. A good range of databases were searched, and additional searches of conference proceedings were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4. The ERG is overall satisfied that the company identified and appraised the relevant randomised trials. The two non-randomised studies presented in the submission did not appear to have been selected systematically. We have focused our attention in this report on the two randomised trials which inform the cost effectiveness model. There is a lack of information on methods of pooling the two included randomised trials but overall it was considered acceptable from the point of view of clinical effectiveness that the trials were pooled.

The populations described in the NICE final scope, including patients with mCRC for whom standard therapies are 'unsuitable', seems approximately similar to the population described by the company, following the anticipated licence, but differs slightly from populations in the trials, which were used to inform the model. Consequently, following the licence it may be possible that patients not represented in the trials receive this medication. This includes patients *"for whom standard therapies are unsuitable"*. It remains unclear in which direction this discrepancy would influence the outcomes.

The phase II trial and RECOURSE, the two included trials identified by the company, were randomised and compared T/T to placebo with both treatment groups in the trials receiving BSC. The ERG confirmed the company's assessment that both trials were of high quality.

Following a request for clarification, the company stated that as there is no internationally accepted definition of BSC for clinical trials. Although both trials ensured consistency on medications excluded from BSC, the nature of BSC provided could vary between trial centres. The nature of BSC provided might also differ from that available in England and Wales.

RECOURSE was an international trial whereas the phase II trial was conducted solely with Japanese participants. The ERG considered that the company had provided evidence that geographical region was not a factor in effectiveness. This meant that results of the Japanese trial could be pooled with RECOURSE. However the ERG draws the committee's attention to the low proportion of UK participants in RECOURSE (9 of 800 participants). It is noted that 394 of 800 participants were from Europe. The ERG further notes that there is an under-representation of non-white, non-Asian populations across the trial (approximately 1% of RECOURSE participants are listed as 'black').

RECOURSE was powered for the primary outcome of OS so may not have had sufficient power to detect all differences between treatment groups for secondary outcomes. The included trials do not

directly assess HRQoL as specified in the NICE scope. Although there is a benefit to patients of the median increase in OS (1.9 months, pooled results) and PFS (0.2 months, pooled results), the quality of life experienced can only be inferred from effects of disease control and occurrence of adverse events.

In the phase II trial no patient in either group had a complete response and one in the T/T group had a partial response. In RECOURSE one patient in the BSC group had a complete response and eight in the T/T group had a partial response. A greater proportion of T/ T patients in both trials had stable disease (42.9% vs. 10.5% in the phase II trial and 42.4% vs. 15.9% in RECOURSE).

The occurrence of any adverse event was similar between T/T and BSC arms for both included trials. The Phase II trial found that serious adverse events [redacted]. In both trials 'treatment-related AEs' were found to be [redacted].

In both trials [redacted]. Nausea, vomiting, decreased appetite and diarrhoea were found to be [redacted] In both trials the following AEs related to myelosuppression were found to be [redacted],

In RECOURSE, more patients in the BSC arm were reported to [redacted]

It should be noted that in the RECOURSE trial all patients had to have received treatment with fluoropyrimidine, oxaliplatin, and irinotecan to be eligible. Patients were further required to have received prior chemotherapy with bevacizumab. However under NICE guidance patients in England would not be able to routinely receive bevacizumab prior to treatment with T/T. The company's interpretation in conjunction with clinical advice was that tumours in patients who had received fewer treatments were likely to be less resistant to additional therapy. This implies that the evidence for T/T presented might underestimate response in a UK population. This is an assumption, but it appears to be fair.

Regarding the CS fulfilling end of life criteria, the ERG believes that the first criterion (short life expectancy) has been met. For the second criterion (extension of life) to be met, NICE usually expects to see *"at least an additional 3 months, compared with current NHS treatment"*. As stated before, pooled estimates showed smaller differences in mean (OS: 2.3 months; PFS: 1.8 months) and median (OS: 1.9 months; PFS: 0.2 months) survival when comparing T/T to BSC (no confidence intervals available). The relevant population will be small but it should be highlighted that the figures presented might be an underestimate as they do not include Wales.

1.4 Summary of cost effectiveness submitted evidence by the company

The company developed a de novo cost effectiveness model to assess the cost effectiveness of T/T compared with BSC as third line or later treatment for patients with mCRC.

An Excel-based partitioned-survival model was constructed, consisting of the health states pre-progression, post-progression and death. Health states were selected according to the clinical pathway

of care and comparable to the structure used in other late-stage cancer models. Because of the poor prognosis of patients, a daily cycle length was applied to ensure the accuracy of survival estimates. The time horizon was 10 years effectively reflecting lifetime in this population.

In the company's base case combined data from the phase II trial and the RECOURSE trial were used to estimate OS and PFS for use in the model. PFS was also used as a proxy for time on treatment. Other parameters such as adverse events and T/T dosing were based on the RECOURSE trial only.

No HRQoL information was collected in the phase II trial or the RECOURSE study. The company conducted a systematic review to identify HRQoL studies from the published literature. In the company's base case, the health state utility values were the average of utilities obtained in the CORRECT study (identified in the systematic review) and the cetuximab NICE CS for the first line treatment of mCRC (not identified in the systematic review). Specific disutilities for adverse events were not incorporated in the model.

Categories considered for resource use and costs were: T/T costs, health state costs, post-progression treatment costs, end of life costs and adverse event costs. In the company's base case, T/T costs were calculated based on the body surface area (BSA), treatment delay and dose reductions obtained from the RECOURSE trial. Moreover, treatment delay was used to calculate the average treatment cycle length and hence also influenced pre- and post-progression medical resource utilisation (MRU). MRU included oral chemotherapy day case attendance, medical oncologist outpatient consultation, home consultation by general practitioners (GPs), community nurse specialist visit, health home visitor, district nurse visit and GP surgery visit. Post-progression treatment costs were calculated based on resource use from the RECOURSE trial. Costs of adverse events that are actively treated in the NHS are included. End-of-life care costs were taken from a published modelling study.

The company's base case incremental cost effectiveness ratio (deterministic, with PAS) was £44,032. One-way deterministic sensitivity analysis, scenario analyses and probabilistic sensitivity analyses were conducted. From the deterministic sensitivity analysis the company concluded that the most influential parameters on the model result were utility values for pre- and post-progression health states, the annual discount rate for quality-adjusted life years (QALYs) and the costs for post-progression treatment. Based on the scenario analyses, the most influential scenarios on the model results were the time horizon over which the costs and benefits of treatment are considered, and the choice of distribution from which efficacy data were fit to and extrapolated. The probabilistic sensitivity analyses indicated that at the PAS price, the probabilities of T/T being the most cost effective treatment are 0% and 77% for willingness-to-pay (WTP) thresholds of £30,000 and £50,000, respectively.

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

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a reasonable extent. The ERG confirmed the company's finding that there was no existing cost-effectiveness model for T/T for the current indication. The ERG questions the sensitivity of the systematic review the company performed to identify HRQoL studies. No systematic reviews were performed for model structure and resource use, which should ideally have been performed, according to the NICE reference case.

The ERG agrees that the chosen model structure, daily cycle and the absence of a half-cycle correction are appropriate for this decision problem.

Even though pooling the effectiveness data from the RECOURSE trial and the phase II trial seems reasonable, the methods were not clearly described in the CS. After response to a clarification question by the ERG, it appeared that individuals from both trials were naïvely combined in one dataset and compared with each other which could generate biased treatment effect estimates. In order for the ERG to assess the quality of pooling, the ERG would have liked to receive a comparison of the current meta-analysis (not stratified by trial) with a meta-analysis in which stratification by trials was performed. If the results of both meta-analyses would have been similar, the ERG would prefer the current meta-analysis to be used in the cost effectiveness model. Without this information, the ERG prefers using a more conservative assumption in its base case analysis by using RECOURSE data only. However, since there are no fundamental arguments which prevent the two trials from being pooled, besides the lack of clarity of the methodology, the ERG also presents its base case analysis based on the pooled effectiveness estimates from both trials.

Concerning the estimation of PFS and OS in the model, the ERG criticised using the Akaike information criterion (AIC) and not visual inspection of log-cumulative hazard plots to decide on using stratified or unstratified models. Based on inspection of log-cumulative hazard plots, the ERG considered it to be reasonable to use unstratified models instead of stratified models in its base case.

It was unclear to the ERG why only RECOURSE data (and not a pooled estimate from RECOURSE and the phase II trial) were used for AEs incidence rates, given that the company base case used pooled PFS and OS using evidence from both clinical trials. The ERG noted that the grade ≥3 AEs rates for the BSC arm reported in two tables of the CS and in the company's cost effectiveness model were not correct for the eight AEs. This was corrected in the ERG base case.

The ERG regards the company's arguments to estimate the health state utilities using an average of the utilities from TA176 and the CORRECT trial as incorrect or based on incorrect information. According to the ERG, the baseline utilities from the CORRECT study are the most plausible estimates for pre-progression, and the post-progression health state utilities, because it is the only study identified by the ERG in which utilities were measured using the European Quality of Life-5 Dimensions (EQ-5D) in a population that resembles the population in this appraisal (second to fourth line population with 74% ≥ third line). Therefore the ERG included utility values from the CORRECT study in its base case.

The ERG noted that the impact of AEs on HRQoL was not incorporated in the analyses, apart from the difference between the pre-progression health state utility values in the base case. Therefore, the ERG explored the estimation of a disutility for adverse events based on the occurrence of adverse events ≥ grade 3. This resulted in a disutility of 0.075 for T/T and 0.018 for BSC, calculated to one week the incremental disutility is -0.001. As these estimates do not include all AEs and heavily rely on assumptions, the ERG used a larger disutility for AEs of 0.01 per cycle for patients receiving T/T in its base case (similar assumption as in the company's base case but based on alternative justifications).

The company uses a parameterised distribution of BSA (log-normal) from RECOURSE to calculate T/T costs. The ERG notes that the population of the RECOURSE trial includes 33% of patients from Japan, which may be expected to have a lower BSA than the UK population. The CS reported that advisory board clinicians agreed with the use of a lower estimate of BSA as compared with the UK general population since mCRC patients would be expected to lose weight. According to the ERG, the non-parametrised distribution of BSA from RECOURSE is more reasonable estimate of BSA to calculate drug costs. As this most likely results in an underestimation of T/T costs, the BSA based on

the UK population (which most likely results in an overestimation of T/T costs) is considered in an exploratory sensitivity analysis.

The ERG also noted that costs for adverse events were almost all estimated to equal a general medicine outpatient visit. The ERG thinks that this assumption is unrealistic and used alternative inputs in an explorative sensitivity analysis, retrieved from the NICE appraisal of TA370. Moreover, the ERG corrected the costs of a medical oncologist outpatient consultation. In addition, the ERG noted that the estimation of medical resource use was mainly based on expert opinion. Given the complete reliance on expert opinion for resource use, the ERG used an alternative source in an explorative sensitivity analysis.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company's submission contained a well-conducted systematic review which addressed the scope issued by NICE. Searches were carried out in line with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4. The CS and response to clarification provided sufficient details for the ERG to appraise the searches. The review identified two methodologically sound randomised controlled trials. The main trial, RECOURSE, was a large, multinational trial. The trials assessed the outcomes outlined by NICE with the exception of quality of life. Overall, the CS is well presented, transparent and in line with the final scope.

1.6.2 Weaknesses and areas of uncertainty

It should be noted that one of the outcomes defined in the scope (HRQoL) was not addressed in either of the included clinical trials (phase II trial and RECOURSE).

There is some uncertainty regarding the generalisability of the two trials as the phase II trial (172 participants) was conducted in Japan and RECOURSE (800 participants) included only nine participants from the UK (394 participants from Europe). However, analyses showed that the effect of T/T did not vary according to geographical location. Additionally, as the definition of BSC was unclear, i.e. there is currently no internationally accepted definition of BSC, it is unclear whether BSC considered in the evidence and hence in the model is representative for BSC in the UK.

The two trials included patients who had received prior chemotherapy with bevacizumab, a drug that is not included in relevant NICE guidance. It can be assumed that the evidence for T/T might underestimate response in a UK population which has received fewer treatments.

It is unclear whether all end of life criteria have been met. Some of the survival results reported in the CS do not show an improvement in life expectancy over three months when comparing T/T to BSC. Furthermore, the figures presented in support of a small patient population might be an underestimate of the relevant population.

The ERG believes incorrect search strategies for HRQoL were reported in the Appendix of the CS. The company response to the ERG clarification letter was that the reported search strategies were correct. However, the results reported in the CS suggest that separate HRQoL searches were conducted, and that four studies with HRQoL data met the inclusion criteria of the review. Without full details of the HRQoL search strategies the ERG was unable to assess their quality. The CS used unnecessary economic terms when searching NHS Economic Evaluation Database (EED; via the Cochrane Library).

Most uncertainty in the health economic model was related to the estimation of progression free survival and overall survival as well as the utility values. Additional uncertainties identified by the ERG included whether or not to use the naïve pooling provided by the company, averaging of utilities from various sources, estimation of resource use (mainly based on expert opinion) and estimation of BSA. Using mainly expert opinion for resource use (instead of empirical data) was considered by the ERG as one of the main weaknesses. This uncertainty might have an impact on the ICER as examined in the exploratory sensitivity analyses.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

Compared with the company base case, the ICER increased by approximately £9,300 to £52,695 in the ERG base case (with PAS). This difference could largely be attributed to a reduction in incremental QALYs gained from 0.172 to 0.144. The difference between the results of the company and the ERG base case are mainly caused by the following changes in the model:

- Fixing errors with adverse events for BSC
- Use of RECOURSE data instead of pooled estimates
- Use of CORRECT utilities only, i.e. not averaging with utilities from the TA176 CS report.

The probability that T/T is cost effective is smaller in the ERG base case compared to the company's base case (0% versus 0% and 37% versus 77% for thresholds of £30,000 and £50,000, respectively).

Given that the pooled analyses might be preferred or might not differ substantially compared with more sophisticated pooling techniques, despite the lack of justification for the use of naïve pooling (i.e. not stratifying by trial), the ERG base case using the pooled evidence is presented as well. In these analyses, pooled evidence is used for OS, PFS, AE, BSA and dose reductions and resulted in an ICER of £49,392.

Exploratory sensitivity analyses illustrated that using the UK general population BSA estimates and an alternative source for resource use had a moderate impact on the ICER (£53,776 and £54,739 respectively). Subgroup analyses based on Kirsten rat sarcoma viral oncogene homolog (KRAS) status indicated that the ICER for the KRAS wild-type and KRAS mutant subgroups would be £53,042 and £50,721 respectively.

2 BACKGROUND

This report provides a review of the evidence submitted by Servier in support of Trifluridine/tipiracil (T/T; trade name Lonsurf®) for the treatment of metastatic colorectal cancer (mCRC) in patients whose disease has progressed after standard therapies or for whom standard therapies are unsuitable.[1]

The background section of the report by the Evidence Review Group (ERG) outlines and critiques the company's description of the underlying health problem and the company's overview of current service provision. The information is taken from Chapter 3 of the company submission (CS) with sections referenced as appropriate.[1]

2.1 Critique of company's description of underlying health problem.

The underlying health problem is mCRC described in the manuscript as *"disease that has spread beyond the large intestine and nearby lymph nodes"*. The company further states that *"this appraisal focuses on mCRC that is classified as Stage IV or Modified Dukes Stage D"* (Section 3.1.1 of the CS).[1]

The company highlights the role of Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations which are *"generally thought to be a negative predictive marker for the treatment effect of an anti-EGFR monoclonal antibody"* (Section 3.1.1 of the CS).[1] They further state that *"KRAS should not directly affect the activity of T / T"*. To support this statement the company refers to the two main trials included in this submission and states that effectiveness has been shown in KRAS wild-type and KRAS mutant tumours.[2, 3]

The company describes the epidemiology of mCRC focusing on the incidence of mCRC in England (Section 3.1.2 of the CS).[1] Colorectal cancer (CRC) is described in the submission as the *"fourth most common cancer in the UK behind breast, lung and prostate cancer, accounting for 12% of all new cases"* (Section 3.1.2 of the CS).[4] The company notes that 26% of patients present with metastatic disease.[5]

The company states that *"approximately 55% of patients initially diagnosed with colorectal cancer Stage II or III who receive initial treatment will ultimately progress to metastatic disease"* (Section 3.1.2 of the CS).[1]

The impact of colorectal cancer on patients, carers and society is briefly considered (Section 3.2 of the CS). The company states that *"psychological distress is common in patients with CRC, with depression and anxiety being particularly common; this is exacerbated further for patients who have a stoma following surgery for their condition"*.[1] Furthermore, the company states that the main aims of treatment for mCRC are *"to relieve symptoms and to improve health-related quality of life (HRQL) and survival"*.[1]

Section 3.4 of the CS describes the life expectancy of patients with mCRC and provides estimates of the number of patients at each line of therapy.[1] The company states that *"trifluridine / tipiracil is licensed for patients who have already received standard recommended treatment for mCRC and are therefore likely to be receiving therapy at third line or later. At this stage of the disease, life expectancy is approximately 6 months"* (Section 3.4.1 of the CS).[1]

The company provides survival data based on a UK source.[6] According to Section 3.4.1 of the CS, "*one year survival is lowest for those diagnosed with stage IV disease (40% for men and 33% for*

women). In addition, the survival of patients with mCRC decreases with each line of therapy. Five year survival for patients with mCRC is 7% and 8% for men and women, respectively".[1]

ERG comment: The ERG considers the company's description of the aetiology and pathology of metastatic colorectal cancer to be appropriate. Descriptions of the disease are taken from National Institute for Health and Care Excellence (NICE) guidance. [CS references 24 and 25]. The clarification of the staging that comprises mCRC gives a more precise definition of the underlying health problem.

The reference on incidence of colorectal cancer supplied by the company was checked and found to be correctly cited and from a reputable source.[4] The reference supporting the statement that 26% of patients present with metastatic disease was found to be a broken web link. The web site is a reputable source (National Cancer Intelligence Network, NCIN) but the provenance of the figure could not be determined. The ERG notes that the CS does not include Wales in its estimates of the annual number of patients with mCRC which has implications for the budgetary impact.

The estimate regarding patients progressing to metastatic disease (*"approximately 55% of patients initially diagnosed with colorectal cancer Stage II or III who receive initial treatment will ultimately progress to metastatic disease")* was taken from a previous technology appraisal and was therefore considered to be reliable.[7]

The ERG considers the statement on the impact of colorectal cancer on patients, carers and society to be appropriate. The statement on the main aims of treatment of mCRC is based on a NICE guideline is therefore considered to be appropriate.[8]

The statement regarding the life expectancy of patients with mCRC receiving treatment at third line or later includes both of the randomised trials in the submission and appears to be appropriate.[2, 3]

The ERG identified an apparent discrepancy in survival between the data presented in Section 3.4.1 of the company submission and the survival in the RECOURSE trial. In particular, one year survival for patients with mCRC was presented as 40% and 33% for men and women, respectively, based on a UK data source.[1] The estimated one year survival in the BSC arm of the RECOURSE trial was 17.6% (Table 25 of the CS) which suggests that the survival in the trial is much lower.[1] The company was asked to explain this apparent discrepancy. In the response to request for clarification, the company stated that the Cancer Research UK (CRUK) data presented reflect all patients with mCRC irrespective of time since diagnosis of metastatic disease, number of lines of chemotherapy received etc.[9] Therefore the CRUK data are not reflective of the population in the decision problem of this appraisal (patients who have received two or more lines of chemotherapy).

The effectiveness of T/T in regard to KRAS mutations will be discussed in Section 3 of the ERG's report.

2.2 Critique of company's overview of current service provision

The company states that "*there are currently no recommended therapeutic options for patients who have failed second-line treatment*".[1]

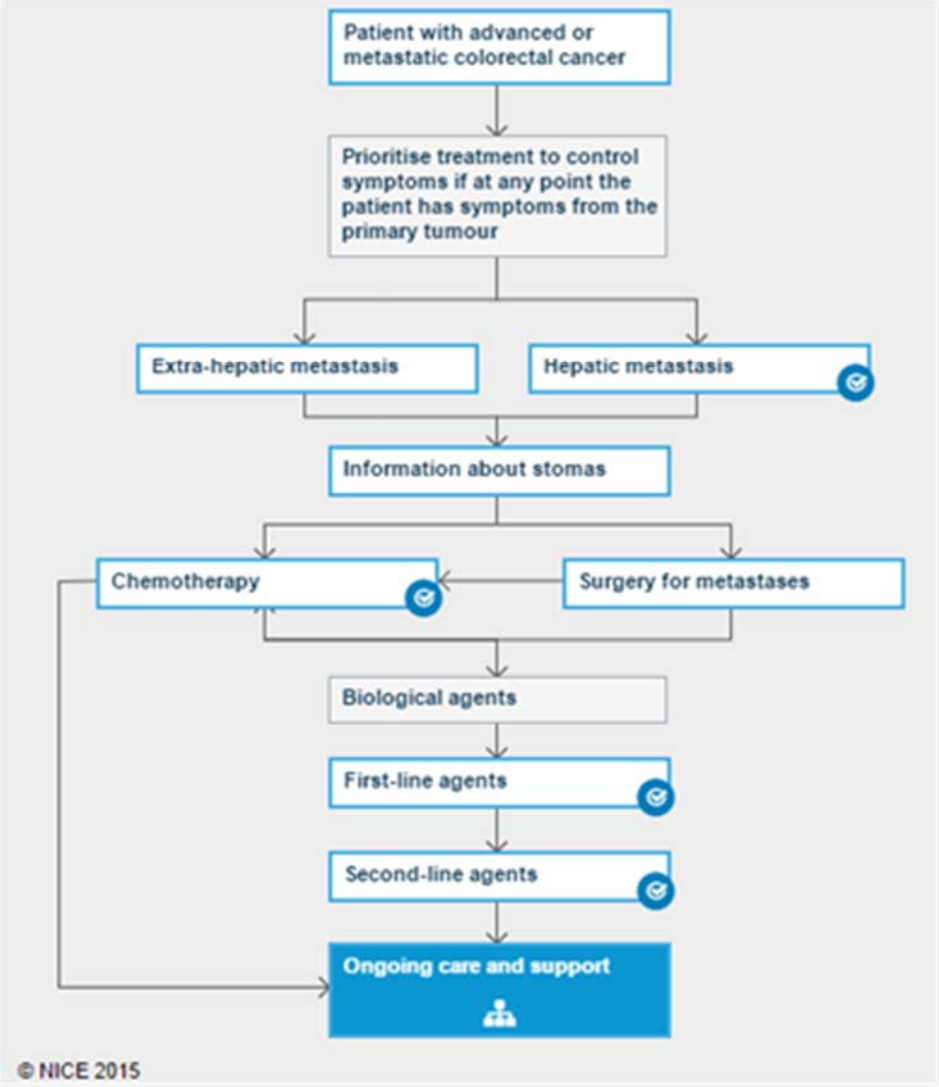
According to the CS, *"clinical experts at the recent advisory board highlighted that trifluridine / tipiracil would be a preferred option to regorafenib based on tolerability"*.[1]

The company provides estimates of the number of mCRC patients at each line of therapy using a previous technology assessment as a basis[10] and adapted using clinical opinion (Section 3.4.2 of the CS).

Figure 8 in Section 3.4.2 of the CS provides an estimate of the number of patients with mCRC by treatment option. The company states that *"trifluridine / tipiracil would fit into the treatment pathway at third line or beyond. It is estimated that at this stage there would be approximately 2600 patients who may be eligible for and are motivated to receive further treatment"*.

The company's overview of the current clinical pathway for patients with metastatic colorectal cancer is given below. According to the CS, *"trifluridine/tipiracil provides a therapeutic option for patients with tumours that have progressed following second-line treatment and who are well enough and motivated to receive further therapeutic intervention"*.[1]

Figure 2.1: NICE clinical pathway for patients with metastatic colorectal cancer
(Based on figure 3 of the CS[1])



ERG comment: The company's description of the pathway is taken from NICE guidance which is appropriate and relevant to the decision problem.[11]

The ERG agrees with the company that *"there are currently no recommended options for patients who have failed second-line treatment"*. This is correct as regorafenib is licensed in the UK for the treatment of mCRC, however, it is not recommended by NICE due to a non-submission (TA334 – terminated appraisal). The ERG notes (as is outlined by the company) that options may be provided for patients such as repeating a previous regimen, enrolling on a clinical trial or using mitomycin C + 5FU or capecitabine.[12] However, it should be noted that the statement that T/T *"would be a preferred option to regorafenib based on tolerability"* is based on clinical opinion alone.[13]

The ERG notes that estimates of the number of patients with mCRC by treatment option based partially on clinical opinion may be unreliable. The ERG further notes that the estimates appear to be based on England only and do not include Wales.

3 Critique of company's definition of decision problem

The company presents its response to the decision problem in Section 1.1 of the CS. This is reproduced below.

Table 3.1: Summary of the decision problem
(Based on Table 1 of the CS[1])

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with metastatic colorectal cancer whose disease has progressed after standard therapies or for whom standard therapies are unsuitable	Final scope	
Intervention	Fixed dose combination of trifluridine and tipiracil hydrochloride	Final scope	
Comparator(s)	Best supportive care	Final scope	
Outcomes	• overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.	• overall survival • progression-free survival • response rates • adverse effects of treatment	Trifluridine/tipiracil was in-licensed by Servier Laboratories Ltd from Taiho Pharmaceutical. Health-related quality of life data were not collected in the phase III clinical trial
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Final Scope. The economic analysis will be presented as reported in the final scope (December 2015) and in accordance with the NICE guide to the methods of technology appraisal (2013).	
Subgroups to be considered	None specified		

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Special considerations including issues related to equity or equality	No special considerations, including issues related to equity or equality have been identified.		
NHS = National Health Service; NICE = National Institute for Health and Care Excellence			

3.1 Population

The patient population described in the final scope is *"adults with metastatic colorectal cancer whose disease has progressed after standard therapies or for whom standard therapies are unsuitable"*.[14]

ERG comment: The definition of the relevant population addressed in the CS is in line with the decision problem described by NICE. However, it is noteworthy to highlight some points:

- The main clinical evidence submitted by the company, the RECOURSE trial, does not include participants for whom standard therapies are unsuitable.[2] All patients had to have received treatment with fluoropyrimidine, oxaliplatin, and irinotecan to be eligible. This includes those who were refractory to treatment (disease progressed) and those who were intolerant (treatment discontinued due to toxicity or could not be re-administered for medical reasons). Furthermore, participants of the RECOURSE trial were required to have received prior chemotherapy with bevacizumab. However, under NICE guidance patients in England and Wales would not be able to routinely receive bevacizumab prior to treatment with trifluridine/tipiracil.[1]
- The company's interpretation in conjunction with clinical advice was that tumours in patients who had received fewer treatments were likely to be less resistant to additional therapy.[13] This implies that the evidence for T/T presented in the CS might underestimate response in a UK population. This is an assumption, but it appears to be fair.
- According to Table 15 of the CS, all participants of the included phase II randomised controlled trial (RCT) were recruited in Japan whereas participants of RECOURSE were from Japan, Europe, USA and Australia.[1] Potential implications for the generalisability of the trial results for patients in the UK are discussed in Section 4.2 of this report.
- In Section 1.1 of the CS, it is stated that, if approved, T/T offers an option for those patients who are *"well enough and motivated to receive further treatment"*.[1] This statement is not further explained. Section 6.2 of the CS considers the projected uptake of T/T and states that 20% of the eligible population might receive treatment in the first year of availability before reaching a steady state of approximately 40% by year three of availability.[1] These estimates appear to be based solely on clinical opinion and it is unclear how this has been elicited.
- Trial participants appeared to reflect those seen in clinical practice. Both trials include male and female participants and patients with colon and rectum cancer. Both included participants with KRAS wild-type and mutation positive status. In RECOURSE 79% of patients had been diagnosed with metastatic cancer for 18 months or more. Sixty-one per cent had received at least four prior treatment regimens.[1]
- Across the trials there is an under-representation of non-white, non-Asian populations. In RECOURSE nine patients (1%) are listed as 'black'. Although there is no evidence of any

differential effects of the drug based on ethnicity, this aspect is drawn to the attention of the committee.

3.2 Intervention

The intervention is trifluridine/tipiracil. Section 2.1.4 of the CS states that *"trifluridine/tipiracil is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and a thymidine phosphorylase (TPase) inhibitor, tipiracil hydrochloride, at a molar ratio 1:0.5 (weight ratio, 1:0.471)"*.[1]

According to the CS, a positive Committee for Medicinal Products for Human Use (CHMP) opinion for Lonsurf® was expected in late February 2016, with marketing authorisation in May 2016 (Section 2.2.4 of the CS).[1] The company notes that *"trifluridine/tipiracil is licensed in Japan and the US and up to December 2015 had been received by over 12,000 patients"* (Section 2.2.6 of the CS).[15]

The company stated that trifluridine/tipiracil is marketed as an oral tablet with dosing based on body surface area at a recommended starting dose of 35mg/m^2 followed by individual adjustments for safety and tolerability. An average course of treatment is 28 days with management in secondary care either as a chemotherapy day case or outpatient setting (Sections 2.3.1 and 2.4.1 of the CS).[1]

ERG comment: The CS reflects the scope which is a *"fixed-dose combination of trifluridine and tipiracil hydrochloride"*.[14]

The ERG identified that on 25 February 2016, the European Medicines Agency (EMA) issued a positive summary of opinion outlining the full indication: *"Lonsurf is indicated for 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. It is proposed that Lonsurf be prescribed by physicians experienced in the administration of anticancer therapy"*.[16] The number of patients receiving T/T is taken from an internal communication by the company.[15]

The included trials had a 35mg/m^2 dosage. The phase II trial allowed a reduction of 10 mg/day if necessary and RECOURSE allowed a maximum of three reductions in dose in decrements of 5 mg/m^2 (Table 15 of the CS).[1]

3.3 Comparators

The comparator is best supportive care (BSC). The scope issued by NICE recommended BSC as there are no currently recommended treatments for patients who have failed second line treatment.

For the phase II trial, *"all necessary support was provided to patients, with the exception of concomitant use of other anti-cancer drugs or other investigational drugs"*.[9] In RECOURSE, *"all necessary support was provided to patients which included permitted concomitant medications and therapies and study medication"*.[9] Specifically patients were *"not to receive other investigational anti-tumour agents or antineoplastic chemotherapy, hormonal therapy or immunotherapy. Palliative radiotherapy was not permitted while the patient was receiving study treatment"*.[9]

ERG comment: The CS is based on two placebo-controlled trials where both treatment and placebo groups received BSC. The ERG asked for clarification on the definitions of BSC used in the included trials, the guidance regarding BSC given to the centres involved in the included trials and the applicability of the BSC to the UK setting. In their response to the request for clarification[9], the company stated that *"there is currently no internationally accepted definition of BSC for clinical*

trials". Although both trials ensured consistency on medications excluded from BSC, the nature of BSC provided could vary between trial centres. The nature of BSC provided might also differ from that available in England and Wales.

The ERG notes that, according to the CS[1], in order to obtain a positive opinion of the CHMP, the company provided additional information in the submission including a comparison to regorafenib.[1] *"Regorafenib is not recommended by NICE due to a non-submission"* and this comparison does not form part of the final scope for this CS.

3.4 Outcomes

Outcomes of interest are overall survival, progression-free survival, response rates, adverse effects of treatment and health-related quality of life.[14]

ERG comment: The two RCTs included in the clinical effectiveness part of the CS did not collect quality of life data.[2, 3] Data to populate the economic model will be discussed in the cost effectiveness section.

3.5 Other relevant factors

The company did not offer any special considerations, including issues related to equity or equality. [redacted] (Section 2.3.2 of the CS).

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company stated in Section 4.1 of the CS that *"a systematic review was conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of trifluridine / tipiracil compared with best supportive care (BSC) for patients with advanced / metastatic colorectal cancer receiving treatment at the third line or beyond"*.[1]

ERG comment: The systematic review will be critiqued in this section of the report. It should be noted that the evidence presented in the CS compared trifluridine/tipiracil in combination with best supportive care (T/T arm) to placebo in combination with BSC (BSC arm).

4.1.1 Searches

The literature searches reported in the CS were well documented and easily reproducible. A good range of databases were searched, and additional searches of conference proceedings were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[17]

Description and critique of the company's search strategies

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies, was used to inform this critique.[18] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[19] The ERG has presented only the major limitations of each search strategy in the main report. Further criticisms of each search strategy can be found in Appendix 1.

Clinical effectiveness

The CS states that a systematic review was conducted to retrieve relevant clinical data from the published literature regarding the efficacy and safety of trifluridine/tipiracil compared with BSC for patients with advanced/metastatic colorectal cancer receiving treatment at the third line or beyond.

Searches were conducted on 26 October 2015 in MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, Embase and the Cochrane Library (Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, the NHS Economic Evaluation Database (NHS EED), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment Database (HTA). The host provider for each database was listed; the date span of the databases searched and the specific date the searches were conducted were provided. The company additionally searched conference proceedings: American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Detailed search strategies for the database searches were reported in Appendix 3. The CS did not provide full details of the conference proceedings searches. Full details of the conference proceedings searches for the utility review were provided in response[9] to the ERG request for clarification letter.[20] These searches could have been used for the clinical effectiveness review, as generic search terms for advanced and metastatic colorectal cancer were used, but it is not clear if they were.

The company translated the research question into appropriate search strategies and the ERG considered the searches to be satisfactory. Searches were clearly structured and divided into population and intervention/comparator facets, using an appropriate combination of index terms, free text and synonyms for the interventions and comparators. The search strategies included Boolean,

truncation and proximity operators. No date or language limits were used. Study design limits to identify RCTs and non-RCTs were applied. The study design filters were not referenced, so it was unclear whether the filters used were published objectively derived filters. However, the search filters appeared to be those designed by and available from the website of the Scottish Intercollegiate Guidelines Network (SIGN).[21]

The search strategies included all currently available comparators alongside the intervention, though only BSC was considered in the NICE scope. Including the comparators in the search strategy would not have affected the search results, i.e. more records were retrieved, without missing relevant T/T studies.

It is possible that the facet of search terms for 'advanced/metastatic' included in the search strategies was too restrictive, and that combining the metastatic colorectal cancer facet with T/T and the study design filters would have been sufficient.

Searches of conference proceedings were conducted. The CS reports the names of the conferences searched and which years (2013-15) in the appendix, but does not give specific details about the search methods used and exact dates searched. The CS reports that no studies were identified from the conference searches, although three conference abstracts were included (Table 14 of the CS).[1] The three conference proceedings searched were: ASCO, ESMO, and ISPOR.

A search of trials registers, such as ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP), for unpublished and ongoing trials would have been a useful addition to the literature searches.

Indirect and mixed treatment comparisons
No searches were conducted.

Non-randomised and non-controlled evidence
The same search strategies and databases used for the clinical effectiveness literature searches were used to identify non-RCT evidence. The search strategies included a study design filter for non-RCTs.

Adverse events
The same search strategies and databases used for the clinical effectiveness literature searches were used to identify adverse events data. Guidance by the Centre for Reviews and Dissemination[22] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. Despite the inclusion of a non-RCT search filter the ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the study design limits. Safety data were taken directly from the company's two trials (RECOURSE[2] and phase II trial[3]).

4.1.2 Inclusion criteria

Section 4.1.2 and Appendix 3 of the submission describe the methods used to select studies for inclusion in the review. The company states that *"identified studies were independently assessed by two reviewers in order to ascertain whether they met the pre-defined inclusion/exclusion criteria, and any discrepancies were resolved by a third reviewer"*.[1]

The inclusion criteria of the review are given in Table 4.1 below.

Table 4.1: Eligibility criteria used in search strategy
(Based on Table 13 of the CS[1])

	Inclusion criteria	Exclusion criteria	Comments
Population	Adult patients with advanced/ mCRC receiving treatment at third line or beyond	Patients receiving treatment at first or second line	According to NICE scope
Interventions	Trifluridine/tipiracil	-	According to NICE scope
Comparators	BSC	-	Searches were conducted to identify studies investigating all currently available comparators for trifluridine/tipiracil (to support HTA submissions in other territories); however, comparators considered relevant for the current STA were restricted to BSC according to the NICE scope[†]
Outcomes	Efficacy: Overall survival 1-year survival rate Progression-free survival Time to progression Response rates (complete response, partial response, stable disease) Objective response rate Disease control rate Safety: All-grade AEs of interest Grade 3 or 4 AEs of interest HRQoL	-	-
Study design	RCTs with no restriction on phase or blinding	Non-randomised, observational studies	-
Language restrictions	No restriction	-	-

[†] Screening of publications by title and abstract was performed to include all currently available treatments; any studies that were not relevant according to the NICE scope were then excluded upon full publication review.
AE = adverse event; BSC = best supportive care; CS = company submission; mCRC = metastatic colorectal cancer; HRQoL = health-related quality of life; HTA = health technology assessment; NICE = National Institute for Health and Care Excellence; RCT = randomised controlled trial, STA = single technology assessment

ERG comment: The methods used to select studies for the review appear to be appropriate.

The inclusion criteria for the review population are more specific than that given in the NICE scope. The final scope[14] states that the population of interest is *"adults with mCRC whose disease has progressed after standard therapies or for whom standard therapies are unsuitable"* whereas the

inclusion criteria in the CS[1] are for *"adult patients with advanced/mCRC receiving treatment at third line or beyond"*.

The CS does not provide a definition of best supportive care.[14] Following a request for clarification, the company stated that as there is no internationally accepted definition of BSC for clinical trials.[9]

A range of relevant outcomes are included in the review which includes those specified in the final scope.[14]

The review has no restrictions on study eligibility based on language which is appropriate given the multinational nature of the trials.

4.1.3 Critique of data extraction

The company states that *"relevant information was extracted into the Single Technology Appraisal (STA) template by a reviewer. A second reviewer checked the data extraction, and any inconsistencies were resolved through discussion"*.[1]

ERG comment: The methods used to extract data for the review appear to be appropriate.

4.1.4 Quality assessment

No specific mention is made in the manuscript of the involvement of two reviewers in the assessment of the quality of studies included in the review.[1]

ERG comment: It is reasonable to assume that two reviewers were involved in the assessment of the quality of the included studies given the reporting of the systematic review methods for data extraction.

4.1.5 Evidence synthesis

The company states in Section 4.9 that *"a pooled analysis using individual patient data was conducted for the Phase II and RECOURSE trials, examining OS and PFS"*.[1]

ERG comment: Justification for pooling the two included trials and a full explanation of pooling methods was not provided in the company submission.[1] The company was asked to clarify this.[20] In their response, the company stated that *"both trials were conducted in a patient population that is relevant to the decision problem for the appraisal and are consistent with the proposed marketing authorisation. (...) ...there is no evidence of a difference in efficacy based on ethnicity"*.[9] This statement was supported by a reference to a pre-specified geographic regional subgroup analysis which showed no significant differences between geographic regions in overall survival (OS) and progression-free survival (PFS). The ERG is satisfied that pooling the two trials for the clinical effectiveness section of the CS is acceptable given similarities of design, disease characteristics, intervention and outcomes. However, due to a lack of information about the statistical methods used to pool the two trials as well as any measure or test of statistical heterogeneity the ERG cannot fully comment on the statistical pooling. The forest plot provided for OS and PFS does show that the trial results appeared to be homogenous, and the pooled results are in line with the individual trial results, so it seems that the pooling was appropriate.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The company states in Section 4.2 that *"the systematic review of clinical evidence identified two unique RCTs of trifluridine / tipiracil versus BSC in the population of interest to this submission. (...) ...In addition, three linked abstracts were identified"*.[1]

According to the CS, 193 studies were excluded after consulting the full papers (Figure 10 of the CS).[1] Bibliographic details and reasons for exclusion were listed in Appendix 3.6 of the CS.[23]

The company identified an ongoing trial (TERRA), a study in Chinese and south East Asian patients. They stated that the trial was due for completion at the end of 2015 with a clinical study report (CSR) estimated to be available in Summer 2016.[1] The company was asked to clarify that no results were available or to provide any results.[20] In their response, the company stated that no data were currently available for this trial and that the CSR was expected in July 2016.[9]

Section 4.11 of the CS provided details and results of two non-randomised studies.[1] The company was asked to clarify how these studies were identified and selected for inclusion in the CS as the inclusion criteria for the review specified only RCTs.[20] The company replied that *"these studies were not identified via a specific search, however Servier were aware that they had been presented and as they are relevant to the decision problem it was decided to present them in section 4.11 of the company evidence submission"*.[9]

According to the CS, *"the Phase II study was the primary licensing study for trifluridine/tipiracil in Japan. It involved 172 refractory mCRC patients who had previously been treated with, or were not candidates for available therapies (Fluoropyrimidine, oxaliplatin and irinotecan). The pivotal study for trifluridine/tipiracil is the RECOURSE trial, which studied 800 end-stage mCRC patients. These patients were all refractory or intolerant to all available therapies. The results of these studies have allowed for a successful marketing authorisation application in Japan and the US and are the basis for the application within the EU"*.[1]

A comparison of the population, intervention, comparator, outcomes and study designs for the two trials is given in Table 4.2. Information to populate the table was taken from Tables 14 and 15 of the company's submission.[1]

Table 4.2: Comparison of population, intervention, comparator, outcomes and study design
(Based on Tables 14 and 15 of the CS[1])

Trial no. (acronym)	Not reported (Phase II trial, no acronym)	NCT01607957 (RECOURSE)
Population	Adult patients aged ≥20 years with histologically or cytologically confirmed unresectable metastatic colorectal adenocarcinoma with a previous treatment history of ≥2 regimens of standard chemotherapy	Adult patients aged ≥18 years with biopsy-documented adenocarcinoma of the colon or rectum who had received ≥2 prior regimens of standard chemotherapy
Intervention	Trifluridine/tipiracil + BSC	
Comparator	Placebo + BSC	
Primary Outcome	Overall survival (OS)	
Secondary Outcomes	• Progression-free survival (PFS) • Time to treatment failure (TTF)	

Trial no. (acronym)	Not reported (Phase II trial, no acronym)	NCT01607957 (RECOURSE)
	• Disease control rate (DCR)	
	• Response rate • Duration of response • Efficacy of trifluridine/tipiracil in patients with or without KRAS mutations • Adverse event profile and tolerability	• Overall response rate (ORR) • Duration of Response • Subgroup analysis by KRAS status on OS and PFS • Safety and tolerability
Trial Design	Multi-centre, double blind, randomised (in a 2:1 ratio), placebo controlled trial	Multi-centre, double blind, randomised (in a 2:1 ratio), placebo controlled trial
BSC = best supportive care; CS = company submission; DCR = disease control rate; KRAS = Kirsten rat sarcoma viral oncogene homolog; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RCT = randomised controlled trial; TTF = time to treatment failure		

Table 4.3 provides more detail on the methodology of the two trials while Table 4.4 presents the outcome definitions used in these trials. Characteristics of participants in the two RCTs are presented in Table 4.5.

Table 4.3: Methodology of included RCTs
(Based on Table 15 of the CS[1] and CSRs[24, 25])

	Phase II trial	RECOURSE
Location	Japan	Australia, Europe, Japan, United States
Trial Design	Multi-centre, double blind, randomised (in a 2:1 ratio), placebo controlled trial	
Eligibility criteria for participants	• Previous treatment with ≥2 regimens of standard chemotherapy • Adequate bone marrow, hepatic and renal function within 7 days of enrolment	
	• ≥20 years old • ECOG PS 0-2 • Histologically or cytologically confirmed unresectable metastatic colorectal adenocarcinoma • Refractory or intolerant to a fluoropyrimidine, irinotecan, oxaliplatin • Measurable lesions as per the RECIST	• ≥18 years old • ECOG PS 0-1 • Biopsy documented adenocarcinoma of the colon or rectum • Patients were also required to have received chemotherapy with each of the following agents: fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, cetuximab or panitumumab if KRAS wild-type
Setting	Secondary care oncology, gastroenterology or general medicine outpatient departments	
Trial drugs	• 35 mg/m^2 T/T taken orally after morning and evening meals • 2 tablet doses were used in order to achieve the correct dose • T/T was taken in a 28-day cycle; a 2-week cycle of 5 days of treatment followed by a 2-day rest period and then a 14-day rest period • Placebo was matched to T/T tablets for taste, colour and size • Treatment continued until tumour progression, unacceptable toxic effects, or withdrawal of consent • No cross-over between groups after progression or toxic effects	
	• In patients who had AEs, the dose could be reduced by 10 mg/day as judged necessary	• Protocol allowed for a maximum of three reductions in dose in decrements of 5 mg/m^2

	Phase II trial	RECOURSE
	• Except in cases when deemed necessary from the perspective of safety or ethics, such as the treatment of an AE, other anti-cancer drugs or other investigational drugs were not to be used concomitantly.	• Other than BSC, permitted concomitant medications and therapies and study medication, patients were not permitted to receive any other medications and therapies, including other anticancer therapies, such as chemotherapy, immunotherapy, biological response modifiers or endocrine therapy, during the study treatment period. • Palliative radiotherapy was not permitted while the patient was receiving study treatment.
Primary Outcome	• Overall survival (OS)	
Secondary Outcomes	• Progression-free survival (PFS) • Time to treatment failure (TTF) • Disease control rate (DCR) • Duration of response	
	• Response rate • Efficacy of trifluridine/tipiracil in patients with or without KRAS mutations • Adverse event profile and tolerability	• Overall response rate (ORR) • Subgroup analysis by KRAS status on OS and PFS • Safety and tolerability
Pre-planned subgroups	• Sex (male / female) • Age (<65 years / ≥65 years) • Primary site (colon / rectum)	

	• PS (0 / 1-2)
	• Number of metastatic groups (1 / 2 / 3 / ≥4)
	  • Liver metastasis
	  • Lung metastasis
	  • Lymph node metastasis
	  • Peritoneum metastasis
	• Previous treatment
	  • Previous surgery
	  • Adjuvant chemotherapy
	  • Palliative chemotherapy
	  • Bevacizumab
	  • Cetuximab
	• KRAS mutation status
		• KRAS mutation status
		• Time since diagnosis
		• PS (0 / 1)
		• Geographic region (Japan / Rest of World
		• Number of metastatic sites
		• Number of prior regimens

AE = adverse event; BSC = best supportive care; CS = company submission; CSR = clinical study report; DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; KRAS = Kirsten rat sarcoma viral oncogene homolog; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PS = performance status; RECIST = Response Evaluation Criteria in Solid Tumours; T/T = trifluridine/tipiracil; TTF = time to treatment failure.

Table 4.4: Definition of relevant outcomes in the included RCTs

(Based on Table 15 of the CS[1])

	Phase II trial	RECOURSE
Overall survival	Time between randomisation and death from any cause or the date of last follow-up	Time (in months) between randomisation and death from any cause.

	Phase II trial	RECOURSE
Progression-free survival	Defined as the time (in months) from randomisation to the date that the patient's condition reached progressive disease (PD). If the patient died before reaching PD, the date of death was considered the date PD was reached. For patients that had not reached PD at the point that analysis was performed, and for patients in which the date that PD was reached was unknown, PFS time was censored at the date of the patient's final assessment prior to data cut-off. The randomisation date was used for cases in which lesion evaluation had not been performed after randomisation, and the initiation date of other (post-treatment) anti-cancer therapy was used when other anti-cancer therapy was initiated before the patient reached PD.	Defined as the time (in months) from the date of randomisation until the date of the investigator-assessed radiological disease progression or death due to any cause. Patients who were alive with no radiological disease progression as of the analysis cut-off date were censored at the date of the last tumour assessment. Patients who received non-study cancer treatment before disease progression, or patients with clinical but not radiological evidence of progression, were censored at the date of the last radiological evaluable tumour assessment before the non-study cancer treatment was initiated.
Response rates	Based on Response Evaluation Criteria in Solid Tumours (RECIST), the tumour shrinkage effect was evaluated and the response rate was calculated. The response rate was the percentage of patients in which the best overall response was determined to be complete response (CR) or partial response (PR) in each treatment group. The determination of the antitumor effect was to be performed in accordance with RECIST Ver. 1.0. At the independent image assessment site (CRO), determination of antitumor effect was made in accordance with RECIST Ver. 1.0 as well as RECIST Ver. 1.1 as a reference.	Overall response rate (ORR): Based on investigator review of radiological images and following RECIST criteria (version 1.1, 2009). ORR was defined as the proportion of patients with objective evidence of CR or PR with no confirmatory scan required. The primary assessment of ORR was for the ITT population, restricted to patients with measurable disease (at least 1 target lesion) at baseline. At the analysis stage, the best overall response was assigned for each patient as the best response recorded from all responses recorded from the start of treatment through the treatment period (excludes assessments during follow-up). If applicable, responses recorded after radiological disease progression or after initiation of non-study anti-tumour therapy were excluded. A best response assignment of SD required that SD be maintained for at least 6 weeks from the start of treatment.
Adverse events of treatment	Assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).	Standard safety monitoring and grading were performed using National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03. The evaluation of safety was based on the incidence, severity, and causality of AEs and SAEs and other safety assessments including physical examination, vital signs, ECOG performance status, 12-lead ECG, and clinical laboratory evaluations.
Health-related quality of life	Not assessed in the trial	

	Phase II trial	RECOURSE
AE = adverse event; CR = complete response; CRO = contract research organisation; CS = company submission; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ITT = intention-to-treat; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; RCT = randomised controlled trial; RECIST = Response Evaluation Criteria in Solid Tumours; SAE = serious adverse events; SD = stable disease		

Table 4.5: Characteristics of participants in the included RCTs
(Based on Tables 18 and 19 of the CS[1])

	Phase II trial		RECOURSE	
	T/T (n=114)	BSC (n=58)	T/T (n=534)	BSC (n=266)
Age (median, range)	63 (28 – 80)	62 (39 – 79)	63.0 (27-82)	63.0 (27-82)
Gender (M/F)	64 (57%); 48 (43%)	28 (49%); 29 (51%)	326 (61.0); 208 (39.0)	165 (62.0); 101 (38.0)
Race	Asian: 114 (100%)	Asian: 59 (100%)	White: 306 (57.3); Asian: 184 (34.5); Black: 4 (0.7)	White: 155 (58.3); Asian: 94 (35.3); Black: 5 (1.9)
Geographic location (%)	Japan: 100	Japan: 100	Japan: 33.3; Europe: 50.7; USA: 12.0; Australia: 3.9	Japan: 33.1; Europe: 49.6; USA: 13.2; Australia: 4.1
ECOG PS	0: 72 (64%); 1: 37 (33%); 2 (3%)	0: 35 (61%); 1: 21 (37%); 2: 1 (2%)	0: 301 (56.4); 1: 233 (43.6)	0: 147 (55.3); 1: 119 (44.7)
Primary tumour site	Colon: 63 (56%); Rectum: 49 (44%)	Colon: 36 (63%); Rectum: 21 (37%)	Colon: 338 (63.3); Rectum: 196 (36.7)	Colon: 161 (60.5); Rectum: 105 (39.5)
Number of metastatic sites	1: 25 (22%); 2: 43 (38%); 3: 27 (24%); 4: 17 (15%)	1: 11 (19%); 2: 20 (35%); 3: 12 (21%); 4: 14 (25%)	NR	NR
Time since diagnosis of metastasis	NR	NR	<18 months: 111 (20.8); ≥18 months: 423 (79.2)	<18 months: 55 (20.7); ≥18 months: 211 (79.3)
Metastatic organ	Liver: 65 (58%); Lung: 87 (78%); Lymph: 48 (43%); Peritoneum: 11 (10%)	Liver: 38 (67%); Lung: 44 (77%); Lymph: 23 (40%); Peritoneum: 17 (30%)	NR	NR
Previous treatment and reason	Surgical history: 103 (92%); Adjuvant chemotherapy: 54 (48%)	Surgical history: 50 (88%); Adjuvant chemotherapy: 15 (26%)	NR	NR
Number of palliative chemotherapies	2: 17 (15%); ≥3: 95 (85%)	2: 13 (23%); ≥3: 44 (77%)	2: 95 (17.8); 3: 119 (22.3); ≥4: 320 (59.9)	2: 45 (16.9); 3: 54 (20.3); ≥4: 167 (62.8)

	Phase II trial		RECOURSE	
	T/T (n=114)	BSC (n=58)	T/T (n=534)	BSC (n=266)
Fluoropyrimidine-based treatment	Refractory: 109 (97%); Intolerant: 3 (3%)	Refractory: 55 (96%); Intolerant: 2 (4%)	100%	100%
Oxaliplatin-based treatment	Refractory: 95 (85%); Intolerant: 17 (15%)	Refractory: 45 (79%); Intolerant: 12 (21%)	100%	100%
Irinotecan-based treatment	Refractory: 106 (95%); Intolerant: 6 (5%)	Refractory: 56 (98%); Intolerant: 1 (2%)	100%	100%
Bevacizumab	87 (78%)	47 (82%)	100%	99.6%
Cetuximab	71 (63%)	36 (63%)	NR	NR
Regorafenib	NR	NR	17.0%	19.9%
Anti-EGFR (if wild-type KRAS)	NR	NR	99.6%	99.3%
KRAS mutational status	Wild-type: 54 (55%); Mutation-positive: 45 (45%)	Wild-type: 24 (48%); Mutation-positive: 26 (52%)	Wild-type: 262 (49.1); Mutation-positive: 272 (50.9)	Wild-type: 131 (49.2); Mutation-positive: 135 (50.8)

CS = company submission; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; F = female; KRAS = Kirsten rat sarcoma viral oncogene homolog; M = male; NR = not reported; PS = performance status; RCT = randomised controlled trial; T/T = Trifluridine/tipiracil

ERG comment: The ERG examined the list of excluded studies and considered all of them to have been appropriately excluded. Furthermore, the ERG is satisfied that no data from the ongoing TERRA trial could have been used to inform the CS. The ERG does not consider it appropriate to comment on two non-randomised studies in detail as they should have been excluded from the systematic review. Therefore, only the two identified RCTs (phase II trial and RECOURSE) will be discussed in this section.

As can be seen in Table 4.2, although the two studies were conducted at different phases of development they are similar in terms of population eligibility criteria, intervention and comparator, primary and secondary outcomes and trial design.

The methodology of the included studies is presented in Table 4.3 and discussed below.

Location

The phase II trial was located in Japan whereas RECOURSE was a worldwide trial. The company was asked to clarify the number of UK participants in RECOURSE and to provide baseline characteristics and results and to consider the representativeness of the two trials for a UK setting.[20] The response for request for clarification confirmed that nine patients in five centres were recruited from the UK (seven patients in T/T group and two in BSC arm).[9] Characteristics of the UK participants were provided. As the participant numbers were extremely small the company did not provide results for this subpopulation. This appears reasonable. The company cited the multivariate analysis including geographic region and the pre-specified geographical regional subgroup analysis of RECOURSE and stated *"as there is no evidence of a difference in efficacy based on ethnicity, the included patients are*

generalizable to the UK setting".[9] The ERG considers this to be reasonable but draws the attention of the committee to the lack of participants from England and Wales.

Trial design
Both trials are multi-centre, randomised with a placebo control group which is a rigorous design. More comments on the quality of the trial design will be made in the section on trial quality (below).

Eligibility criteria for participants
Both trials were in adult participants with confirmed advanced colorectal cancer previously treated with ≥ 2 regimens of standard chemotherapy. This matches the final scope which refers to *"adults with metastatic colorectal cancer whose disease has progressed after standard therapies or for whom standard therapies are unsuitable"*.[14] All patients in the phase II trial and RECOURSE had received fluoropyrimidine, irinotecan and oxaliplatin.

Furthermore, in RECOURSE patients were required to have received prior chemotherapy with bevacizumab. However under NICE guidance patients in England would not be able to routinely receive bevacizumab prior to treatment with T/T. According to the CS, *"due to recent funding changes within England, there is currently no means of obtaining bevacizumab, cetuximab or panitumumab (third or fourth line) within the NHS, apart from if a patient is included in a clinical trial or has private medical insurance. Whilst many trial patients had previously received bevacizumab, cetuximab or panitumumab, it may not be possible for future English mCRC patients to do so. There is no biological reason why trifluridine/tipiracil should not work in patients who have not received these therapies. Indeed within the Phase II study approximately 80% of patients had received bevacizumab and 60%,* [sic!] *cetuximab; meaning that not all patients had received a biological therapy, despite this the results were consistent with the RECOURSE study. Expert clinical opinion considers that patient populations who are not as highly pre-treated as the population in RECOURSE would respond better because their tumours are less resistant to treatment"*.[1, 13] Figure 19 of the CS (*"overall survival in prespecified subgroups in the Phase II trial"*) seem to support the comment, i.e. patients who have not received bevacizumab (hazard ratio (HR) 0.37, 95% confidence interval (CI) 0.16 to 0.86) or cetuximab (HR 0.41, 95% CI 0.22 to 0.76) show better OS than people who have not received these drugs (HR 0.63, 95% CI 0.42 to 0.95 and HR 0.69, 95% CI 0.44 to 1.09, respectively). The CS concludes that *"it seems patients who have not received bevacizumab or cetuximab do better, although statistically there is no interaction"* (section 4.6 of the CS).[1] The company's interpretation in conjunction with clinical advice was that tumours in patients who had received fewer treatments were likely to be less resistant to additional therapy. This implies that the evidence for T/T presented might underestimate response in a UK population. This is an assumption, but it appears to be fair.

In the phase II trial, patients with ECOG (Eastern Cooperative Oncology Group) performance status (PS) 2 were eligible whereas in RECOURSE they were ineligible (Table 4.5). The proportion of patients with ECOG PS 2 in the phase II trial was 3% so this should not make a major difference to overall results. Similar proportions of ECOG PS 0 and 1 were noted in both trials.

Setting
Both trials were conducted in secondary care oncology, gastroenterology or general medicine outpatient departments.

Trial drugs
Both trials had a similar drug regimen. The main difference was that in the phase II trial patients who had adverse events (AEs), the dose could be reduced by 10 mg/day as judged necessary whereas in

RECOURSE the protocol allowed for a maximum of three reductions in dose in decrements of 5 mg/m^2. Concomitant therapies (not shown in Table 4.3) permitted were similar.

Primary outcome
Both trials had overall survival as a primary outcome which is line with the final scope.[14]

Secondary outcomes
These were similar across the trials and included progression-free survival, response rates and adverse effects of treatment as specified by the NICE scope.[14] As noted in Section 3.4 of this report neither trial assessed health-related quality of life as specified in the NICE scope.[14]

The ERG wished to examine the definitions of progression-free survival, progression and stable disease particularly given their importance in the economic model. For both trials, the ERG asked for clarification on the assessment methods e.g. how many assessors were involved and training to ensure consistency of outcome ascertainment across trial centres (Table 4.4).

- Progression-free survival was defined similarly across the two trials. In both trials if the patient died before reaching progressive disease (PD), the date of death was considered the date PD was reached.[1]
- In RECOURSE progression was defined as *"at least a 20% increase in the sum of diameters of the target lesions, taking as a reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Definitive new lesion presence also indicates progression"*.[2] The company stated that the definition of progression in the phase II trial was in the company submission but it was not. In the CSR progressive disease was defined as *"an increase of 20% or more in the maximum diameter sum of target lesions compared with the smallest maximum diameter sum (including the pre-treatment sum). However, if the maximum diameter sum is 10 mm or less, then an increase in the longest diameter sum of 20% or more is not considered PD"*.[24]
- In RECOURSE stable disease was defined as *"neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameters while on study"*. To get a *"best response"* of *"stable disease"* response has to last for six weeks.[2] For the phase II trial, the company advised that *"the response has not reached complete response (CR) or partial response (PR) in radiologic assessments over at least six weeks since the start of study drug administration and it has been confirmed that progressed disease (PD) has not occurred"*.[9]
- In response to request for clarification, the company confirmed that for both trials training provided to each centre was consistent across all study centres. The company further stated that in order to ensure consistency across study centres all secondary efficacy endpoints in the phase II trial were subject to independent radiologic assessment.[9] Centres in RECOURSE received an imaging manual to ensure consistency and an audit plan was put in place. The ERG was satisfied with the measures in place.

Adverse events in both trials were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).[1] The company was asked to confirm if all adverse events from the included trials had been included in the submission.[20] The company replied that details of all adverse events were either in the manuscript or in the clinical study reports (CSRs).[9]

The ERG examined the reports of adverse events in the two trials and provides an overview in this report.

Pre-planned subgroups
These were similar across the two trials and included variables that might be expected to impact on results, for example KRAS mutation status, age, primary site and number of prior treatment regimens.[1]

The phase II trial also included an assessment of those who had taken bevacizumab whereas in RECOURSE all patients had to have received this treatment. Thirty-five patients (22%) of the patients in the phase II trial did not receive bevacizumab. Both those receiving bevacizumab and those who did not benefited in terms of overall survival. Those who did not receive bevacizumab, and are thus directly appropriate to the England and Wales population, represent a small percentage of the trial populations (approximately 4%).

RECOURSE conducted a subgroup analysis of participants from Japan compared to participants from the rest of the world. This was used to show the applicability of the phase II trial conducted solely in Japan as results were found to be similar. The company stated *"as RECOURSE included Japanese patients, it was possible to observe whether all patients responded to trifluridine/tipiracil in a similar manner; as would be expected from the known pharmacology of the compound. In patients treated with trifluridine/tipiracil, outcomes and response for pre-specified regional subgroups were similar, with non-significant tests for interaction. Hence, it is possible to generalise the results of both studies to Western populations"* (Section 4.6 of the CS).[1] The ERG believes this to be reasonable.

Sample size calculations and analysis methods
According to the CS, for the phase II trial *"a sample size of 162 patients with a one-sided significance level of 10% was necessary to verify superiority in overall survival (OS) with a power of 80%, with an expected HR of 0.67. Median OS was anticipated to be 9.0 months in the trifluridine/tipiracil group and 6.0 months in the placebo group. A clinically relevant HR was estimated as 0.70. Patients continued to receive the study treatment (with group assignments remaining concealed) until the primary analysis of OS was done. The efficacy analysis was done in the intention-to-treat (ITT) population, and the safety analyses in the per-protocol population, when the number of deaths in the trial reached 121. The Kaplan-Meier method was used to estimate survival distribution. A stratified log-rank test was used and adjusted by the allocation factor, for comparisons between the two groups, and a Cox proportional hazards model to estimate HRs, the two-tailed 80% CIs corresponding to the significance level, and 95% CIs".*[1]

For RECOURSE, *"the study was designed to have 90% power to detect a HR for death of 0.75 (a 25% reduction in risk) in the trifluridine/tipiracil group compared with the placebo group, with a one-sided type I error rate of 0.025. Given the treatment assignment ratio of 2:1 (trifluridine/tipiracil: placebo), it was calculated that 800 patients had to be enrolled in the study, and at least 571 events (deaths) would be required for the primary analysis. OS (the primary endpoint) and radiologically confirmed PFS were analysed in the ITT population with the use of a two-sided, stratified log-rank test, with the HR and two-sided 95% confidence intervals based on a stratified Cox model and the associated Kaplan-Meier survival estimates. The primary analysis of OS includes follow-up data (including death events) obtained up to the date of the 571st death observed in the study. Patients having a documented survival status (alive or dead) after this date were censored at the cut-off date, but are they included in an updated analysis, which is used in the economic analysis. The median survival times were determined from the Kaplan-Meier curves. Rates of objective response and disease control were*

compared with the use of Fisher's exact test in the subgroup of the ITT population that had measurable disease at baseline".[1]

ERG comment: The sample size calculations in both trials were based on the primary endpoint of OS only, therefore neither trial was powered for secondary outcomes. Both trials used one-sided significance levels in the sample size calculation although in RECOURSE that was equivalent to the standard two-sided 95% CI which was reported in the results. In Phase II they used a larger significance level of a one-sided 10% level (equivalent to a two-sided 80% CI) without justifying this choice. However the 95% CIs were reported in the submission which use a stricter significance level and correspond with the RECOURSE results. Both trials reached their recruitment targets for numbers of participants and deaths so both appear to be adequately powered for OS. Both trials also used appropriate statistical analysis methods for all outcomes.

Quality Assessment

Table 21 of the company submission presents the quality assessment results of the included trials. It is reproduced in Table 4.6. ERG comments can be found below the table.

Table 4.6: Quality assessment of the included RCTs
(Based on Table 21 of the CS[1])

	Phase II	RECOURSE
Was the randomisation carried out appropriately?	**Yes** Following confirmation of eligibility as a subject for randomisation, on the basis of probability theory minimising methods, patients were assigned by the registration centre to the two treatment groups (trifluridine/tipiracil group and placebo group) at a ratio of 2:1. So as to ensure balance between the therapy groups, subjects were to be stratified at the time of randomisation according to the following stratification factors: • Performance Status: 0 vs. 1/2 At the registration centre, on the basis of a random assignment table, a drug number including the appropriate drug that was distributed to each implementing medical institution was assigned. The drug number was recorded in the raw data of each patient. The assignment was a dynamic allocation and thus caution was taken that the drug numbers were conferred randomly. Note that in cases in which the investigational drug of a drug number assigned to a patient was not used, other patients were not to use it, including the same patient in a later study period. For details of the random assignment and drug number assignment, the "Registration manual" was referred to. Rationale for setting of allocation adjustment factors; 'PS (0, 1/2)' is a general prognosis factor in cancer clinical trials and it was established considering the difference in efficacy and safety evaluations due to differences in the patient's condition.	**Yes** Once patient confirmation of eligibility and the criteria for randomisation had been met, patients were centrally randomised in a 2:1 ratio to trifluridine/tipiracil or placebo via an IWRS based on a dynamic allocation method (biased coin). The IWRS assigned kit numbers corresponding to the patient's treatment assignment and informed the study site user of the kit number that had been assigned to the patient for the dispensing of study drug. If a patient was mistakenly given a kit(s) of study medication that was not the kit assigned by the IWRS, resulting in the patient being initiated in the alternate arm from which they were assigned at randomisation, the patient continued to receive this treatment for the rest of the study. Study medication administration was to begin within 3 days following randomisation.
Was the concealment of treatment allocation adequate?	**Yes** This study was blinded for all the concerned parties of implementing medical institutions (such as patients, investigator or sub-investigators, and study research staff) as well as the	**Yes** This was a double-blind study. Trifluridine/tipiracil tablets of each strength, 15-mg or 20-mg, and the corresponding placebo tablets, 15-mg and 20-mg, were identical in appearance and

	Phase II	RECOURSE
	sponsor. The investigator or a sub-investigator was to prescribe to the patient an investigational drug of the investigational drug number assigned by the registration centres. In cases where information was necessary on the treatment group to which a patient was assigned in order to manage symptoms of the patient during an emergency resulting from, for example, a serious adverse event during the course of the study, the investigator was to contact a specific management service. Unblinding of the study was to be made after the events specified in the "Statistical analysis implementation period" were reached. The investigational drug assignment manager was to confirm that closing out of all applicable cases was completed by the sponsor. In addition, prior to the unblinding, the investigational drug assignment manager was to confirm the sealed status of the collected investigational drug and confirm that the keycode for emergency unblinding was appropriately stored and managed.	were packaged in identical containers. During the conduct of the study, the treatment assignment was unknown to all patients, investigators, and ancillary study personnel at each study site. During the conduct of the study, assigned treatment was unknown to the study team at Taiho Oncology, Inc. and Taiho Pharmaceutical Co., Ltd. except for pre-specified personnel involved in pharmacovigilance reporting activities and clinical trial material management. Among the CROs who assisted in the conduct of the study, treatment assignment was unknown except for personnel involved in drug labelling and distribution. Unblinding of the study treatment by the investigator was not to occur unless needed to manage a patient's medical condition. In an emergency, when specific knowledge of the patient's treatment assignment was needed to manage a patient's medical condition, the investigator could unblind the patient by calling the IWRS to obtain the patient's treatment assignment. If unblinding occurred, the investigator was not to disclose the unblinding information.
Were the groups similar at the outset of the study in terms of prognostic factors?	**No** There were some slight differences in some of the subgroups; namely sex, metastatic site, number of prior chemotherapy regimens and KRAS status.	**Yes** The groups were balanced in terms of KRAS status, time since diagnosis of 1st metastasis, region, BRAF status, age, race, gender, primary tumour site, ECOG score, number of prior regimens, and number of metastatic sites.
Were the care providers, participants and outcome assessors blind to the treatment allocation?	**Yes** See above regarding concealment of treatment allocation	**Yes** See above regarding concealment of treatment allocation
Were there any expected imbalances in drop-outs between groups?	**No** Please see patient disposition	**No** Please see patient disposition
Is there any evidence to	**No**	**No**

	Phase II	RECOURSE
suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention to treat analysis?	**Yes**	**Yes**

BRAF = serine/threonine-protein kinase B-Raf; ECOG = Eastern Cooperative Oncology Group; IWRS = interactive voice/web response system; KRAS = Kirsten rat sarcoma viral oncogene homolog; PS = performance status

ERG comments: Randomisation and concealment of treatment allocation were carried out appropriately in both trials. Patients in the phase II trial were stratified on ECOG performance status (0 vs. 1/2) whereas stratification for RECOURSE was based on KRAS mutation status.

In terms of prognostic factors, participants in RECOURSE were balanced between treatment groups. The phase II trialists noticed some slight differences in terms of sex, metastatic site, number of prior chemotherapy regimens and KRAS status. The ERG notes that these differences did not appear to bias the trial in favour of T/T.

Procedures for blinding of patients, care providers and outcome assessors appear to be appropriate.

Drop-out: The ERG found no evidence of differential dropout between treatment groups in the two trials and an ITT analysis was included in both trials. In the phase II trial, two patients did not receive the allocated treatment (1 T/T, 1 BSC – reasons supplied) and one had a protocol violation. These patients were omitted from the efficacy analysis but the latter was included in the safety analysis. In RECOURSE two patients did not receive the allocated treatment (1 T/T, 1 BSC). Six patients were lost to follow-up (three in each group) and one patient on T/T dropped out (Figure 12).[1] All patients were included in efficacy analyses with the exception of two who had not received treatment.[1]

Measurement of more outcomes than reported: The ERG agrees with the assessment in the CS.

Results of trials and pooled analyses

Table 4.7 details the results of the two included trials and the pooled analysis for the primary and secondary outcomes. A comparison of discontinuation rates in the two trials is given in Table 4.8. Adverse events in the phase II trial and RECOURSE are reported in Table 4.9 (all grades) and Table 4.10 (grade ≥3).

Table 4.7: Results of the included RCTs

(Based on Figure 27, Tables 22, 23 and 29 as well as Sections 4.7.1, 4.9 and 5.7.2 of the CS[1])

Outcome	Phase II	RECOURSE	Pooled Analysis*
Outcomes in the final scope[14]			
Number of deaths	T/T: 75 (67%) BSC: 48 (84.2%)	*Original analysis (574 deaths)* T/T: 364 (68.2%) BSC: 210 (78.9%) *Updated analysis (712 deaths)* T/T: NR BSC: NR	T/T: 538 (83.3%) BSC: 297 (92%)
Overall survival (OS)	*Median* T/T: 9.0 months (95% CI 7.3 to 11.3) BSC: 6.6 months (95% CI 4.9 to 8.0)	*Original analysis (574 deaths, median)* T/T: 7.1 months (95% CI 6.5 to 7.8) BSC: 5.3 months (95% CI 4.6 to 6.0) *Updated analysis (712 deaths, median)* T/T: 7.2 months (95% CI 6.6 to 7.8) BSC: 5.2 months (95% CI	*Median* T/T: 7.3 months BSC: 5.4 months *Mean* T/T: 9.1 months BSC: 6.8 months

HR OS	0.56 (95% CI 0.39 to 0.81)	4.6 to 5.9 *Original analysis (574 deaths)* 0.68 (95% CI 0.58 to 0.81) *Updated analysis (712 deaths)* 0.69 (95% CI 0.59 to 0.81)	0.67 (95% CI 0.58 to 0.78)
Progression-free survival (PFS) **HR PFS**	*Median (IRC)* T/T: 2 months (95% CI 1.9 to 2.8) BSC: 1 month (95% CI 1.0 to 1.0) *IRC* 0.41 (95% CI 0.28 to 0.59)	*Median* T/T: 2 months (95% CI 1.9 to 2.1) BSC: 1.7 months (95% CI 1.7 to 1.8) 0.48 (95% CI 0.41 to 0.57)	*Median* T/T: 1.9 months BSC: 1.7 months *Mean* T/T: 3.7 months BSC: 1.9 months 0.46 (95% CI 0.40 to 0.53)
Response rates	*IRC* *CR:* 0 in both groups *PR:* T/T: 1; BSC: 0 *SD:* T/T: 48 (-42.9%); BSC: 6 (-10.5%) *Progression of disease:* T/T: 53 (-47.3%); BSC: 44 (-77.2%)	*CR:* T/T: 0; BSC: 1 (0.4%) *PR:* T/T: 8; BSC: 0 *SD:* T/T: 213 (-42.4%); BSC 41 (-15.9%) *Progression of disease:* T/T: 260 (-51.8%); BSC 195 (-75.6%)	NA
Adverse effects of treatment	See tables 4.9 and 4.10		NA
Health-related quality of life	NR	NR	NA
Outcomes not defined in the final scope[14]			
Median time to treatment failure	*IRC* T/T: 1.9 months; BSC: 1 month	T/T: 1.9 months; BSC: 1.7 months	NA
HR time to treatment failure	*IRC* 0.40 (95% CI 0.28 to 0.56)	0.50 (95% CI 0.42 to 0.58)	NA
Disease control rate (CR + PR + SD; n (%))	T/T: 49 (-43.8%); BSC 6 (-10.5%)	T/T: 221 (44%); BSC: 42 (16.3%)	NA
Treatment discontinuation	See table 4.8		NA

[*] Using the updated RECOURSE analysis of 712 deaths (8 October 2014)

BSC = best supportive care; CI = confidence interval; CR = complete response; CS = company submission; HR = hazard ratio; IRC = independent review committee; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; PR = partial response; RCT = randomised controlled trial; SD = stable disease; T/T = trifluridine/tipiracil

Table 4.8: Comparison of discontinuation rates in the included RCTs

(Based on Table 11 and Figure 12 of the CS[1] and the CSRs[24, 25]. Numbers extracted from the CS. Where a discrepancy has been identified, the information from the CSR has been extracted as well.)

	Phase II trial						RECOURSE					
	Trifluridine/tipiracil			BSC			Trifluridine/tipiracil			BSC		
	n	Number of events	%	n	Number of events	%	n	Number of events	%	n	Number of events	%
Discontinued treatment (any reason)	114	109	95.6	58	57	98.3	534	496	93	266	263	>99
Discontinued treatment due to AE/SAE	114	4 [redacted]	3.5 [redacted]	58	1	1.7	534	18 [redacted]	4	266	4	2
Discontinued treatment due to death	114	NR	NR	58	0	0	534	7	1	266	4	2

AE = adverse event; CS = company submission; CSR = clinical study report; SAE = serious adverse event

Table 4.9: Comparison of adverse events in the RECOURSE trial and phase II trial (all grades)

(Based on Tables 41 and 43 of the CS[1], the CSRs[24, 25] and Mayer et al. 2015[2]. Numbers extracted from the CS. Where the information was not reported in the CS or a discrepancy has been identified, relevant information from the CSR and/or Mayer et al. 2015 have been extracted as well.)

	Phase II						RECOURSE					
All grades AE	**Trifluridine/tipiracil**			**BSC**			**Trifluridine/tipiracil**			**BSC**		
	n	**Number of events**	**%**	**n**	**Number of events**	**n**	**n**	**Number of events**	**%**	**n**	**Number of events**	**%**
Any event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	533	524	98.3	265	247	93.2
Any SAE	113	41[*] (21 patients)	18.6	57	8 (5 patients)	8.8	533	158	29.6	265	89	33.6
Any treatment-related AE	113	109[‡*]	96.5	57	40[‡]	70.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	113	73	64.6	57	16	28.1	533	258[†]	48.4	265	63	23.8
Vomiting	113	38	33.6	57	14	24.6	533	148[†]	27.8	265	38	14.3
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	533	208[†]	39.0	265	78	29.4
Diarrhoea	113	43	38.1	57	12	21.1	533	170[†]	31.9	265	33	12.5
Abdominal pain[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	533	113[†]	21.2	265	49	18.5
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	113	81	71.7	57	1	1.8	528[§]	358 Mayer: 353	67.8 Mayer: 67	263	2	0.8
Leucopenia	113	86	76.1	57	2	3.5	528[§]	407	77.1	263	12	4.6

	Phase II						RECOURSE					
All grades AE	**Trifluridine/tipiracil**			**BSC**			**Trifluridine/tipiracil**			**BSC**		
	n	**Number of events**	**%**	**n**	**Number of events**	**n**	**n**	**Number of events**	**%**	**n**	**Number of events**	**%**
Anaemia	113	82	72.6	57	9	15.8	528[§]	404	76.5	263	87	33.1
Thrombocytopenia	113	44	38.9	57	1	1.8	528[§]	223	42.2	263	21	8.0
Treatment related death	113	0[*]	0	57	0	0						
Death due to AE												

[*] Page 112 of CS

[ǂ] per patient

[†] Adverse events of any grade that are listed as most common occurred in 10% or more of patients in the trifluridine/tipiracil group and in a greater percentage in that group than in the BSC group.

[#] Diarrhoea and/or nausea and/or vomiting

[§] The denominator for the percentage of patients with laboratory abnormalities is the number of patients with at least one post baseline measurement during treatment.

AE = adverse event; CS = company submission; CSR = clinical study report; SAE = serious adverse event

Table 4.10: Comparison of adverse events in the RECOURSE trial and phase II trial (grade ≥3)

(Based on Tables 42 and 44 of the CS[1], the CSRs[24, 25] and Mayer et al. 2015[2]. Numbers extracted from the CS. Where the information was not reported in the CS or a discrepancy to the CSR has been identified, relevant information from the CSR and/or Mayer et al. 2015 have been extracted as well.)

	Phase II						RECOURSE					
Grade ≥3 AE	**Trifluridine/tipiracil**			**BSC**			**Trifluridine/tipiracil**			**BSC**		
	n	**Number of events**	**%**	**n**	**Number of events**	**%**	n	**Number of events**	**%**	n	**Number of events**	**%**
Any event							533	370	69.4	265	137	51.7
Any treatment-related AE							[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea†	113	5	4.4	57	0	0.0	533	10	1.9	265	3	1.1
Vomiting†	113	4	3.5	57	0	0.0	533	11	2.1	265	1	0.4
Decreased appetite†							533	19	3.6	265	13	4.9
Diarrhoea†	113	7	6.2	57	0	0.0	533	16	3.0	265	1	0.4
Abdominal pain†							533	13 [redacted]	2.4 [redacted]	265	10	3.8
Neutropenia§	113	57	50.4	57	0	0.0	528	200 [redacted]	37.9 [redacted]	263	2 Mayer: 0	0.8 Mayer: 0
Leucopenia§	113	32	28.3	57	0	0.0	528	113	21.4	263	12 Mayer: 0	4.6 Mayer: 0
Anaemia§	113	19	16.8	57	3	5.3	528 [redacted]	96 [redacted]	18.2 [redacted]	263 [redacted]	87 [redacted] Mayer: 8	33.1 [redacted] Mayer: 3

	Phase II						RECOURSE					
Grade ≥3 AE	**Trifluridine/tipiracil**			**BSC**			**Trifluridine/tipiracil**			**BSC**		
	n	**Number of events**	**%**	**n**	**Number of events**	**%**	n	**Number of events**	**%**	n	**Number of events**	**%**
Thrombocytopenia[§]	113	5	4.4	57	0	0.0	528	27	5.1	263	21	8

[†] Adverse events of any grade that are listed as most common occurred in 10% or more of patients in the trifluridine/tipiracil group and in a greater percentage in that group than in the BSC group.

[§] The denominator for the percentage of patients with laboratory abnormalities is the number of patients with at least one post baseline measurement during treatment.

[ǂ] per patient

AE = adverse event; CS = company submission; CSR = clinical study report; NR = not reported; SAE = serious adverse event

ERG comments: Results are reported for the original analysis of RECOURSE (574 deaths, 24 January 2014) and the updated analysis (712 deaths, 8 October 2014). The pooled results use the updated data from RECOURSE. This appears reasonable.

Overall survival
Based on the updated analysis of 712 deaths in RECOURSE an increase in median overall survival of two months in the T/T group was observed (T/T: 7.2 months, BSC: 5.2 months). This was statistically significant (HR 0.69; 95% CI 0.59 to 0.81). The phase II trial showed an increase in median overall survival of 2.4 months (T/T: 9.0 months, BSC: 6.6 months). This was statistically significant (HR 0.56; 95% CI 0.39 to 0.81). In the pooled analysis, there was an increase in survival of 1.9 months (T/T: 7.3 months, BSC: 5.4 months). This was statistically significant (HR 0.67; 95% CI 0.58 to 0.78). The pooled mean increase in survival is 2.3 months (T/T: 9.1 months, BSC: 6.8 months). It is noted that, based on the trial data, the increase in survival for T/T compared to BSC is less than that specified in end of life care (minimum of three months, see Section 7).

Progression-free survival
Median PFS was similar in RECOURSE and in the pooled results. The pooled results showed an increase of 0.2 months (T/T: 1.9 months, BSC: 1.7 months). This was statistically significant (0.46; 95% CI 0.40 to 0.53; $p < 0.0001$). The mean PFS increase was 1.8 months (T/T: 3.7 months, BSC: 1.9 months).

Response rates
In the phase II trial no patient in either group had a complete response and one in the T/T group had a partial response. In RECOURSE one patient in the BSC group had a complete response and eight in the T/T group had a partial response. A greater proportion of T/ T patients in both trials had stable disease (42.9% vs. 10.5% in the phase II trial and 42.4% vs. 15.9% in RECOURSE).

Adverse effects of treatment
Rates of discontinuation (for any reason, due to adverse events (AEs), due to serious AE (SAEs) or due to death) were found to be broadly similar between T/T and BSC arms in the phase II trial and RECOURSE (summarised in Table 4.8). In both trials, one discrepancy was noted between the company submission[1] and the respective clinical study report[24,25]; this was the number of patients who discontinued due to AE. This appears to be a minor difference which should not influence the overall result.

All adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 in the RECOURSE trial, whilst the Common Terminology Criteria for Adverse Events (CTCAE Ver. 3.0 Japanese translation, Japan Clinical Oncology Group (JCOG)/ Japan Society of Clinical Oncology (JSCO) version) was used for the phase II trial. The ERG compared the rates of all major adverse events and in particular noted those associated with myelosuppression which the Food and Drug Administration (FDA) considered an important side effect of this drug[26, 27] and gastrointestinal side effects which are considered important by the Committee for Medicinal Products for Human Use (CHMP).[16]

Any AE or SAE were similar between T/T and BSC arms for the RECOURSE trial.[25] The phase II trial did not report data for any AE, however numbers were reported in Table 12.2.1-1 (p. 217) of the clinical study report (CSR) for the phase II trial and were [redacted].[24] [redacted]. The phase II trial

reported numbers for 'adverse drug reactions' in the text of the company submission (p. 112).[1] The definition of 'adverse drug reaction' was "*those that were determined to have a positive relationship with the investigational drug"* (Section 9.5.3.2.6 of the CSR); which would be consistent with 'treatment-related AE' reported in the CSR of RECOURSE (Table 35 of the CSR).[25] In both trials 'treatment-related AEs' were found to be [redacted].

In both trials the following gastrointestinal related AE were found to be [redacted] (see Table 4.9 for details). Results for abdominal pain were similar in both arms for the RECOURSE trial as reported in the CS[1] or the CSR (Table 37)[25]; and for the phase II trial (results identified in the CSR[24]). Gastrointestinal disorders were recorded as a class in the CSR for the phase II trial (Table 12.2.3.1-1) and RECOURSE (Table 52) and therefore are reported here. In both trials [redacted].

In both trials the following AEs related to myelosuppression were found to be [redacted], see Table 4.9. The results were inconsistently reported between the submission and the clinical study reports and the publication of RECOURSE.[2] These discrepancies may be due to differences between using number of events and number of patients as the numerator; however it did not change the overall direction of the results.

In the CS, only the phase II trial reported treatment-related deaths and found none occurred. Results for this AE (Table 35 of the CSR) were identified in the CSR of the RECOURSE trial[25]; only one death was reported for the T/T arm. 'Death due to AE' was not reported within the CS but was identified in the CSR for both trials. In RECOURSE, more patients in the BSC arm were reported to [redacted].[24]

Adverse events which were of a higher severity (≥3 grade) are shown in Table 4.10. Results for any AE were found to be higher in the T/T arm of the RECOURSE trial (69.4% vs. 51.7%). in addition any treatment related AE (Table 35 of the CSR) were found to [redacted] (see Table 4.10 for details). Corresponding events related to myelosuppression [redacted].

Overall, more treatment related adverse events occurred in the T/T treatment arm rather than BSC. [redacted].

Health-related quality of life

Neither of the two included trials assessed health-related quality of life.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The company submission did not present an indirect comparison and/or multiple treatment comparison.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

The company submission did not present an indirect comparison and/or multiple treatment comparison.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The company's submission includes a systematic review of the available evidence for T/T compared to BSC for patients with advanced/metastatic colorectal cancer receiving treatment at the third line or beyond. Although some issues were highlighted in searching for studies of adverse events for the systematic review, the ERG is overall satisfied that the company identified and appraised the relevant randomised trials. The two non-randomised studies in the adverse effects section of the submission did not appear to have been selected systematically. We have focused our attention in this report on the two randomised trials which inform the cost effectiveness model.

There is a lack of information on methods of pooling the two included randomised trials but overall it was considered acceptable from the point of view of clinical effectiveness that the trials were pooled.

The two included trials (phase II trial and RECOURSE) were randomised and compared T/T to placebo with both treatment groups in the trials receiving best supportive care. Our evaluation of the quality confirmed the company's assessment that both trials were of high quality.

RECOURSE was an international trial whereas the phase II trial was conducted solely with Japanese participants. The ERG considered that the company had provided evidence that geographical region was not a factor in effectiveness. This meant that results of the Japanese trial could be pooled with RECOURSE. However the ERG draws the committee's attention to the low proportion of UK participants in RECOURSE (9 of 800 patients). However 394 of 800 were from Europe. The ERG further notes that there is an under-representation of non-white, non-Asian populations across the trial (approximately 1% of RECOURSE participants are listed as 'black').

Considering further the issue of applicability of the trials, the population in RECOURSE is a more treated population than might be expected in practice in England and Wales. Patients were required to have received chemotherapy with fluoropyrimidine, oxaliplatin, irinotecan and bevacuzimab. They were also required to have received cetuximab or panitumumab if KRAS wild-type. Bevacuzimab is not currently available in England and Wales. A small number in the phase II trial had not received bevacuzimab (22%) but the phase II trial included fewer participants than RECOURSE. Those who did not receive bevacizumab, and are thus appropriate to the England and Wales population, represent a small percentage of the trial populations (approximately 4%). The company states that T/T might be expected to work better in a less treated population based on clinical advice. This appears to be reasonable but is drawn to the attention of the committee.

The scope issued by NICE recommended comparing T/T to best supportive care (BSC) as there are no currently recommended treatments for patients who have failed second line treatment. The CS is based on two placebo-controlled trials where both treatment and placebo groups received BSC. The ERG

asked for clarification on the definitions of BSC used in the included trials, the guidance regarding BSC given to the centres involved in the included trials and the applicability of the BSC to the UK setting. The company clarified that there is no internationally accepted definition of BSC for clinical trials. Although both trials ensured consistency on medications excluded from BSC, the nature of BSC provided could potentially vary between trial centres. The nature of BSC provided might also differ from that provided in England and Wales given that a very small number of participants were from centres in England and Wales.

In relation to outcomes, the ERG notes that the company provided two analyses of overall survival for the RECOURSE trial, an original (24 January 2014, 574 deaths) and an updated analysis (8 October 2014, 712 deaths). This updated, post-hoc analysis was requested during the CHMP review and the ERG considers it appropriate to present this analysis in the submission to maximise the data available. The ERG notes that the pooled analysis for overall survival was based on the updated analysis of RECOURSE.

In the pooled analysis there was an increase in median overall survival of 1.9 months (T/T: 7.3 months, BSC: 5.4 months, no CIs reported). The pooled mean increase in overall survival is 2.3 months (T/T: 9.1 months, BSC: 6.8 months, no CIs reported). It is noted that, based on the trial data, the increase in survival is less than that specified in end of life care (minimum of three months).

The main trial, RECOURSE, was powered for the outcome of overall survival so may not have had sufficient power to detect all differences between treatment groups for secondary outcomes. The included trials do not directly assess health-related quality of life as specified in the NICE scope. Although there is a benefit to patients of the mean increase in overall survival of 2.3 months (pooled result) the quality of life experienced can only be inferred from effects of disease control and occurrence of adverse events. A significant benefit of T/T for progression-free survival has been shown although this is modest. In terms of disease control, a greater proportion of T/ T patients in both trials had stable disease (42.9% vs. 10.5% in the phase II trial and 42.4% vs. 15.9% in RECOURSE). However numbers achieving partial response or complete response were very small overall.

Rates of adverse events and serious adverse events were similar between T/T and BSC for the RECOURSE trial.[25] The phase II trial was found to be similar between treatment arms for adverse events but SAE were found to be higher in the T/T arm (18.6% vs. 8.8%).[24] The phase II trial reported numbers for 'adverse drug reactions'.[1] The definition was found to be consistent with 'treatment-related AE' reported in the CSR of RECOURSE.[25] In both trials 'treatment-related AEs' were found to be higher in the T/T arms than in the BSC arms (85.7% vs. 54.7% and 96.5% vs. 70.2%, respectively).

In RECOURSE, more patients in the BSC arm were reported to die from AE than in the T/T arm (11.3% vs. 3.2%)[25], whilst in the phase II trial only one case of death due to AE was reported in the T/T treatment arm (Table 12.3.1.1-1 of the CSR).[24]

We compared the rates of all major adverse events and in particular noted those associated with myelosuppression which the Food and Drug Administration (FDA) considered an important side effect of this drug[26, 27] and gastrointestinal side effects which are considered important by the Committee for Medicinal Products for Human Use (CHMP).[16]

Rates of discontinuation (for any reason, due to adverse events (AEs), due to serious AE (SAEs) or due to death) were found to be broadly similar between T/T and BSC in the phase II trial and RECOURSE.

5 COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness and health-related quality of life evidence

5.1.1 Objective and searches of cost effectiveness review

A systematic review of the published literature was conducted by the company to identify cost effectiveness studies assessing the treatment of patients with mCRC with T/T compared with BSC as third line or later treatment.

Cost effectiveness

The CS states that a systematic review of the published literature was conducted to identify cost effectiveness studies assessing the treatment of patients with mCRC with trifluridine/tipiracil compared to BSC as third line or later treatment.

The searches were conducted on 26 October 2015 in the same databases searched for the clinical effectiveness searches: MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, Embase and the Cochrane Library (CENTRAL, the Cochrane Database of Systematic Reviews, NHS EED, DARE, and HTA). The host provider for each database was listed; the date span of the databases searched and the specific date the searches were conducted were provided. The company additionally searched conference proceedings: American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Detailed search strategies for the database searches were reported in appendix 6 of the CS.[23] The CS did not provide details of the conference proceedings searches. Full details of the conference proceedings searches for the utility review were provided in response[9] to the ERG clarification letter.[20] These searches could have been used for the cost effectiveness review, as generic search terms for advanced and metastatic colorectal cancer were used, but it is not clear if they were.

The company translated the research question into appropriate search strategies and the ERG considered the searches to be satisfactory. Searches were clearly structured and divided into population, intervention/comparator and cost-effectiveness facets. The search strategies included Boolean, truncation and proximity operators. No date or language limits were included. It was not clear whether a validated study design filter was used for the cost effectiveness facet of search terms.

The searches for cost effectiveness were quite precise, and may have retrieved additional studies with a more sensitive search strategy, i.e. searching for 'economic evaluation OR models', rather than 'economic evaluation AND models'.

All databases included in the Cochrane Library were searched, when only NHS EED and HTA include relevant studies. Further, the search strategy used in the Cochrane Library contained a study design search filter limiting the results to economic evaluations. The ERG considered this to be overly restrictive and unnecessary as the Cochrane databases are pre-filtered resources, i.e. the database of relevance to this search, NHS EED, only contains economic evaluations.

A search of other economic resources, such as the cost effectiveness analysis (CEA) Registry and ScHARRHUD, for cost-utility analyses might have been a useful addition to the literature searches.

Resource identification, measurement and valuation
Searches were not conducted for healthcare resource use identification. Resource costs were identified from two recent NICE technology appraisals, TA242[7] and ID794.[28]

5.1.2 Inclusion/exclusion criteria used in the study selection

Screening of publications by title and abstract was performed to include all currently available treatments; any studies which were not relevant according to the NICE scope were then excluded upon full publication review. Table 5.1 presents the eligibility criteria used for the review.

Table 5.1: Inclusion/exclusion criteria used in the study selection
(Based on Appendix 6 of the CS[1])

	Inclusion criteria
Population	Adult patients with advanced/metastatic CRC receiving treatment at third line or beyond
Interventions	T/T
Comparators	BSC
Outcomes	ICERs Range of ICERs as per sensitivity analyses Assumptions underpinning model structures Key cost drivers Sources of clinical, cost and quality of life inputs Discounting of costs and health outcomes Model summary and structure
Study design	Cost-utility analyses
Language restrictions	None

BSC = best supportive care; CRC = colorectal cancer; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; STA = Single Technology Appraisal

ERG comment: The in- and exclusion criteria seem appropriate for the objective of this review.

5.1.3 Included/excluded studies in the cost effectiveness review

In total, 890 potentially relevant studies were identified of which zero remained after exclusion of duplicates (85 excluded), reviewing title and abstracts (719 excluded) and full paper reviewing (86 excluded). No additional relevant publications were identified via hand searching.

ERG comment: The rationales for excluding studies after full paper reviewing seem appropriate (see Table 2 of Appendix 6 of the CS[1]) given the defined in- and exclusion criteria.

5.1.4 Conclusions of the cost effectiveness review

There were no relevant studies identified in the literature that assess the treatment of patients with mCRC with T/T compared with BSC as third line or later treatment.

ERG comment: The ERG agrees with the conclusions from the company that none of the selected studies were relevant for the decision problem given the in- and exclusion criteria defined by the company.

5.1.5 Objective and searches of health-related quality of life review

No health-related quality of life (HRQoL) data were collected in either the phase II trial[3] or the RECOURSE trial.[2] Therefore, the company conducted a systematic review to identify HRQoL studies from the published literature relevant to the decision problem.

The CS states that a systematic review was conducted to identify HRQoL studies from the published literature relevant to the decision problem; in particular, studies reporting European Quality of Life-5 Dimensions (EQ-5D) health state utility values (in line with the NICE preferred method) relating to patients with advanced/mCRC receiving third line treatment or beyond were considered eligible for inclusion.

The search strategies reported in Appendix 10 of the CS were identical to those reported in Appendix 6 for the cost effectiveness review[23], and the database search results reported here did not correspond with those reported in Section 5.4.2 and Figure 35 (flow chart) of the CS.[1] The ERG asked for clarification that the correct search strategies for identifying HRQoL studies had been reported.[20] In response the company stated that although the captions for MEDLINE and Embase were incorrect, the 'search strategies themselves were correct'.[9] The captions for the MEDLINE and Embase search strategies provided were actually identical to those already reported in the CS.[1] The search strategies reported in Appendix 10 were designed to identify cost effectiveness studies, not HRQoL studies. Without full details of the HRQoL search strategies the ERG was unable to assess their quality.

The company reported additionally searching conference proceedings: ASCO, ESMO and ISPOR. The CS did not provide full details of the conference proceedings searches. Full details of the conference proceedings searches for the utility review were provided in response[9] to the request for clarification.[20]

A search of other economic resources, such as the CEA Registry and ScHARRHUD, for cost-utility analyses might have provided additional useful HRQoL data.

The list of excluded studies reported in Table 7 (Section 10.7 of the CS) were identical to those excluded studies reported for the cost effectiveness review in Table 2 (Section 6.7). In response to the request for clarification[20] asking if the list of excluded studies was correct, the company reported that the list was correct.[9]

5.1.6 Inclusion/exclusion criteria used in the study selection

In the CS,[1] it is stated that studies reporting EQ-5D health state utility values (in line with the NICE preferred method) relating to patients with advanced/mCRC receiving third line treatment or beyond were considered eligible for inclusion.

ERG comment: The in- and exclusion criteria seem appropriate.

5.1.7 Included/excluded studies in the health-related quality of life review

The company identified a total of 547 papers through the electronic searches. After removal of 83 duplicates and exclusion of 436 papers after title and abstract review, 28 full papers were reviewed. Full paper reviewing resulted in four relevant papers for final inclusion (see Figure 35 of the CS[1]).

No additional relevant publications were identified via hand searching. A full list of studies excluded on the basis of full publication review is available in Appendix 10 of the CS along with a rationale for exclusion.

ERG comment: The rationales for excluding studies after full paper reviewing seem appropriate (see Table 7 of Appendix 10 of the CS[1]).

5.1.8 Conclusions of the health-related quality of life review

The company concluded that there were two HRQoL studies[29-31] that may meet the requirements of the NICE reference case. However, assessment of consistency with the NICE reference case and quality assessment were hampered by limited reporting of details regarding methods of elicitation and valuation, the patient recruitment process, eligibility criteria and response rates (see Tables 58 and 59 of the CS[1]).

ERG comment: The ERG agrees with the conclusions from the company that two out of the four included studies[29-31] might potentially be consistent with the NICE reference case. Nevertheless, it is unclear whether these studies meet the requirements of the NICE reference case on all aspects. Moreover, the company was unclear why the study by Siena et al. (i.e. the CORRECT study)[29, 30] was preferred as the source for HRQoL data above the study by Chang et al.[31] which might potentially be consistent with the NICE reference case. This was clarified by the company in the clarification letter[9] by stating that Chang et al.[31] *"did not provide health-state specific utility values for use in the model"* and that is was *"only abstracts and did not present utility values by progression status".*[9] The ERG thinks this is reasonable.

Additionally, the ERG identified relevant studies for the estimation of health state utilities (see Section 5.2.8) that were not in the list of excluded papers after full reading, and therefore presumably not identified in the systematic review by the company. As a result, the sensitivity of the systematic review may be questioned, and other potentially relevant studies may be overlooked. This lack of sensitivity might be because the company did not specifically search for relevant studies on health-related quality of life, but instead used the search for relevant cost effectiveness studies to identify model inputs for health-related quality of life.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.2: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source / Justification	Signpost (location in CS)
Model	A partitioned-survival model was constructed to evaluate the cost-effectiveness of T/T compared with BSC in adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies.		5.2.2 (pg. 130)
States and events	The model was based on disease progression, consisting of the health states pre-progression, post-progression and death.	Health states were selected according to the clinical pathway of care and comparable to the structure used in other late-stage cancer models.	5.2.2 (pg. 130)
Comparators	Best supportive care.	As there is currently no	5.2.3

	Approach	Source / Justification	Signpost (location in CS)
		recommended treatment for patients in the population covered by the anticipated T/T licence, the company selected BSC as the comparator.	(pg. 131)
Population	Adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan- based chemotherapy, anti-VEGF biological therapies, and anti-EGFR therapies.	The population in the analysis is similar to the population in the scope but slightly different from the populations in the phase II trial and RECOURSE study that were used to inform input parameters.	5.2.1 (pg. 129-130)
Treatment effectiveness	The intervention was defined by the company is an orally administered combination of trifluridine, a thymidine-based nucleic acid analogue, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride. It is administered at a dose of 35mg/m2 twice daily, 5 days a week, with 2 days of rest, for 2 weeks, followed by a 14-day rest period. This treatment cycle is repeated every 4 weeks.	The intervention defined in the NICE final scope was 'fixed dose combination of trifluridine and tipiracil hydrochloride'.	5.2.3 (pg. 131)
Adverse events	The company incorporated costs of adverse events if they were actively treated in the NHS, as verified with clinical and medical oncologists.	RECOURSE trial	5.5.4 (pg. 161-163)
Health related Quality of Life	Health related quality of life information was not collected in the phase II study and the RECOURSE trial. Estimates for health state utilities were based on literature and assumptions. Disutilities for adverse events were not explicitly modelled, and based on assumption.	Health state utilities for pre and post progression were based on the average of values reported in the CORRECT study[30] and the company submission of TA176[32].	5.4 (pg. 148 - 155)
Resource utilisation and costs	Drug costs were estimated from the RECOURSE trial, taking into account dosage (based on BSA), dose reduction, treatment delay, and time on treatment. The weighted average cost	TA794[28] for mCRC, RECOURSE trial, and expert opinion. Unit costs for the regularly scheduled follow-up procedures were determined	5.5 (pg. 155 - 165)

	Approach	Source / Justification	Signpost (location in CS)
	in the third cycle was [redacted] at list price. MRU costs were based on expert opinion and included oral chemotherapy day case attendance and health home visitor for patients treated with T/T (£203). Patients receiving BSC had a medical oncologist outpatient consultation and a health home visitor (£182). For all patients GP home consultation, community nurse specialist visits, district nurse visits, and GP surgery visits were included in post-progression (£193). The RECOURSE trial data was used to estimate the average cost of post-progression treatment per patient, which was £1,549 for T/T and £1,487 for BSC, but were incorporated on average for all patients (£1,528). End-of-life care costs included health care, social care and charity care. The total end-of-life care cost of £6,910 was applied in the model as a lump sum upon death for both arms. The company incorporated costs of adverse events if they were actively treated in the NHS. These events were included at rates observed from the RECOURSE trial resulting in £923 for T/T and £426 for BSC.	using the NHS Reference Costs, 2014-15. End-of-life care costs were taken from a modelling study by Round et al.[33]	
Discount rates	3.5 % for utilities and costs	According to NICE reference case	5.2.2 (pg. 131)
Sub groups	Subgroup analysis is not considered in the de novo analysis, given the size of the patient population and that, in RECOURSE, T/T was associated with a clinically relevant prolongation in OS in all treatment subgroups.		5.9 (pg. 188)
Sensitivity analysis	Deterministic and probabilistic sensitivity analyses were conducted. The model was mainly sensitive to changes in health related quality of life inputs and survival estimates.		5.8 (pg. 175 – 188)

	Approach	Source / Justification	Signpost (location in CS)
BSA = body surface area; BSC = best supportive care; EGFR = epidermal growth factor receptor; GP = general practitioner; mCRC = metastatic colorectal cancer; MRU = medical resource utilisation; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; T/T = trifluridine/tipiracil; VEGF = vascular endothelial growth factor			

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Population	As per NICE scope	Y	Population in the CS is per NICE scope, but may differ slightly from population in trials on which evaluation is based (see 5.2.3).
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Y	T/T is evaluated against best supportive care.
Type of economic evaluation	Cost-effectiveness analysis	Y	
Perspective on costs	NHS and Personal Social Services (PSS)	Y	PSS costs are not reported.
Perspective on outcomes	All health effects on individuals	Y	
Time horizon	Sufficient to capture differences in costs and outcomes	Y	Time horizon of 10 years is effectively lifetime as <1% of patients are still alive (5.2.5).
Synthesis of evidence in outcomes	Systematic review	Partly	Ideally, a dedicated systematic review would also have been performed to inform the model structure, quality of life and resource use.
Measure of health effects	Quality adjusted life years (QALYs)	Y	
Source of data for measurement HRQoL	Described using a standardised and validated instrument	Y	HRQoL data were not collected in the phase II and the phase III

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
			clinical trial.
Source of preference data for valuation of changes in HRQoL	Time-trade off or standard gamble	Y	
Discount rate	An annual rate of 3.5% on both costs and health effects	Y	
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Y	
Probabilistic modelling	Probabilistic modelling	Y	BSA was included in the PSA as a stochastic parameter.
Sensitivity analysis		Y	A range of sensitivity analyses were performed.

BSA = body surface area; CS = company submission; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSA = probabilistic sensitivity analysis; PSS = personal social services; QALY = quality-adjusted life year; T/T = trifluridine/tipiracil

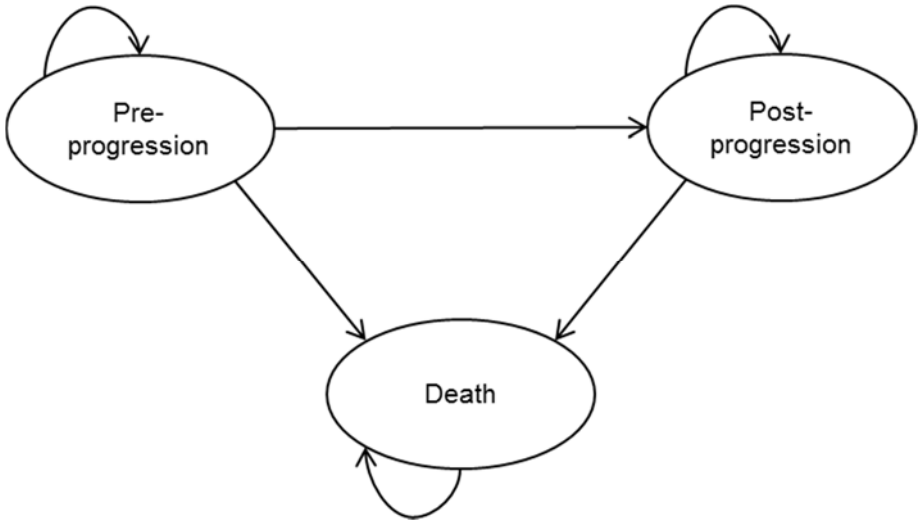
5.2.2 Model structure

An excel-based partitioned-survival model was constructed to evaluate the cost effectiveness of T/T compared with BSC in adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies. The model was based on disease progression, consisting of the health states pre-progression, post-progression and death (Figure 5.1). Health states were selected according to the clinical pathway of care and comparable to the structure used in other late-stage cancer models.

All patients enter the model in the pre-progression state. Patients may transition between health states based on PFS curves that were fitted to the clinical trial data. Patients that have progressed to the post-progression state are not permitted to transition back to the pre-progression state. Patients may transition to the death state from any health state. The model structure is identical for patients treated receiving T/T or BSC.

Because of the poor prognosis of patients, a daily cycle length was applied to ensure the accuracy of survival estimates. A longer cycle length was considered to be inappropriate due to the kinks in the curve caused by the frequency of progression assessment in the clinical trials. Consequently, a half-cycle correction was not deemed to be required.

Figure 5.1: Model structure
(Based on Figure 29 of the CS[1])



ERG comment: Ideally, following the NICE reference case, a systematic approach, including a review, should have been performed to inform the model structure. Nevertheless, the ERG agrees that the chosen model structure, daily cycle and the absence of a half-cycle correction are appropriate for this decision problem.

5.2.3 Population

The company reported that following the anticipated licence, T/T was 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 chemotherapy, anti-VEGF biological therapies, and anti-EGFR therapies.[34] The company considered this population to be reflective of the population discussed in the decision problem and the scope, as well as in the clinical trials from which efficacy data are derived to inform the model (see Table 5.4). In line with the licence, T/T is expected to be used from the third line onwards.

Table 5.4: Populations

NICE final scope	Company (following anticipated licence)	Phase II RCT	RECOURSE
Adults with metastatic colorectal cancer whose disease has progressed after standard therapies or for whom standard therapies are unsuitable.	Adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies including fluoro-pyrimidine-, oxaliplatin- and irinotecan- based chemotherapy, anti-VEGF biological therapies, and anti-EGFR therapies.	Adult patients aged ≥20 years with histologically or cytologically confirmed unresectable metastatic colorectal adenocarcinoma with a previous treatment history of ≥2 regimens of standard chemo-therapy [3]	Adult patients aged ≥18 years with biopsy-documented adenocarcinoma of the colon or rectum who had received ≥2 prior regimens of standard chemo-therapy [2]
EGFR = epidermal growth factor receptor; NICE = National Institute for Health and Care Excellence; RCT = randomised controlled trial; VEGF = vascular endothelial growth factor			

ERG comment: The ERG notes that the populations described in the NICE final scope[14], including patients with mCRC for whom standard therapies are 'unsuitable', seems approximately similar to the

population described by the company, following the anticipated licence, but differs slightly from populations in the trials, which were used to inform the model (Table 5.4). Consequently, following the licence it may be possible that patients not represented in the trial receive this medication. This includes patients *"for whom standard therapies are unsuitable"*. It remains unclear in which direction this discrepancy would influence the outcomes.

5.2.4 Interventions and comparators

The intervention defined in the NICE final scope was *"fixed dose combination of trifluridine and tipiracil hydrochloride"*.[14] The intervention was defined by the company as an orally administered combination of trifluridine, a thymidine-based nucleic acid analogue, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride. It is administered at a dose of 35 mg/m^2 twice daily, five days a week, with two days of rest, for two weeks, followed by a 14-day rest period. This treatment cycle is repeated every four weeks.[34] Following the anticipated licence and the RECOURSE trial protocol, T/T treatment is continued until determination of RECIST-defined disease progression, clinical progression, the development of severe adverse events, withdrawal from the study, death, or a decision by the treating physician that discontinuation would be in the patient's best interest.[2, 35]

As there is currently no recommended treatment for patients in the population covered by the anticipated T/T licence, the company selected BSC as the comparator, in line with the phase II trial and RECOURSE.[2, 3]

ERG comment: The ERG agrees with the selected intervention and comparator. The ERG asked the company to provide the definition of BSC in the trials. The company responded that BSC was defined as follows[9]:

- Phase II trial: All necessary support was provided to patients, with the exception of concomitant use of other anti-cancer drugs or other investigational drugs.
- RECOURSE: All necessary support was provided to patients which included permitted concomitant medications and therapies and study medication. All patients received the best supportive care available but were not to receive other investigational antitumour agents or antineoplastic chemotherapy, hormonal therapy, or immunotherapy. Palliative radiotherapy was not permitted while the patient was receiving study treatment. If used concomitantly with study medication, antiviral drugs that are human thymidine kinase substrates (e.g. stavudine, zidovudine, telbivudine) were to be used with caution because such drugs may theoretically compete with the effect of trifluridine/tipiracil, i.e. trifluridine, for activation via thymidine kinases.

Based on these definitions it is uncertain whether BSC as provided in the trial is representative for the UK.

5.2.5 Perspective, time horizon and discounting

The economic evaluation used the perspective of the National Health Service (NHS). Utilities and costs were discounted at 3.5% over a time horizon of 10 years. The company justified the time horizon of 10 years as being effectively lifetime as less than 1% of patients are still alive (Table 48 of the CS).[1]

ERG comment: The ERG agrees with the chosen discounting rates and agrees that 10 years is effectively a lifetime horizon in this population.

5.2.6 Treatment effectiveness and extrapolation

Data sources and pooling

Overall survival (OS) and progression-free survival (PFS) estimates were obtained from RECOURSE[2] and the phase II trial[3]. The definitions of these endpoints in each trial are provided in Table 15 of the CS[1] (Table 5.5). RECOURSE is an international randomised controlled phase III trial performed in Europe, Australia, the United States and Japan while the phase II trial included only Japanese patients. Both trials used a 2:1 randomisation scheme of T/T+BSC versus placebo+BSC. Trial data were considered mature with 89% and 72.9% of the patients being deceased in RECOURSE and the phase II trial, respectively.[1] Updated OS data from RECOURSE were available, which means that OS data are based on the last known alive date instead of being capped at the 571th death as provided in the publication of the trial (original data).[2]

Table 5.5: Definition of OS and PFS in RECOURSE and the phase II clinical trial
(Based on Table 15 of the CS[1])

Outcomes	Definition in phase II trial	Definition in RECOURSE
Primary outcome: Overall survival (OS)	Time between randomisation and death from any cause or the date of last follow-up	Time (in months) between randomisation and death from any cause
Secondary outcome: Progression-free survival (PFS)	Defined as the time (in months) from randomisation to the **date that the patient's condition reached progressive disease (PD)**. If the patient died before reaching PD, the date of death was considered the date PD was reached. […]	Defined as the time (in months) from the date of randomisation until the **date of the investigator-assessed radiological disease progression** or death due to any cause. […]
CS = company submission; OS = overall survival; PD = progressive disease; PFS = progression-free survival		

In the company base case analysis, effectiveness data from both trials have been pooled (updated RECOURSE data + phase II clinical trial). According to the company, pooling provided a "*meaningful increase in the number of placebo-treated patients*".[1] No detail on the pooling procedure was provided in the cost effectiveness assessment part of the CS.[1] Effectiveness data from RECOURSE only (original and updated data) and from the phase II clinical trial only were used in sensitivity analyses. Results of those analyses are provided in Section 5.2.11 of the current report.

Transition probabilities between health states were based on the area under the curve (i.e. partitioned survival model) from OS and PFS survival curves. The OS curve estimated the proportion of patients which were 'alive' and the PFS curve estimated the proportion of patient which remained in the 'pre-progression' health state, at any point in time. The proportion of patients with progression was estimated by the difference between 'alive' and 'pre-progression' patients. The proportion of deceased patients was estimated by '1-proportion of patients still alive'.

ERG comment: As can be seen in Table 5.5, the definitions for PFS were not identical in both trials, which could have led to different assessment of progression between trials. Furthermore, the trial populations are slightly different. These two factors may have led to heterogeneity between the trials, but did not completely hamper pooling. For a more extensive discussion on reasons to pool the data from both trials, the ERG refers to Section 4.15 of the current report.

Even though pooling the trials seems reasonable, the methods were not clearly described in the CS. The ERG asked clarification on how pooling was performed and the company referred to the meta-analysis presented in Section 4.9 of the CS[1], without providing additional details. As a result, the ERG was unable to critically assess whether the pooling procedure was reasonable (see Section 4.15 of this report). In order for the ERG to critically assess the pooling, the ERG would have liked to receive a comparison of the current meta-analysis (not stratified by trial) with a meta-analysis in which stratification by trials was performed. If the results of both meta-analyses would have been similar, the ERG would prefer the current meta-analysis to be used in the cost effectiveness model. Without this information, the ERG prefers using a more conservative assumption in its base case analysis by using RECOURSE data only. However, since there are no fundamental arguments which prevent the two trials from being pooled, besides the lack of clarity of the methodology, the ERG also presents its base case analysis based on the pooled effectiveness estimates from both trials.

PFS and OS were the only pooled data while other estimates, such as adverse event rates, time on treatment and dose reductions were based on RECOURSE only. The ERG did not understand the rationale behind this choice and asked for pooled estimates for these other estimates (i.e. adverse event rates, time on treatment and dose reductions). The company provided an updated model containing pooled estimates for adverse event rates, time on treatment and dose reductions with its response to the ERG clarification letter. The ERG used this updated model in its analyses.

Model selection for progression-free survival and overall survival
Different stratified by treatment and unstratified parametric survival models were compared to select survival models to represent OS and PFS in the cost effectiveness analysis. In the stratified models, two curve fits were produced for T/T and BSC separately while unstratified models contained a covariate representing the treatment arm. The following candidate survival models were examined:

- Log-logistic (stratified and unstratified)
- Generalised gamma (stratified and unstratified)
- Log-normal (stratified and unstratified)
- Weibull (stratified and unstratified)
- Gompertz (stratified and unstratified)
- Exponential (unstratified)
- Extreme value (stratified and unstratified)

The most suitable survival model was chosen based on the Akaike Information Criterion (AIC) goodness of fit statistics and visual examination. Goodness of fit statistics for PFS and OS survival models are presented in Table 5.6. The curve fits of the different candidate survival models are provided in Appendix 7 of the CS.[1]

Table 5.6: Progression-free survival and overall survival – goodness of fit statistics
(Based on Tables 49 and 50 of the CS[1])

Model	AIC (PFS)	Goodness of fit ranking (PFS)	AIC (OS)	Goodness of fit ranking (OS)
Stratified log-logistic	**9,331**	**1**	**10,898**	**2**
Stratified generalised gamma	9,352	2	10,901	4
Stratified log-normal	9,356	3	10,905	6

Model	AIC (PFS)	Goodness of fit ranking (PFS)	AIC (OS)	Goodness of fit ranking (OS)
Log-logistic	9,385	4	10,896	1
Generalised gamma	9,403	5	10,899	3
Log-normal	9,407	6	10,903	5
Stratified Weibull	9,589	7	10,958	8
Weibull	9,607	8	10,957	7
Stratified Gompertz	9,754	9	11,041	10
Gompertz	9,759	10	11,040	9
Exponential	9,773	11	11,079	13
Extreme value	9,855	12	11,063	12
Stratified extreme value	9,857	13	11,060	11

AIC = Akaike Information Criterion; CS = company submission; OS = overall survival; PFS = progression-free survival

For PFS, the stratified log-logistic model provided the lowest AIC and had a good visual fit. Therefore, it was chosen to represent PFS in the base case analysis (Figure 5.2). For OS, the unstratified log-logistic model had the best AIC estimate. However, the stratified log-logistic model was chosen to represent OS in order to be consistent with the selected model for PFS. Moreover, the stratified log-logistic model provided a good visual fit to the OS Kaplan-Meier curve (Figure 5.3) and was the second best-fitting model according to the AIC (with two AIC points difference with the unstratified log-logistic model). Another argument of the company to use stratified models was the uneven randomisation in both trials (2:1).[1] The chosen survival models for the base case analysis are bold printed in Table 5.6 above. The influence of using alternative survival models was investigated in sensitivity analyses. Results of these sensitivity analyses are presented in Section 5.2.11 of the current report.

Figure 5.2: Stratified log-logistic survival curve for PFS (two years)
(Based on Figure 30 of the CS[1])

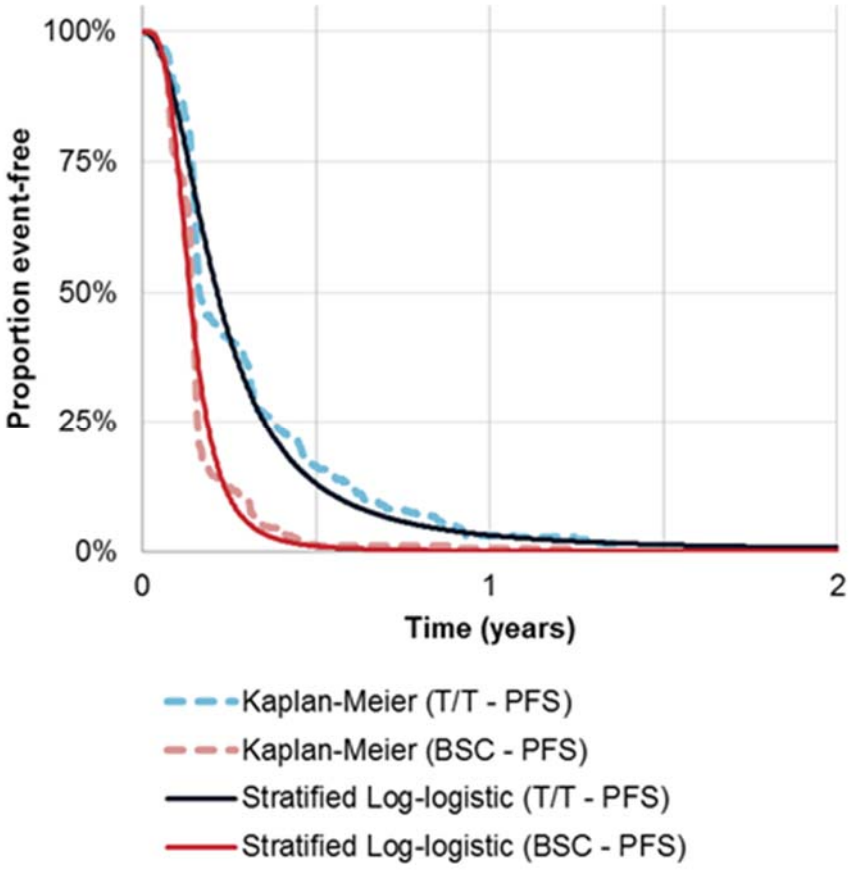
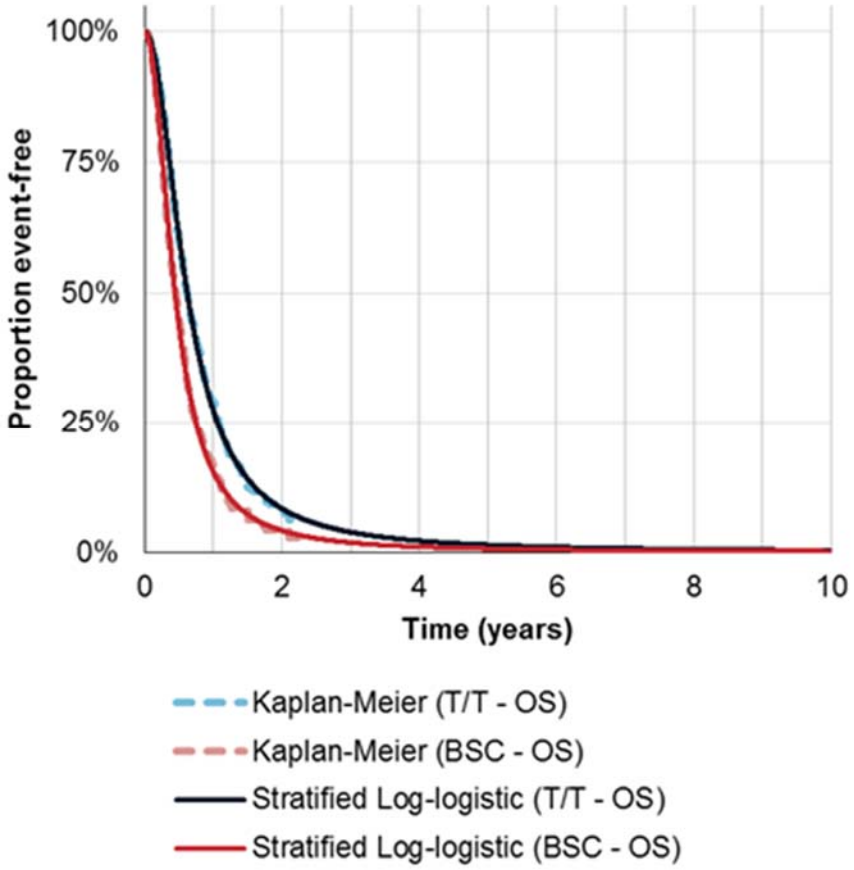


Figure 5.3: Stratified log-logistic survival curve for OS (10 years)
(Based on Figure 32 of the CS[1])



ERG comment: The following issues concerning survival model selection are raised by the ERG: log-cumulative hazard or quantile-quantile (QQ) plots were not used to decide on using stratified or unstratified models, uneven randomisation as an argument for the selection of a stratified model, AIC calculations for stratified models were unclear.

Log-cumulative hazard or QQ plots were not used to decide on using stratified or unstratified models
The use of stratified or unstratified model should be based on a visual examination of log-cumulative or QQ plots, as recommended by the NICE Decision Support Unit (DSU) on survival analysis.[36] This step was missing in the model selection process described in the CS. Therefore, the ERG asked the company to provide these plots for all survival models presented in the CS. In its response to the ERG clarification letter, the company provided the log-cumulative hazard plots for the PFS and OS of the pooled, RECOURSE and phase II population respectively.[9] The QQ plots of the different survival models were not presented. The ERG examined the log-cumulative hazard plots from RECOURSE data only because pooling was not deemed suitable in the current assessment based on above-mentioned arguments. The log-cumulative hazard plots, for the updated RECOURSE data are displayed in Figures 5.4 (OS for the RECOURSE population ('Updated OS')) and 5.5 (PFS for the RECOURSE population).

Figure 5.4: Log-cumulative hazard plot for OS – RECOURSE population
(Based on Figure 3 of the response to request for clarification[9])

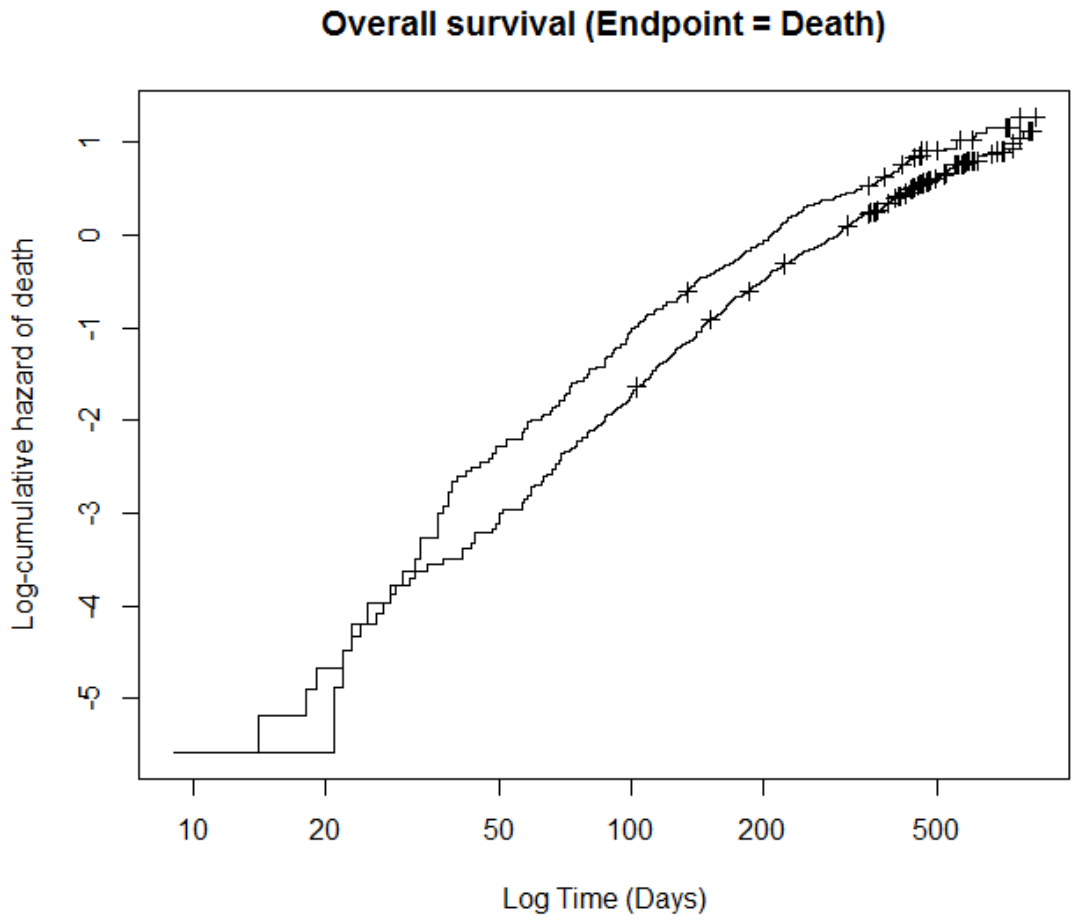
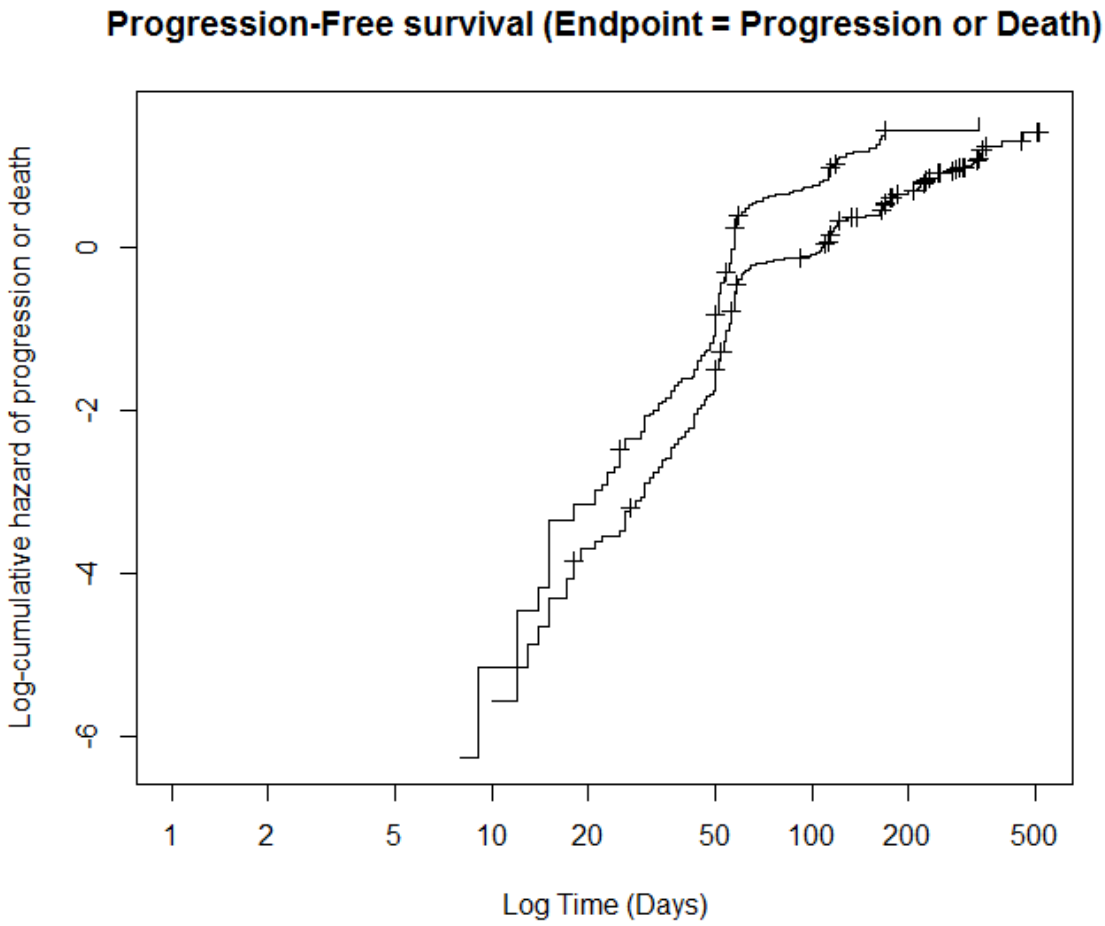


Figure 5.5: Log-cumulative hazard plot for PFS – RECOURSE population
(Based on Figure 6 of the response to request for clarification[9])



Since log-cumulative hazard plots (Figures 5.4 and 5.5) for the RECOURSE population were reasonably parallel, the ERG preferred using unstratified survival models in its base case analysis.

Uneven randomisation as an argument for the selection of a stratified model
Furthermore, uneven randomisation was an argument for the selection of stratified models instead of unstratified models. This was however unclear to the ERG and clarification was asked on this point. The company responded with the following: *"Unequal randomisation (in this case 2:1) implies that unstratified parametric survival models will inherently utilise a relatively larger proportion of patients in the larger patient group (in this case, patients receiving trifluridine/tipiracil) compared with the smaller patients group (in this case, patients receiving placebo) in the estimate of the associated parametric curve parameters."*[9] Because stratified models were deemed suitable, this argument was not taken into account during model selection by the ERG.

AIC calculations for stratified model were unclear
It was unclear to the ERG how the AIC were calculated for stratified models since they presumably led to two curve fits. Comparing AIC from unstratified and stratified survival models consequently leads to a penalty for stratified models since unstratified models contain a covariate that stratified model do not contain. For these reasons, the ERG asked the company to clarify how unique AIC for stratified models were obtained. In its response to the clarification, the company stated that *"AIC scores were obtained for the stratified models using the same methodology as per the unstratified*

models".[9] Pragmatically, the same R function was used to calculate the AIC of stratified and unstratified models. Calculations seemed to be performed correctly according to the ERG.

In order to select the survival models to represent PFS and OS in its base case cost effectiveness analysis, the ERG followed the algorithm provided by the DSU on survival analysis.[36] First, based on the examination of the log-cumulative hazard curves of the RECOURSE population, the ERG does not agree with the choice of stratified model for OS and PFS and preferred using unstratified models since the curves in the plots (Figures 5.4 and 5.5) were reasonably parallel. Second, based on the AIC and visual examination, the ERG thinks that the most appropriate model for both OS and PFS would be the unstratified log-logistic models. These models were used in the ERG base case analysis. Results of this analysis are provided in Chapter 6 of the current report.

5.2.7 Adverse events

The company's cost effectiveness model includes all 'common' adverse events (AEs) based on AEs incidence rates from the RECOURSE trial. 'Common' was defined as AEs that occurred in 10% or more of the patients receiving T/T and which occurred in a higher proportion of patients receiving T/T than in patients receiving BSC. The incidence rates of AEs from the RECOURSE trial are listed in Table 5.7. The bold-printed percentages are the ones that are explicitly used in the model to calculate AEs treatment costs. More details on the costing procedure of AEs are provided in Section 5.2.9 of the current report. No distinction was made between AEs occurring before or after progression.

Table 5.7: Adverse events rates with absolute risk reduction (ARR) from RECOURSE
(Based on Tables 43, 44 and 57 of the CS[1])

	Trifluridine/tipiracil		BSC		ARR % (any grade)	ARR % (grade ≥3 AEs)
	% of events (any grade)	% of grade ≥ 3 AEs	% of events (any grade)	% of grade ≥ 3 AEs		
Any event	98.3	69.4	93.2	51.7	-5.1	-17.7
Any serious event	NA	29.6	NA	33.6	NA	3.9
Nausea†	48.4	**1.9**	23.8	**1.1**	-24.6	**-0.7**
Vomiting†	**27.8**	**2.1**	**14.3**	**0.4**	**-13.4**	**-1.7**
Decreased appetite†	39.0	**3.6**	29.4	**4.9**	-9.6	**1.3**
Fatigue†	35.3	**3.9**	23.4	**5.7**	-11.9	**1.7**
Diarrhoea†	**31.9**	**3.0**	**12.5**	**0.4**	**-19.4**	**-2.6**
Abdominal pain†	21.2	**2.4**	18.5	**3.8**	-2.7	**1.3**
Fever†	**18.6**	**1.3**	**14.0**	**0.4**	**-4.6**	**-0.9**
Asthenia†	18.2	**3.4**	11.3	**3.0**	-6.9	**-0.4**
Febrile neutropenia**	**3.8**	**3.8**	**0.0**	**0.0**	-3.8	**-3.8**
Stomatitis**	8.1	**0.4**	6.4	**0.0**	-1.7	**-0.4**
Hand-foot syndrome**	2.3	0.0	2.3	0.0	0.0	0.0
Cardiac ischaemia** ‡	**0.4**	**0.2**	**0.4**	**0.4**	**0.0**	**0.2**
Neutropenia§	67.8	**37.9**	0.8	**0.8**	-67.0	**-37.1**
Leucopenia§	77.1	**21.4**	4.6	**4.6**	-72.5	**-16.8**
Anaemia§	76.5	**18.2**	33.1	**33.1**	-43.4	**14.9**

	Trifluridine/tipiracil		BSC		ARR % (any grade)	ARR % (grade ≥3 AEs)
	% of events (any grade)	% of grade ≥ 3 AEs	% of events (any grade)	% of grade ≥ 3 AEs		
Thrombocytopenia[§]	42.2	**5.1**	8.0	**8.0**	-34.3	**2.9**
Increase in alanine aminotransferase level[§]	24.0	1.9	26.6	26.6	2.7	24.7
Increase in aspartate aminotransferase level[§]	21.9	4.4	34.7	34.7	12.8	30.3
Increase in total bilirubin[§]	35.4	8.6	26.3	26.3	-9.0	17.8
Increase alkaline phosphatase level[§]	39.0	8.0	45.0	45.0	6.1	37.1
Increase in creatinine level[§]	13.5	0.9	12.2	12.2	-1.3	11.2

Trial data from Mayer et al. 2015[2]. Calculations not possible when absolute risk in placebo group = 0.
All adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.
[†] Adverse events of any grade that are listed as most common occurred in 10% or more of patients in the trifluridine/tipiracil group and in a greater percentage in that group than in the placebo group.
[**] Events associated with fluoropyrimidine treatment.
[‡] Events included acute myocardial infarction, angina pectoris, and myocardial ischaemia.
[§] The denominator for the percentage of patients with laboratory abnormalities is the number of patients with at least one post baseline measurement during treatment.
Bold-printed percentages are the ones that are explicitly used in the model to calculate AEs treatment costs.
AE = adverse event; ARR = absolute risk reduction; BSC = best supportive care; CS = company submission; NA = not applicable

ERG comment: It was unclear to the ERG why only RECOURSE data (and not a pooled estimate from RECOURSE and the phase II trial) were used for AEs incidence rates, especially because PFS and OS in the company base case analysis were based on pooled evidence of both clinical trials. In its clarification letter, the ERG asked for a pooled analysis of AEs incidence rates, based on both trials.[20] The company provided new AEs incidence rates based on both trials. Adverse events were included in this analysis based "*upon the most frequently observed adverse events (defined as occurring with a frequency of at least 3% in the safety population) in the Phase II trial, as reported in the publication by Yoshino et al. (2009). The rates presented in this publication have been selected for inclusion using the same criteria as per the adverse events from the RECOURSE study, which were taken from the publication by Mayer et al. (2015).*" The pooled AEs incidence rates and reasons for exclusion of specific AEs from the costing procedure are presented in Table 5.8.

Table 5.8: Adverse events rates with absolute risk reduction (ARR) from RECOURSE
(Based on Table 4 of the response to request for clarification[9])

Grade 1 or 2 adverse events	**Trifluridine/tipiracil**	**BSC**	**Excluded?**
Diarrhoea	43/113 (38%)	12/57 (21%)	
Febrile neutropenia	5/113 (4%)	0	
Vomiting	38/113 (34%)	14/57 (25%)	
Grade 3 or 4 adverse events	**Trifluridine/tipiracil**	**BSC**	**Excluded?**
Neutropenia	57/113 (50%)	0	
Leucopenia	32/113 (28%)	0	
Anaemia	19/113 (17%)	3/57 (5%)	
Lymphopenia	11/113 (10%)	2/57 (4%)	Yes[a]
Thrombocytopenia	5/113 (4%)	0	
Fatigue	7/113 (6%)	2/57 (4%)	
Diarrhoea	7/113 (6%)	0	
Nausea	5/113 (4%)	0	
Anorexia	5/113 (4%)	2/57 (4%)	Yes[b]
Febrile neutropenia	5/113 (4%)	0	
Vomiting	4/113 (4%)	0	
Reasons for exclusion:			
a: <1% of patients in both arms of the RECOURSE trial experienced Grade ≥3 lymphopenia b: Anorexia is not explicitly reported in the RECOURSE trial – the most similar adverse events would be Grade ≥3 "Weight Decreased" or "Decreased Appetite". "Decreased Appetite" is already included within the model, and "Weight Decreased" only occurred in 1 trifluridine/tipiracil patient (and 0 BSC patients).			
ARR = absolute risk reduction			

The updated version of the cost effectiveness model, provided with the response to the ERG clarification letter, included the pooled AEs incidence rates.[9] Results of this analysis are presented in Section 5.2.11 of the current report.

Since the ERG decided not to use pooled estimates in its base case, the ERG used AEs incidence rates from RECOURSE only. However, the ERG would like to note that the grade ≥ 3 AEs rates for the BSC arm reported in Tables 44 and 57 of the CS, and in the company's cost effectiveness model, are not correct for the following AEs:

- Neutropenia
- Leukopenia
- Anaemia
- Thrombocytopenia
- Increase in alanine aminotransferase level
- Increase in aspartate aminotransferase level
- Increase in total bilirubin
- Increase alkaline phosphatase level
- Increase in creatine level

The ERG corrected these rates, by using the rates reported in the RECOURSE publication (Table 2).[2] The corrected AEs rates are given in italics in Table 5.9 besides the other AEs rates used in the ERG base case analysis. Results of the ERG base case are presented in Section 6 of the current report.

Table 5.9: Adverse events rates used in the ERG base case analysis with ARR from RECOURSE
(Based on Tables 43, 44 and 57 of the CS[1] and Table 2 of RECOURSE[2])

	Trifluridine/tipiracil		BSC		ARR % (any grade)	ARR % (grade ≥3 AE s)
	% of events (any grade)	% of grade ≥ 3 AEs	% of events (any grade)	% of grade ≥ 3 AEs		
Any event	98.3	69.4	93.2	51.7	-5.1	-17.7
Any serious event	NA	29.6	NA	33.6	NA	3.9
Nausea†	48.4	**1.9**	23.8	**1.1**	-24.6	**-0.7**
Vomiting†	**27.8**	**2.1**	**14.3**	**0.4**	**-13.4**	**-1.7**
Decreased appetite†	39.0	**3.6**	29.4	**4.9**	-9.6	**1.3**
Fatigue†	35.3	**3.9**	23.4	**5.7**	-11.9	**1.7**
Diarrhoea†	**31.9**	**3.0**	**12.5**	**0.4**	**-19.4**	**-2.6**
Abdominal pain†	21.2	**2.4**	18.5	**3.8**	-2.7	**1.3**
Fever†	**18.6**	**1.3**	**14.0**	**0.4**	**-4.6**	**-0.9**
Asthenia†	18.2	**3.4**	11.3	**3.0**	-6.9	**-0.4**
Febrile neutropenia**	**3.8**	**3.8**	**0.0**	**0.0**	-3.8	**-3.8**
Stomatitis**	8.1	**0.4**	6.4	**0.0**	-1.7	**-0.4**
Hand-foot syndrome**	2.3	0.0	2.3	0.0	0.0	0.0
Cardiac ischaemia** ‡	**0.4**	**0.2**	**0.4**	**0.4**	**0.0**	**0.2**
Neutropenia§	67.8	**37.9**	0.8	***0.0***	-67.0	***-37.9***
Leucopenia§	77.1	**21.4**	4.6	***0.0***	-72.5	***-21.4***
Anaemia§	76.5	**18.2**	33.1	***0.0***	-43.4	***-18.2***
Thrombocytopenia§	42.2	**5.1**	8.0	***0.0***	-34.3	***-5.1***
Increase in alanine aminotransferase level§	24.0	1.9	26.6	*0.0*	2.7	*-1.9*
Increase in aspartate aminotransferase level§	21.9	4.4	34.7	*0.1*	12.8	*-4.3*
Increase in total bilirubin§	35.4	8.6	26.3	*0.1*	-9.0	*-8.5*
Increase alkaline phosphatase level§	39.0	8.0	45.0	*0.1*	6.1	*-7.9*
Increase in creatinine level§	13.5	0.9	12.2	*0.0*	-1.3	*-0.9*

Trial data from Mayer et al. 2015[2]. Calculations not possible when absolute risk in BSC group = 0.
All adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

	Trifluridine/tipiracil		BSC		ARR % (any grade)	ARR % (grade ≥3 AEs)
	% of events (any grade)	% of grade ≥ 3 AEs	% of events (any grade)	% of grade ≥ 3 AEs		
† Adverse events of any grade that are listed as most common occurred in 10% or more of patients in the trifluridine/tipiracil group and in a greater percentage in that group than in the BSC group.						
** Events associated with fluoropyrimidine treatment.						
‡ Events included acute myocardial infarction, angina pectoris, and myocardial ischaemia.						
§ The denominator for the percentage of patients with laboratory abnormalities is the number of patients with at least one post baseline measurement during treatment.						
Bold-printed percentages are the ones that are explicitly used in the model to calculate AEs treatment costs. The corrected numbers are printed in Italic.						
AE = adverse event; ARR = absolute risk reduction; CS = company submission; ERG = Evidence Review Group						

5.2.8 Health-related quality of life

No health-related quality of life information was collected in the phase II trial or the RECOURSE study. The company conducted a systematic review to identify health-related quality of life studies from the published literature. Four studies were included: Chan et al.[37], Mittmann et al.[38], Chang et al.[31], and Siena et al.[29]. In Chan et al. and Mittmann et al. the Health Utilities Index Mark III (HUI3) instrument was used to determine utilities. This is not in line with the NICE reference case, and for that reason these studies were not used by the company. It was stated that the abstracts from Chang et al. and Siena et al. *"may meet the NICE requirement"*. Siena et al. was a publication based on data from the CORRECT study of regorafenib monotherapy for previously treated metastatic CRC.[30]

In the base case analyses the health state utility values were the average of utilities obtained in the CORRECT study (not from the abstract by Siena et al.[29], but as published in Grothey et al.[30]) and the cetuximab NICE CS for the first-line treatment of mCRC, TA 176[32] (see Table 5.10). The justification for using the CORRECT study as a source of utilities was that this study was conducted at the same disease stage. The justification for using an average of the above-mentioned two sources in the base case is that these are the *"two most appropriate sources"*.

Table 5.10: Summary of utility values for cost effectiveness analysis
(Based on Table 60 of the CS[1])

State	Base case Utility value mean (SE)*	Regorafinib CORRECT study Utility value mean (SE)	Cetuximab NICE CS Utility value (TA176) mean (SE)
Pre-progression – on treatment	0.73 (0.01)	0.73 (NR)	0.73 (NR)§
Pre-progression – BSC	0.74 (0.02)	0.74 (NR)	0.73 (NR)§
Post-progression – T/T	0.64 (0.01)	0.59 (NR)	0.68 (NR)#
Post-progression – BSC	0.64 (0.02)	0.59 (NR)	0.68 (NR)#
Dead	0ß	0ß	0ß

* Average of CORRECT study and the cetuximab NICE company submission for the first-line treatment of mCRC, TA176; § Second line; # Third line; ß NICE reference case.
BSC = best supportive care; CS = company submission; NICE, National Institute for Health and Care Excellence; CS, company submission; SE = standard error; TA = technology appraisal; T/T = trifluridine/tipiracil

In sensitivity analyses the utilities from the CORRECT study and the TA176 were used as health state utility values.

Disutilities for AEs were not incorporated in the model. This is justified in the CS by stating a lack of evidence to estimate disutilities, and by the argument that small changes in health-related quality of life attributable to AEs are already incorporated in the chosen estimates for the health state utilities.

ERG comment: The ERG comments regarding health-related quality of life focus on: the estimation of health state utilities, and not incorporating the impact of adverse events on health-related quality of life in the analysis.

Health state utilities
The ERG has doubts whether the CS for TA176[32] is an appropriate source for health state utilities. The health state utility used for pre-progression (0.73) taken from the TA176 CS report was derived with the HUI3 instrument from the study of Mittmann et al.[38], as became apparent in the Merck Serono response on the ERG's clarification questions[39]. This study by Mittmann et al. was excluded by the company from their systematic review because the method is not in line with the NICE reference case. Moreover, the 0.73 value was mentioned in the TA176 CS report, but as described in the ID794 assessment report[39], another value (0.77 from Bennett et al.[40]) was used in the model. The 0.68 value for post-progression was determined in a population of patients with chemo refractory wild type KRAS metastatic colorectal cancer using EQ-5D and a Quality-Adjusted Time Without Symptoms or Toxicity (Q-TWIST) approach and taken from a poster by Wang et al.[41], The ERG was unable to access the poster but the online abstract does not mention any utility values. Another publication by the same authors (and the same year) does not mention a utility value of 0.68; instead values of 0.63 (panitumumab) and 0.64 (best supportive care) are mentioned for patients with relapse.[42]

The ERG asked the company to clarify why the base case model inputs for health state utilities are based on an average of utilities from the CORRECT study[30] and the TA176 CS report[32]. The company answered that TA176 was selected as *"an appropriate source for an upper bound of health state*

utilities, given that the utility used for patients in pre-progression was taken from patients on second-line treatment".[9] The lower bound estimate was taken from the CORRECT study, because the toxicity profile of regorafenib *"may be deemed worse than the 'acceptable toxicity profile' of trifluridine/tipiracil given the increased incidence of Grade ≥3 hypertension and hand-foot syndrome associated with regorafenib treatment"*.[9]The ERG thinks this latter argument is incorrect because the health state utilities in the BSC group were very similar to the utilities in the regorafenib group (0.74 and 0.73 pre-progression and 0.59 and 0.59 post-progression, respectively). Moreover, the quoted pre-progression utilities were determined at baseline.[30]

The ERG also asked the company to justify why other NICE appraisals that may contain relevant information (e.g. TA118[43], TA212[44], TA307[45] and ID794[39, 46, 47]) were not used. The company responded that utility values in TA307 were commercial in confidence, and that in TA212 the same values as in TA176 were used. The company considered the utility values from TA118 and ID794 for pre-progression inappropriate, as these values are higher than the values in TA176.[9] The ERG agree that the utilities used in TA118 are less relevant, but for other reasons than stated by the company: non NICE reference methods were used (direct time trade-off [48] and Q-TWIST[49]), and utilities were obtained in an adjuvant population. The ERG thinks that in TA176 and ID794 potentially relevant information can be found.

In summary, according to the ERG, the arguments to estimate the health state utilities based on an average of the utilities mentioned in the CS report of TA176 and the CORRECT trial are incorrect. Therefore, the ERG prepared an overview of health state utilities used or presented in the above-mentioned appraisals, as well as more recent or other publications from the authors or studies included in these appraisals (CS or ERG report), see Table 5.11. According to the ERG there is paucity of robust evidence on health related quality of life in metastatic colorectal cancer, especially beyond first line. In this light the omission to collect health related quality of life information in the phase II trial and the RECOURSE study is particularly problematic. When disregarding the studies not using the NICE reference case methodology[38, 41, 42], the utilities for pre progression range from 0.68[50] for chemotherapy refractory patients to 0.77[40] for second line. The post-progression health state utilities range from 0.59[30] from the CORRECT study to 0.66[51] or 0.64[52] for a Finnish end stage or palliative population, respectively. According to the ERG, the baseline utilities from the CORRECT study are the most plausible estimates for pre-progression and the post-progression utilities because it is the only study identified by the ERG in which utilities were measured using the EQ-5D in a population that resembles the population in this appraisal (second to fourth line population with 74% ≥ third line). Therefore the ERG included utility values from the CORRECT study in its base case.

Table 5.11: Overview of utility values from the literature

Source	Population of metastatic colorectal cancer	UK	Instrument	Pre progression			Post progression		
				Mean	Mean	SD (N)			SD (N)
Grothey 2013[30] (CORRECT) this submission	26% 1st / 2nd line 26% 3rd line 48% 4th line	Worldwide including UK	EQ-5D UK tariff	Regorafenib* Placebo*	0.73 0.74	0.25 (500) 0.27 (253)	Regorafinib Placebo	0.59 0.59	0.31 (500) 0.34 (253)
Bennett 2011[40] (NCT0339183) TA176 model; ID794	2nd line	Worldwide including UK	EQ-5D UK tariff	PAN* FOLFIRI*	0.77 0.76	0.23 (263) 0.25 (267)			
Wang 2011[42] (NCT00113763) TA176, ID794	Chemo refractory wild-type KRAS	Worldwide including UK	EQ-5D UK tariff & Q-TWIST	No toxicity PAN PAN No toxicity BSC Toxicity PAN Toxicity BSC	0.77 0.66 0.60 0.44	NR (104) NR (103) NR (37) NR (13)	PAN BSC	0.63 0.64	NR (68) NR (63)
Farkkila 2013[52]	All lines	Finland	EQ-5D UK tariff	Non palliative	0.82	0.20 (108)	Palliative	0.64	0.31 (41)
Farkkila 2014[51]	End stage§	Finland	EQ-5D UK tariff	Mean 0.66, SD 0.30, N 57					
Stein 2014[53]	All lines, no brain metastasis	UK, Netherlands	EQ-5D UK tariff		0.74	0.23 (42)		0.73	0.29 (32)
Odom 2011[50] (NCT0339183)	Chemo refractory	Worldwide including UK	EQ-5D UK tariff	PAN* BSC*	0.72 0.68	0.24 (188) 0.25 (175)			
Koukakis 2016[54] (NCT00113763)	3rd / 4th line RAS wild type			PAN# BSC#	0.78 0.73	NR (62) NR (60)			

* Baseline values; § no chemo- or radiotherapy or within 6 months before death; [3]Median values instead of mean
BSC = best supportive care; EQ-5D = European Quality of Life-5 Dimensions; FOLFIRI = chemotherapy combining folinic acid, fluorouracil and irinotecan; KRAS = Kirsten rat sarcoma viral oncogene homolog; NR = not reported; PAN = panitumumab; SD = standard deviation; TA = technology appraisal; UK = United Kingdom

Impact of adverse events on health related quality of life

The ERG noted that the impact of AEs on health-related quality of life was not incorporated in the analyses, apart from the difference between the pre-progression health state utility values in the base case. Patients receiving T/T had more grade >2 adverse events in general, and for instance more neutropenia, leukopenia, anaemia, and gastro intestinal events than placebo in the RECOURSE trial, see Tables 44 and 45 of the CS.[1] Therefore, the ERG questions the justification that the 0.01 utility difference between the utility scores 0.73 (pre-progression on treatment) and 0.74 (pre-progression BSC) captures the difference in AEs impact on quality of life. Therefore, the ERG asked the company to incorporate the impact of adverse events on health-related quality of life in the economic analysis.[20] The company responded that it was not feasible to explicitly model the impact of adverse events on health-related quality of life because they did not have a detailed insight into the two sources they used to estimate utilities (CORRECT study[30] and TA176[32]). Moreover, the company argued that the utilities they used already incorporated the impact of adverse events.[9]According to the ERG, these arguments are incorrect, for the following reasons:

1. Regarding the first argument (not feasible to explicitly model the impact of adverse events), the incidence of adverse events is known from the phase II study and RECOURSE, and for instance from the recent NICE diagnostic assessment report by Freeman et al.[55], a review on the impact of common adverse events on health-related quality of life in colorectal cancer is available. This information was also used in the ID794 assessment report.[39]
2. Regarding the second argument (already incorporated the impact of adverse events), as the 0.73 and 0.74 utility values used are the baseline utility values measured in the CORRECT trial, any difference between those values is probably due to randomness and cannot be due to differential impact of treatment related adverse events.

The ERG explored the estimation of a disutility for adverse events based on the RECOURSE occurrence of adverse events ≥ grade 3 as reported in Table 5.9. The ERG based the disutilities for adverse events on the ones reported in Freeman et al.[55] and the ID794 assessment report[39] and, similar to these two appraisals, assumed a disutility duration of one week. Disutilities for thrombocytopenia, nausea, decreased appetite, hand-foot syndrome and vomiting were not reported in these sources and assumed to be the same as for fatigue. For fever, febrile neutropenia and cardiac ischemia the same disutility as for neutropenia was assumed. This resulted in a disutility of 0.075 for T/T and 0.018 for BSC, calculated to one week the incremental disutility is -0.001. As these estimates do not include all AEs and heavily rely on assumptions, in the base case the ERG used a larger disutility for AEs of 0.01 per cycle for patients receiving T/T (similar to the company's base case, i.e. 0.74 (on T/T) - 0.73 (on BSC), but based on alternative justifications).

5.2.9 Resources and costs

The company based its resource use and costs on the company submission of a recent NICE technology appraisal in mCRC (ID794).[28] Additional resource use was based on published literature and expert opinion.

Drug costs

T/T is available in 15 mg or 20 mg tablets, in pack sizes of 20 and 60. Unit costs of these pack sizes were presented in at the list price (Table 5.12). Dosage was based on BSA, where pack size could cater for all doses (Table 62 of the CS).

Table 5.12: Unit costs of treatment
(Based on Table 61 of the CS[1])

Treatment	Unit dose (mg)	Pack size	Unit cost	Source
Trifluridine/tipiracil	15	20	£500	Servier
		60	£1,500	
	20	20	£667	
		60	£2,000	
CS = company submission; mg = milligram				

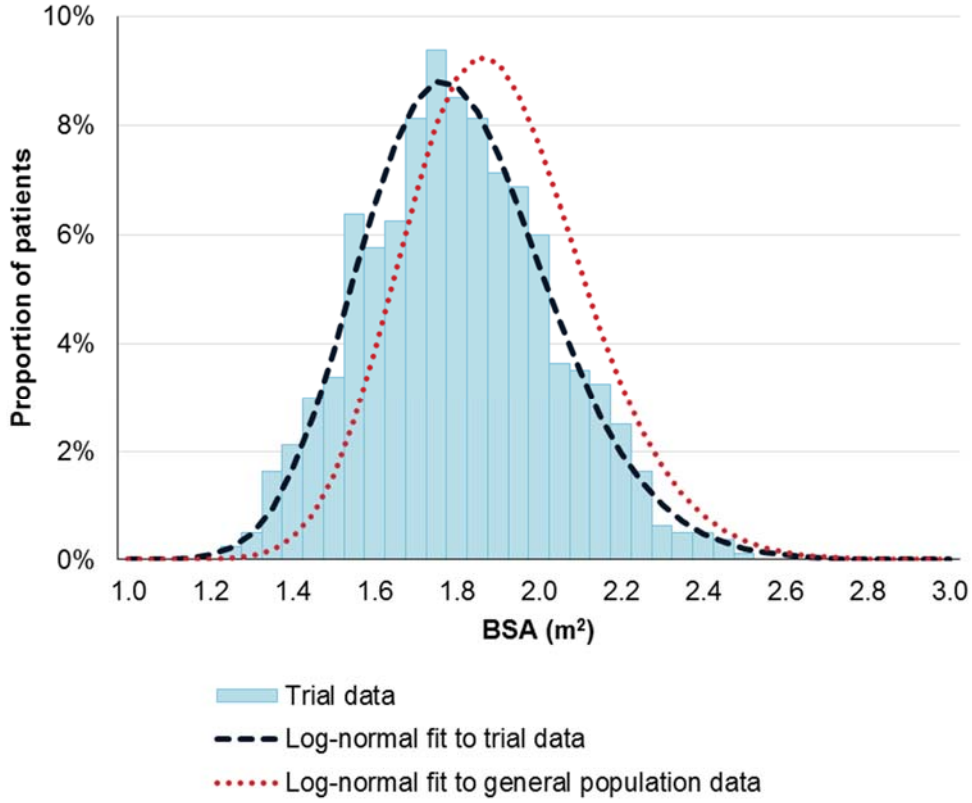
The RECOURSE trial data were used to calculate the BSA distribution in the population. In order to calculate T/T dosing, patients were categorised into 10 groups, each group having an assigned dosage. The distribution of BSA used in the model base case was derived from a log-normal fit to the distribution of BSA in the RECOURSE trial, which the company reports was done *"to produce a more realistic estimate of the distribution of patient BSA"*. The CS reports that *"clinicians at the advisory board indicated that patients with mCRC would be expected to lose weight, given their disease status, and therefore agreed with the use of a lower estimate of BSA compared with the general population particularly at the line of treatment relevant to the decision problem"*.[13] Distributions of the BSA are presented in Table 5.13 and Figure 5.6.

Table 5.13: T/T based on BSA
(Based on Tables 55 and 62 of the CS[1])

BSA (m^2)	Distribution of BSA				
	Dosage (mg; 2x daily)	Cost per cycle (list price)	RECOURSE data	Log-normal fit to RECOURSE data	Log-normal fit to general population data*
< 1.07	35	£1,167	0.00%	0.00%	0.00%
1.07 - 1.22	40	£1,333	0.13%	0.19%	0.01%
1.23 - 1.37	45	£1,500	2.38%	2.15%	0.39%
1.38 - 1.52	50	£1,667	9.25%	9.55%	3.58%
1.53 - 1.68	55	£1,833	19.88%	22.47%	14.70%
1.69 - 1.83	60	£2,000	27.00%	25.97%	25.26%
1.84 - 1.98	65	£2,167	21.38%	20.57%	26.14%
1.99 - 2.14	70	£2,333	12.63%	12.13%	18.35%
2.15 - 2.29	75	£2,500	5.75%	4.72%	7.82%
≥2.30	80	£2,667	1.63%	2.25%	3.75%
Weighted average cost per cycle (list price)			[redacted]	[redacted]	[redacted]

* General population data applies to Health Survey for England data sourced by Porter et al. 2015.[56]
BSA = body surface area; CS = company submission; mg = milligram; T/T = trifluridine/tipiracil

Figure 5.6: Distribution of body surface area
(Based on Figure 33 of the CS[1])



BSA = body surface area: CS = company submission

The distribution of patients' BSA was used to calculate the weighted average cost per patient in the first treatment cycle. From cycle 2 onwards, this price was then adjusted according to the proportion of patients who experienced a dose reduction in the RECOURSE trial.[2] To all prices, the confidential discount of [redacted] was then applied.

Dose reduction

In the RECOURSE trial, 53 (9.9%) patients receiving T/T treatment had a single dose reduction, 18 (3.4%) had two reductions, and two (0.4%) had three reductions.[2] To account for these dose reductions, the proportion of patients receiving each dose for a given treatment cycle was adjusted in the subsequent treatment cycles. In the first cycle, all patients were expected to receive the T/T dose based on BSA in the first treatment cycle. Subsequently, patients from each dosing group with a dose reduction were moved to the dosing group (see BSA categories in Table 5.13) below for the next treatment cycle. This means that 9.9%, 3.4% and 0.4% of the patients receiving T/T were moved to the dosing group below their current group in the second, third and fourth cycle respectively. After the fourth cycle, it was assumed that all patients remained on their current dose until discontinuation of treatment. The proportion of patients receiving each dose of T/T per cycle is (based on the log-normal fit to RECOURSE data) shown in Table 5.14 and presented in Figure 34 of the CS.[1]

Table 5.14: Proportion of patients receiving T/T
(Based on Table 56 of the CS[1])

BSA (m^2)	Dosage (mg; 2x daily)	Cycle 1	Cycle 2	Cycle 3	Cycle 4+
< 1.07	35	0.00%	0.02%	0.04%	0.04%
1.07 - 1.22	40	0.19%	0.38%	0.47%	0.48%
1.23 - 1.37	45	2.15%	2.88%	3.15%	3.18%
1.38 - 1.52	50	9.55%	10.83%	11.24%	11.28%
1.53 - 1.68	55	22.47%	22.82%	22.91%	22.91%
1.69 - 1.83	60	25.97%	25.44%	25.25%	25.22%
1.84 - 1.98	65	20.57%	19.73%	19.45%	19.42%
1.99 - 2.14	70	12.13%	11.40%	11.16%	11.14%
2.15 - 2.29	75	4.72%	4.47%	4.39%	4.38%
≥2.30	80	2.25%	2.03%	1.96%	1.95%
Weighted average cost per cycle (list price)		[redacted]	[redacted]	[redacted]	[redacted]

BSA = body surface area; CS = company submission; mg = milligram

Treatment delay
The incorporation of treatment delays into the model allowed additional medical resource use for patients who experience a delay in treatment. As the additional medical resource use applies to all patients, regardless of treatment received, the average delay in treatment initiation was calculated for both T/T and BSC patients (Table 5.15). This resulted in an applied cycle length of 30.72 days for T/T and 29.40 days for BSC.

Table 5.15: Average delay in treatment initiation
(Based on Table 54 of the CS[1])

	Trifluridine/tipiracil	BSC
Total number of cycles	1828	598
Total number of delayed cycles	752	228
Average delay in treatment initiation for delayed patients	6.61 days	3.67 days
Average delay in treatment initiation for all patients (A)	2.72 days	1.40 days
Protocol treatment cycle length (B)	28 days	28 days
Applied treatment cycle length in model (A+B)	30.72 days	29.40 days

BSC = best supportive care; CS = company submission

Time on treatment
Treatment with T/T is continued until disease progression, clinical progression, the development of severe AEs, withdrawal from the study, death, or a decision by the treating physician that discontinuation would be in the patient's best interest. Not all of these factors were included in the estimation of time on treatment due to lack of available data. The company expected their estimated time on treatment to be an overestimation of the observed time on treatment and hence used PFS as a proxy for time on treatment.

Medical resource use
The company identified medical resource use items following consultation with clinical experts, due to a lack of published literature on the medical resource use of patients in this setting. An overview of

medical resource use costs can be found in Table 5.16. Medical resource use cost per health state were £203 for T/T and £182 for BSC in pre-progression, and £193 in post-progression in both arms. All other resource costs (including social care for patients toward the end of life) were assumed to be captured in the end-of-life care cost applied for all patients upon death.

Table 5.16: Summary of medical resource use
(Based on Tables 64 and 65 of the CS[1])

MRU item	Occurrence per treatment cycle†			Unit cost (£)	Reference
	Pre-P		PP		
	T/T	BSC			
Oral chemotherapy day case attendance*	1			192.32	NHS reference costs 2014-15: Day case and Regular Day/Night; SB11Z; Deliver exclusively oral chemotherapy
Medical oncologist outpatient consultation		1		170.85	NHS reference costs 2014-15: 370; Medical Oncology - Outpatient, consultant led
GP home consultation			0.25	96.92	PSSRU 2013: GP - per out of surgery visit lasting 23 minutes (without qualifications) - inflated using PSSRU 2015 inflation indices
Community nurse specialist visit			1	44.00	PSSRU 2015: Nurse Specialist (Community) Cost per hour (without qualifications) - 10.4 (contact assumed to last 1 hour)
Health home visitor	0.25	0.25	1	44.00	PSSRU 2015: Health Visitor Cost per hour (without qualifications) - 10.3 (contact assumed to last 1 hour)
District nurse visit			1	44.00	PSSRU 2015: Health Visitor Cost per hour (without qualifications) - 10.1 (contact assumed to last 1 hour)
GP surgery visit			1	37.00	PSSRU 2015: GP consultation (Per patient contact lasting 11.7 minutes, without qualifications) - 10.2
Average MRU	£203	£182	£193		

* Patients who experience a delay in treatment initiation incur the cost of an additional oral chemotherapy day case attendance.
† MRU items are incurred according to an average unadjusted treatment cycle (i.e. 28 days). Adjustments for delays in treatment initiation are captured by the repeat chemotherapy day case attendance.
BSC = best supportive care; CS = company submission; GP = general practitioner; MRU = medical resource utilisation; NHS = National Health Service; PP = post-progression; Pre-P = pre-progression; PSSRU = Personal Social Services Research Unit; T/T = trifluridine/tipiracil

Post-progression treatment costs

Following treatment discontinuation in post-progression, 42% of the RECOURSE trial patients received non-study anti-tumour treatments.[2] The RECOURSE trial data was used to estimate the average cost of post-progression treatment per patient, which was £1,549 for T/T and £1,487 for BSC (Appendix 11 of the CS).[1] Clinical experts confirmed that prior treatment with T/T is not expected to have an effect on the choice of treatments available following progression at this line of therapy.

Therefore, the average cost per patient for all patients post-treatment was used in both arms of the model (£1,528). A sensitivity analysis was performed with different costs of post-progression treatment per patient of £1,549 for T/T and £1,487 for BSC (Table 69 of the CS).[1]

End of life

End of life care costs were taken from a modelling study by Round et al, which estimates the cost of caring for people at the end of life.[33] Costs for end of life from this source take into account health care (£4,854), social care (£1,489) and charity care (£470), and excludes the cost of informal care as per the NICE reference case.[17] The total end of life care cost of £6,910 was applied in the model as a lump sum upon death for both arms.

Adverse events

The company incorporated costs of adverse events if they were actively treated in the NHS, as verified with clinical and medical oncologists. The adverse events incorporated in the CS model are presented in Table 5.17. Incorporating these adverse events at their unit costs to the rates observed from the RECOURSE clinical trial yielded a cost of AEs of £923 for T/T and £426 for BSC (table 68 of the CS).[1] These costs are applied one time, at the start of the model.

Table 5.17: Adverse events included in the model

(Based on Table 67 of the CS[1])

Adverse event	Actively treated		Cost of treatment		Reference (see notes for sources)	
	All grades	Grade ≥3	Grade ≤2	Grade ≥3	Grade ≤2	Grade ≥3
Nausea		✓		£158.43		**a**
Vomiting	✓	✓	£158.43	£158.43	**a**	**a**
Decreased appetite		✓		£158.43		**a**
Fatigue		✓		£158.43		**a**
Diarrhoea	✓	✓	£158.43	£158.43	**a**	**a**
Abdominal pain		✓		£139.52		**b**
Fever	✓	✓	£158.43	£158.43	**a**	**a**
Asthenia		✓		£158.43		**a**
Febrile neutropenia	✓	✓	£2,583.98	£2,583.98	**c**	**c**
Stomatitis		✓		£158.43		**a**
Hand-foot syndrome		✓		£158.43		**a**
Cardiac ischaemia	✓	✓	£158.43	£158.43	**a**	**a**
Neutropenia		✓		£1,227.95		**d**
Leucopenia		✓		£158.43		**a**
Anaemia		✓		£799.00		**e**
Thrombocytopenia		✓		£643.48		**f**

Adverse event	Actively treated		Cost of treatment		Reference (see notes for sources)	
	All grades	Grade ≥3	Grade ≤2	Grade ≥3	Grade ≤2	Grade ≥3
References: a NHS Reference costs 14-15: Outpatient visit, general medicine[57]; b NHS Reference costs 14-15: Outpatient visit, pain management[57]; c NICE DSU report[58]; d NHS Reference costs 14-15: Average non-elective inpatient stay[57]; e PENTAG ERG Report for cetuximab[39]; f NHS Reference costs 14-15: Weighted cost of thrombocytopenia based on complications and comorbidities score.[57] CS = company submission; DSU = Decision Support Unit; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PenTAG = Peninsula Technology Assessment Group						

Table 5.18: Health states and associated costs per treatment cycle
(Based on Table 66 of the CS[1])

Health state	Items	Value		CS Reference
		T/T	BSC	
Pre-progression	Technology¥	[redacted]	£0	Table 63
	MRU*	£203	£182	Table 65
Progressed	Technology	£0		Table 63
	MRU	£193		Table 65
Non-health state costs applied as a lump sum	Adverse events†	£923	£426	Table 68
	End of life‡	£6,910		Section 5.5
	Post-progression treatmentΔ	£1,528		Table 69

* additional chemotherapy day case attendance applies for patients experiencing delays.
† applied for all patients in the first model cycle.
‡ applied upon death.
Δ applied upon progression.
¥ based on average BSA in RECOURSE of 1.78 m^2.
BSC = best supportive care; CS = company submission; MRU = medical resource utilisation; T/T = trifluridine/tipiracil

ERG comment: Following the NICE reference case[17], *"evidence should be presented to demonstrate that resource use and cost data have been identified systematically"*. Hence, a more systematic approach, including a review, would have been desirable to inform model parameters on resources use and costs. After a request in the clarification letter, the company explained that a review of NICE technology appraisals and the associated assessment reports in mCRC was undertaken and these data were presented at advisory boards and face to face meetings. However, a review with broader search objectives and strategy (e.g. including other interventions than T/T only) would potentially identify cost effectiveness studies relevant for informing the model produced by the company (e.g. model structure, health state utility, resource use and BSC parameters). For instance, the studies by Goldstein et al.,[59] Starling et al.,[60] Shiroiwa et al.[61] and Hoyle et al.[62] which were identified by the company but eventually excluded (see Table 2 in Appendix 6 of the CS[1]), might have been relevant for informing the model. In particular regarding resource use and costs.

The ERG has the following specific issues with the modelling of resources use and costs:

- estimation of BSA to calculate drug costs,
- estimation of dose reductions,
- estimation of treatment delay,
- estimation of time on treatment,
- assuming equal post-progression costs for T/T and BSC,
- estimation of medical resource use,
- calculation of end-of-life costs,
- calculation of adverse event costs.

These issues are discussed below and addressed in the ERG's additional analyses.

Estimation of BSA to calculate drug costs
The CS reported that advisory board clinicians agreed with the use of a lower estimate of BSA (following from the log-normal distribution fitted to the RECOURSE data) as compared with the general UK population since mCRC patients would be expected to lose weight. The ERG, however, notes that the population of the RECOURSE trial includes 33% of patients from Japan, which may be expected to have a lower BSA than the UK population.[13]

The company reports that the non-parameterised distribution of BSA from RECOURSE was also explored, as well as the application of a log-normal fit of BSA from general population data, which were explored as scenario analyses. The results of these scenario analyses were initially not reported, but were provided after requesting this in the clarification letter.[9] According to the ERG, the non-parametrised distribution of BSA from RECOURSE is a reasonable estimate of BSA to calculate drug costs. As this most likely results in an underestimation of T/T costs, the BSA based on the UK population (which most likely results in an overestimation of T/T costs) is considered in an exploratory sensitivity analysis.

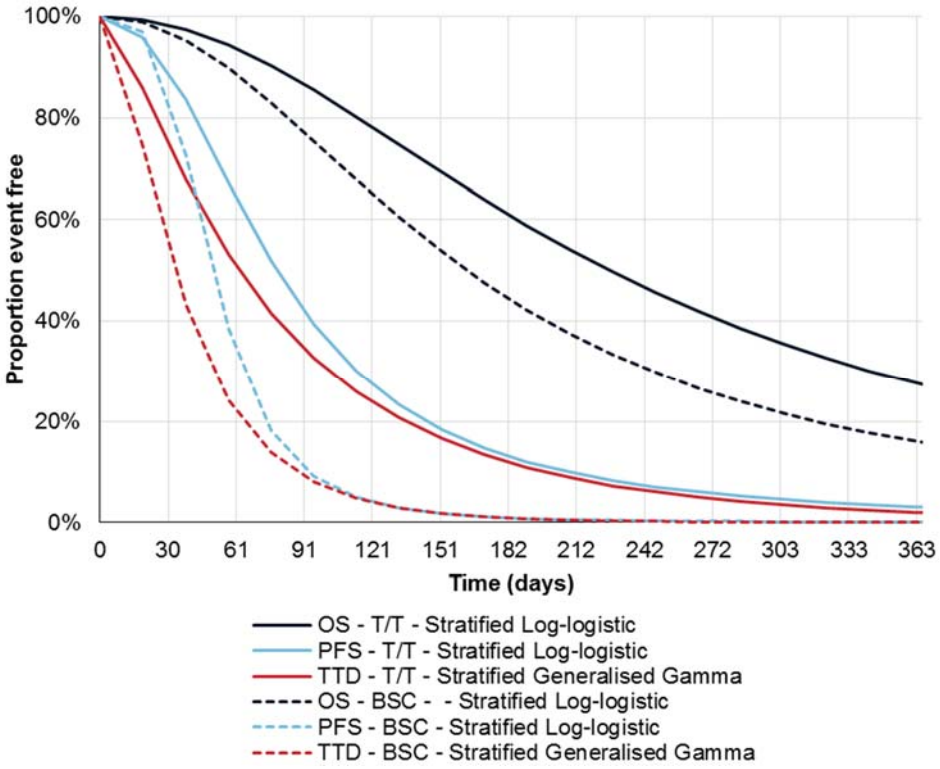
Estimation of dose reductions
Dose reductions for T/T were estimated based on the RECOURSE trial. Although the assumption that in case of a dose reduction patients were moved to the dosing group below their current group can be questioned, the impact of the assumption is probably small (informally explored by the ERG).

Estimation of treatment delay
The company applied a cycle length of 30.72 days for T/T and 29.40 days for BSC in the model to account for treatment delay, as observed in RECOURSE. This leads to slightly more medical resource use in BSC over the time horizon of the model. The estimate of 29.40 days was calculated based on BSC treatment (see company's response on clarification question B8[9]), and is thus not representative for clinical practice. In its base case the ERG applied the same cycle length for T/T and BSC.

Estimation of time on treatment
The ERG asked the company to clarify why PFS was used to approximate time on treatment, while it seems that empirical data was available to estimate this. The company responded: *"...time on treatment was not explicitly reported in either of the clinical trials from which efficacy data were derived, (...) but data are available regarding the start and end time of treatment for patients within both studies, from which an estimate of TTD (time to treatment discontinuation) may be derived."*[9]

The provided additional analyses based on the assumption that all remaining patients experience the event of treatment discontinuation at the end time of treatment (i.e. no patients have been censored at this time, due to available data). The company tested different survival curves to represent time to treatment discontinuation (TTD). Since the stratified generalised gamma provided the best AIC estimate, it was chosen to represent TTD in the cost-effectiveness model provided in the response to the ERG clarification letter (Figure 5.7).[9]

Figure 5.7: Estimation of OS, PFS and TTD used in the economic model
(Based on Figure 9 of the response to the request for clarification[9])



BSC = best supportive care; OS = overall survival; PFS = progression free survival; T/T = trifluridine/tipiracil; TTD = time to treatment discontinuation

Given that not all relevant factors were included in the estimation of time on treatment (as stated by the company, see above) and the assumption that all patients experience the event of treatment discontinuation at the end time of treatment (i.e. no patients have been censored at this time, due to available data), the ERG regards the company's approach to use PFS as proxy as reasonable. Hence, this was used in the ERG base case. The ERG used time on treatment in an explorative sensitivity analysis.

Assuming equal post-progression costs for T/T and BSC
The ERG asked the company to clarify why the cost of post-progression treatment was assumed to be the same for both groups of patients. The company stated that *"clinical expert opinion at the advisory board held in January 2016 suggested that the costs would be approximately equal following progression given that patients would be expected to be eligible for the same treatment following progression and that patient prognosis following progression at this late stage of disease is similarly poor across treatment groups. Analysis of the data demonstrated that costs between trifluridine/tipiracil versus BSC patients were approximately equal (£1,549 versus £1,487)".*[9] As

empirical data are available for both treatments, the ERG would prefer to use the empirical estimates instead of assuming equal costs for both treatments. Hence, treatment specific post-progression costs were incorporated in the ERG base case.

Estimation of medical resource use
The estimation of medical resource use was based on expert opinion, while empirical evidence could have been collected in the phase II trial and RECOURSE. Given the complete reliance on expert opinion for resource use, the ERG used an alternative source in an explorative sensitivity analysis. Accordingly, it was assumed that there were no medical oncologist outpatient consults for BSC and costs of computed tomography (CT) scans were included for T/T (assuming one scan per three cycles costing £112 each).[62]

The ERG noted a small error in the costs of a medical oncologist outpatient consultation (the ERG could not replicate the cost estimate reported in the CS). This was recalculated by the ERG using the weighted average of WF01A, WF01B, WF01C and WF01D from NHS reference costs 2014-15: £168.40, instead of £170.85.[57] This was corrected in the ERG's analyses.

Calculation of end-of life costs
Considering the end-of-life costs calculated based on Round et al.[33], the ERG notes that charity care costs (£470), consisting of hospice inpatient days and hospice outpatient visits, neither falls within NHS nor PSS cost. The paper by Round et al. reports that *"charities also provide care through other means, often paid for in part by local authorities and the health service – these costs will have been captured where possible in the social care element of spending"* (p.902). Hence, only the reported health care (NHS, £4,854) and social care (PSS, £1,489) costs in this study are relevant. These costs are included as end-of-life costs in the ERG base case.

Calculation of adverse event costs
The ERG noted that several adverse events in Table 57 in the CS (an overview of adverse events observed in the RECOURSE trial) are missing from Table 67 (an overview of adverse events for which costs are incorporated in the model). The ERG asked the company to include all adverse events reported in Table 57 in an updated version of Table 67 and to include these adverse events in the model analyses, which the company did in a sensitivity analysis.

Table 5.19: Adverse events included in the model
(Based on Table 67 of the CS[1] and Table 5 of the response to request for clarification[9])

Adverse event	Actively treated		Cost of treatment		Reference (see notes for sources)	
	All grades	Grade ≥3	Grade ≤2	Grade ≥3	Grade ≤2	Grade ≥3
Nausea		✓		£158.43		**a**
Vomiting	✓	✓	£158.43	£158.43	**a**	**a**
Decreased appetite		✓		£158.43		**a**
Fatigue		✓		£158.43		**a**
Diarrhoea	✓	✓	£158.43	£158.43	**a**	**a**
Abdominal pain		✓		£139.52		**b**
Fever	✓	✓	£158.43	£158.43	**a**	**a**
Asthenia		✓		£158.43		**a**

Adverse event	Actively treated		Cost of treatment		Reference (see notes for sources)	
	All grades	Grade ≥3	Grade ≤2	Grade ≥3	Grade ≤2	Grade ≥3
Febrile neutropenia	✓	✓	£2,583.98	£2,583.98	**c**	**c**
Stomatitis		✓		£158.43		**a**
Hand-foot syndrome		✓		£158.43		**a**
Cardiac ischaemia	✓	✓	£158.43	£158.43	**a**	**a**
Neutropenia		✓		£1,227.95		**d**
Leucopenia		✓		£158.43		**a**
Anaemia		✓		£799.00		**e**
Thrombocytopenia		✓		£643.48		**f**
Increase in alanine aminotransferase level		✓		£158.43		**a**
Increase in aspartate aminotransferase level		✓		£158.43		**a**
Increase in total bilirubin		✓		£158.43		**a**
Increase alkaline phosphatase level		✓		£158.43		**a**
Increase in creatine level		✓		£158.43		**a**

References: a NHS Reference costs 14-15: Outpatient visit, general medicine[57]; b NHS Reference costs 14-15: Outpatient visit, pain management[57]; c NICE DSU report[58]; d NHS Reference costs 14-15: Average non-elective inpatient stay[57]; e PENTAG ERG Report for cetuximab[39]; f NHS Reference costs 14-15: Weighted cost of thrombocytopenia based on complications and comorbidities score.[57]

CS = company submission; DSU = Decision Support Unit; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PenTAG = Peninsula Technology Assessment Group

The ERG also noted that costs for adverse events were almost all estimated to equal a general medicine outpatient visit. The ERG thinks that this assumption is unrealistic and used alternative inputs (see Table 5.20), retrieved from the NICE appraisal of bortezomib TA370.[63, 64]

Table 5.20: Alternative inputs for the costs of adverse events

Adverse event	ERG estimate	Source
Neutropenia Grade 3-5*	£167.28	NHS reference costs 2013-2014; HRG code: XD25Z
Thrombocytopenia Grade 3*	£570.97	NHS reference costs 2013-2014; NEI_S; weighted average of HRG codes: SA12G, H, J, and K
Thrombocytopenia Grade 4-5*	£2,191.65	NHS reference costs 2013-2014; NEI_L; weighted average of HRG codes: SA12G, H, J, and K
Anaemia Grade 3*	£516.66	NHS reference costs 2013-2014; NEI_S; weighted average of HRG codes: SA04G, H, J, K and L
Anaemia Grade 4-5*	£1,853.10	NHS reference costs 2013-2014; NEI_L; weighted average of HRG codes: SA04G, H, J, K and L
Leukopenia Grade 3-5*	£167.28	Costs assumed to be equal to neutropenia

Adverse event	ERG estimate	Source
Fatigue Grade 3-5*	£12.00	NICE ERG report abiraterone (TA259), table 24, p. 64.
Diarrhoea Grade 3*	£572.80	NHS reference costs 2013-2014; NEI_S; HRG code: PF26B
Febrile neutropenia Grade 3#	£999.20	NHS reference costs 2013-2014; NEI-S; weighted average of PM45A, B, C and D; Febrile Neutropenia with Malignancy; Short Stay
Febrile neutropenia Grade 4/5#	£5,379.59	NHS reference costs 2013-2014; NEI_L; Weighted average of PM45A, B, C and D; Febrile Neutropenia with Malignancy; Long stay
Diarrhoea Grade 4/5#	£579.21	NHS reference costs 2013-2014; NEI_S; Weighted average of PF26A&B; Other Gastrointestinal Disorders with CC Score 1+; Short Stay

* Retrieved from table 6.21 of assessment report TA370[63]; # Retrieved from table 61 CS TA370 [64]; TA259 [65]
CS = company submission; ERG = Evidence Review Group; NHS = National Health Service; TA = technology appraisal

5.2.10 Cost effectiveness results

At the list price, T/T is associated with an incremental cost effectiveness ratio (ICER) of [redacted] per additional QALY gained (see Table 5.21). At the commercial in confidence patient access scheme (PAS) price, T/T is associated with an ICER of £44,032 per additional QALY gained.

Table 5.21: Base-case results without and with patient access scheme
(Based on Tables 72 and 73 of the CS[1])

	Total			Incremental			
Technologies	**costs (£)**	**QALYs**	**LYG**	**costs (£)**	**QALYs**	**LYG**	**CER (£) (QALYs)**
BSC	10,286	0.42	0.66				
T/T without PAS	[redacted]	0.59	0.92	[redacted]	0.17	0.27	[redacted]
T/T with PAS	16,386	0.59	0.92	7,574	0.17	0.27	44,032

BSC = best supportive care; CER = cost-effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALYs = quality-adjusted life years; T/T = trifluridine/tipiracil

The company also provided disaggregated model results: QALYs, life years (LYs) and costs per health state (Tables 5.22 and 5.23). The cost difference of £7,574 is predominantly accrued in the pre-progression state.

Table 5.22: Summary of QALY and life year gain by health state
(Based on Tables 75 and 76 of the CS[1])

Health state	QALY T/T	QALY BSC	Increment	Absolute increment	% absolute increment
Pre-progression	0.22	0.12	0.10	0.10	61%
Post-progression	0.37	0.30	0.07	0.07	39%
Total	0.59	0.42	0.17	0.17	100%
Health state	**LY T/T**	**LY BSC**	**Increment**	**Absolute increment**	**% absolute increment**
Pre-progression	0.30	0.16	0.15	0.15	55%
Post-progression	0.62	0.50	0.12	0.12	45%
Total	0.92	0.66	0.27	0.27	100%

BSC = best supportive care; LY = life year; QALY = quality-adjusted life year; T/T = trifluridine/tipiracil

Table 5.23: Summary of costs by health state and category – PAS price
(Based on Table 78 of the CS[1])

Health state	Costs T/T (£)	Costs BSC (£)	Increment (£)	Absolute increment (£)	% absolute increment
Pre-progression	**8,325**	**869**	**7,456**	**7,456**	**100%**
Drug costs	6,550	0	6,550	6,550	88%
Monitoring	852	443	409	409	5%
Adverse events	923	426	497	497	7%
Post-progression	**2,860**	**2,672**	**188**	**188**	**100%**
Drug costs	1,511	1,519	-8	8	4%
Monitoring	1,348	1,152	196	196	96%
Total	**17,859**	**10,286**	**7,574**	**7,574**	**100%**
Drug costs	8,062	1,519	6,542	6,542	85%
Monitoring	2,200	1,595	605	605	8%
Adverse events	923	426	497	497	6%
End of life*	6,675	6,745	-71	71	1%

* End-of-life care costs apply for all patients irrespective of progression status.
BSC = best supportive care; CS = company submission; PAS = Patients Access Scheme; T/T = trifluridine/tipiracil

ERG comment: In response to questions posed by the ERG, the company carried out updated analyses. These analyses differ from the original base case with respect to the use of pooled estimates for adverse events rates, time on treatment and dose reductions instead of RECOURSE data only, and the incorporation of costs for adverse events that were previously missing. Moreover, the company corrected an error in the number of AE for BSC. However an error in AE for T/T was induced (both errors were corrected in the ERG base case). In the updated analysis T/T is associated with an ICER of [redacted] per additional QALY gained. At the commercial in confidence PAS price, T/T is associated with an ICER of £42,674 per additional QALY gained (deterministic results, Table 5.24).

Table 5.24: Updated results with and without patient access scheme ([redacted]) – deterministic

Technologies	Total			Incremental			
	Costs (£)	QALYs	LYG	Costs (£)	QALYs	LYG	ICER (£)
BSC	10,116	0.42	0.66				
T/T without PAS	[redacted]	0.59	0.92	[redacted]	0.17	0.27	[redacted]
T/T with PAS	17,456	0.59	0.92	7,340	0.17	0.27	42,674

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; T/T = trifluridine/tipiracil

The ERG noted that only the deterministic results were provided, while according to the NICE Methods Guide[17] probabilistic methods provide the best estimates of mean costs and outcomes in non-linear decision models. In response to the ERG's clarification question the company provided the probabilistic results for all analyses (base case outcomes and sensitivity analyses). In the updated probabilistic analysis T/T is associated with an ICER of [redacted] per additional QALY gained (Table 5.25). At the commercial in confidence PAS price, T/T is associated with an ICER of £44,057 per additional QALY gained (probabilistic results).

Table 5.25: Updated results with and without patient access scheme ([redacted]) – probabilistic

Technologies	Total			Incremental			
	Costs (£)	QALYs	LYG	Costs (£)	QALYs	LYG	ICER (£)
BSC	10,205	0.42	0.66				
T/T without PAS	[redacted]	0.59	0.92	[redacted]	0.17	0.26	[redacted]
T/T with PAS	17,424	0.59	0.92	7,219	0.17	0.26	44,057

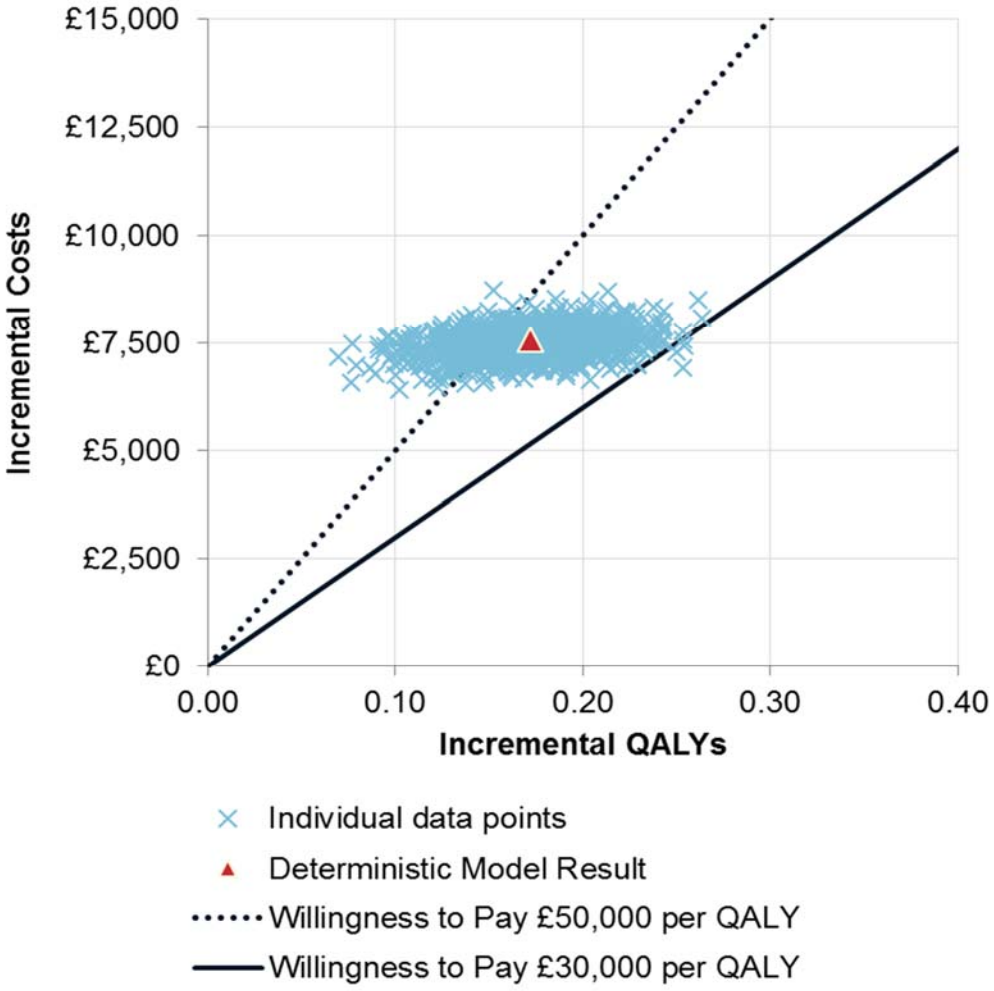
BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; T/T = trifluridine/tipiracil

5.2.11 Sensitivity analyses

Probabilistic sensitivity analysis

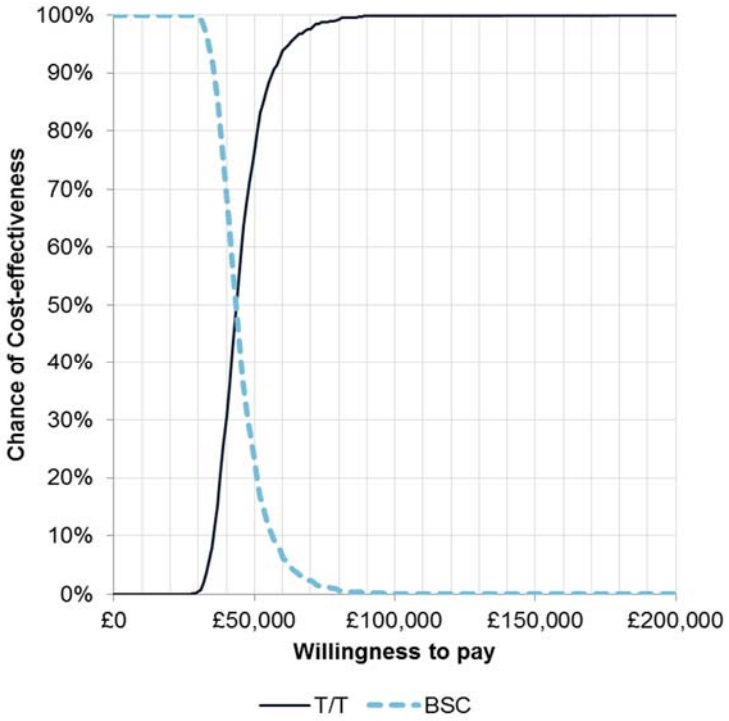
The company carried out a probabilistic sensitivity analysis (PSA) with 1,000 draws and used these simulation results to inform PSA scatterplots and cost effectiveness acceptability curves (CEAC). It is stated that *"the PSA scatterplots demonstrate an even spread of points in regards to the deterministic model result, with the majority of uncertainty shown in the estimation of the QALY gain as expected. This is likely driven by the variability in the utility values chosen, due to the lack of information regarding the uncertainty in these estimates"*.[1] The CEACs show that at the list price, the probabilities of T/T being the most cost effective treatment are 0% and 36% for willingness-to-pay (WTP) thresholds of £30,000 and £50,000, respectively (Figures 5.8 and 5.9). At the PAS price, the probabilities of T/T being the most cost effective treatment are 0% and 77% for WTP thresholds of £30,000 and £50,000, respectively.

Figure 5.8: Probabilistic sensitivity analysis scatter plot – PAS price
(Based on Figure 38 of the CS[1])



CS = company submission; PAS = patient access scheme; QALY = quality-adjusted life year

Figure 5.9: Cost effectiveness acceptability curve – PAS price
(Based on Figure 40 of the CS[1])



BSC = best supportive care; CS = company submission; PAS = patient access scheme; T/T = trifluridine/tipiracil

ERG comment: In the PSA, the minimum and maximum of multiple parameters was assumed to be +/- 20% of the mean, and a triangular distribution was used, also when information seemed to be available to estimate variance (see Table 70 of the CS[1]). This was the case for parameters estimated based on RECOURSE data (treatment delay, dosing, resource use), or expert opinion (resource use). The ERG asked the company to use the empirical data (either from RECOURSE or expert opinions) if possible to estimate the variance for input parameters (e.g. for treatment delay per patient per cycle and post-progression costs) and provide the estimated distributions.[20] In response, the company provided standard errors to estimate a distribution for post-progression costs in the PSA based on empirical data, but not for treatment delay (or other model inputs) due to a time constraint.[9] It turned out that the bounds for post-progression costs produced by the empirical data were smaller than the bounds produced using +/- 20% of the mean. The company provided an adjusted model with a setting to use the empirically derived distribution, but did not use this setting in the updated results.

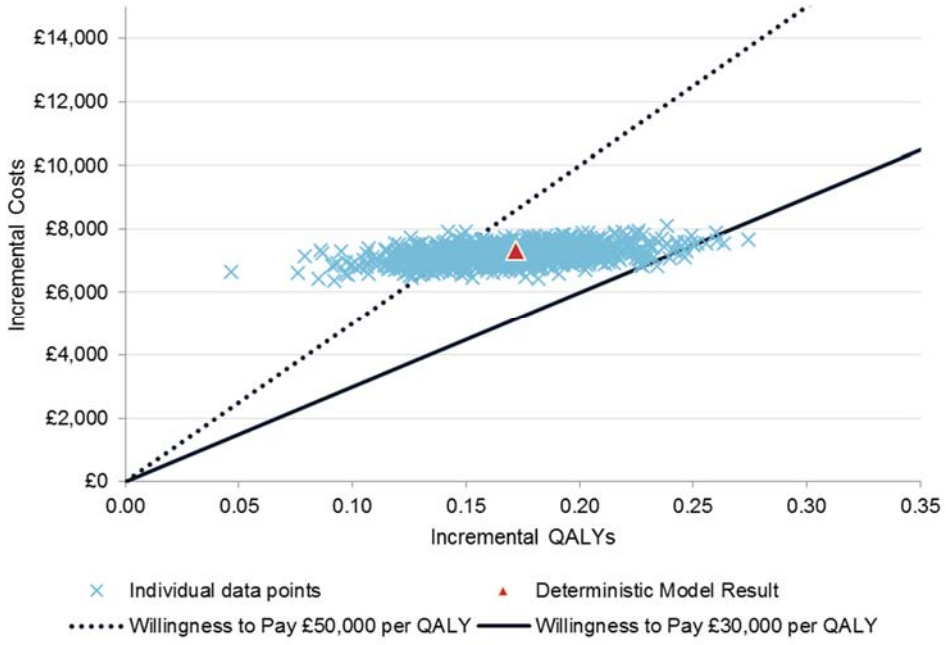
BSA (to calculate treatment dosage and hence costs) was included in the PSA, which is incorrect as variance in BSA is an indication of patient variability and not of parameter uncertainty. In its additional analysis the ERG set BSA as fixed in the PSA.

The PSA was presented correctly. However, the ERG thinks the argument that the PSA scatterplots *"demonstrate the majority of uncertainty shown in the estimation of the QALY gain as driven by the variability in the utility values chosen, due to the lack of information regarding the uncertainty in these estimates"* is somewhat flawed. The choice of scale for the axes of the scatterplot influences the visual inspection of the spread. The use of non-symmetrical scales (regarding the QALY threshold), easily biases this visual inspection. In this case, symmetrical scales based on a threshold of

30,000/QALY would have produced a slightly more symmetrical scatter, hence suggesting that uncertainty in costs and QALYs is less different.

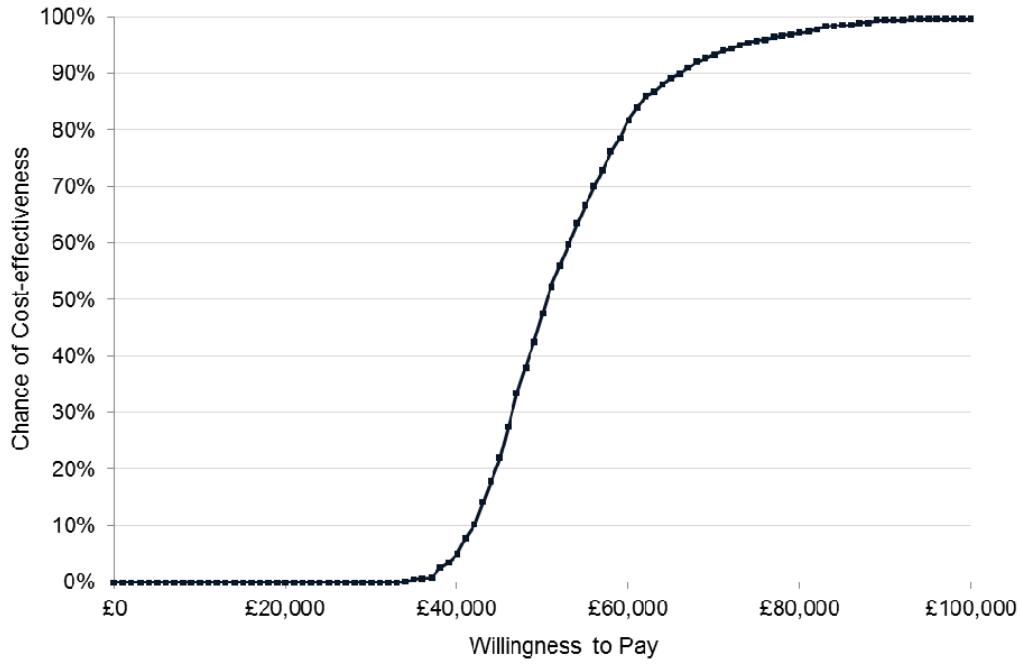
In response to clarification questions the company provided a PSA scatterplot and CEAC of the updated analysis (Figures 5.10 and 5.11).

Figure 5.10: Updated probabilistic sensitivity analysis scatter plot – PAS price
(Based on Figure 13 of the response to the request for clarification[9])



PAS = patient access scheme; QALY = quality-adjusted life year

Figure 5.11: Updated cost effectiveness acceptability curve – PAS price
(Based on Figure 14 of the response to the request for clarification[9])

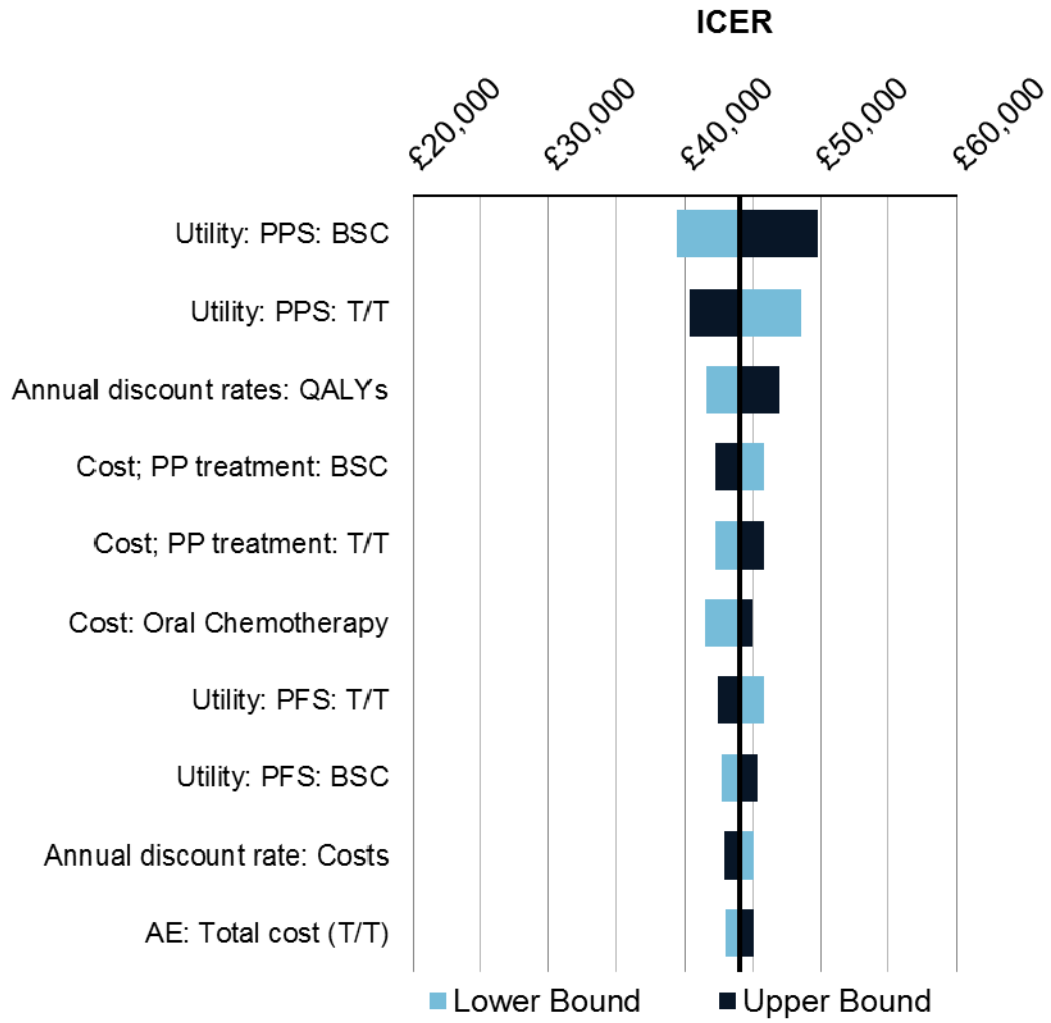


PAS = patient access scheme

Deterministic sensitivity analyses

The company performed deterministic sensitivity analyses (Figure 5.12) and presented the 10 most influential ones in tornado diagrams (with list price and with PAS).

Figure 5.12: One-way sensitivity analysis: Tornado diagram – PAS price
(Based on Figure 42 of the CS[1])



AE = adverse event; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; PFS = progression-free survival; PP = post-progression; PPS = post-progression survival; QALY = quality-adjusted life year; T/T = trifluridine/tipiracil

ERG comment: In response to clarification questions the company provided the probabilistic results of the updated scenario analyses.[9] The ICERs with the PAS price range from £38,128 per QALY gained for the analysis based on the phase II study population, to £57,576 per QALY gained when using a stratified log logistic model for OS and PFS (Table 5.26).

Table 5.26: Scenario analysis results for the updated analysis - probabilistic
(Based on Table 23 of the response to the request for clarification[9])

Input	Base case	Scenario	ICER (List price)	ICER (PAS price)
Updated			[redacted]	£44,057
Time horizon	10 years	2 years	[redacted]	£56,629
		4 years	[redacted]	£49,674
		6 years	[redacted]	£47,019
		8 years	[redacted]	£45,686
Patient population	Pooled	RECOURSE	[redacted]	£49,661
		Phase II	[redacted]	£38,128
Comparator	BSC	RFB	[redacted]	83% T/T dominates
Subgroup	Updated OS	Original OS	[redacted]	£47,369
OS and PFS curve choice	Stratified log-logistic	Generalised Gamma	[redacted]	£52,234
		Log-logistic	[redacted]	£48,644
		Log-normal	[redacted]	£49,618
		Stratified Generalised Gamma	[redacted]	£57,576
		Stratified Log-normal	[redacted]	£45,848
Resource use	Total cost	+20% of total cost	[redacted]	£46,491
		-20% of total cost	[redacted]	£45,381
Utility source	Pooled sources	Cetuximab NICE submission	[redacted]	£46,487
		CORRECT study	[redacted]	£47,972
		CORRECT study – BSC utility used for all patients	[redacted]	£45,590
Discounting (Costs, LYs, QALYs)	3.5%, 0%, 3.5%	0%, 0%, 0%	[redacted]	£44,779
		6%, 6%, 6%	[redacted]	£46,999
PP treatment cost by treatment arm	Equal costs	Unequal costs	[redacted]	£48,181
KRAS status	All patients	Wild type	[redacted]	£45,919
		Mutant type	[redacted]	£51,881
BSA from RECOURSE	Not used	Used	[redacted]	£47,216
Revised TTD estimate	Used	Not used	[redacted]	£45,623
Derived SE for PP treatment cost	Not used	Used	[redacted]	£47,216
RECOURSE only AEs	Not used	Used	[redacted]	£47,216
Additional AEs	Used	Not used	[redacted]	£45,623

AE = adverse event; BSC = best supportive care; BSA = body surface area; ICER = incremental cost-effectiveness ratio; LY = life year; KRAS = Kirsten rat sarcoma viral oncogene homolog; NICE = National Institute for Health and Care Excellence; OS = overall survival; PAS = patient access scheme; PFS = progression-free survival; PP = post-progression; QALY = quality-adjusted life year; RFB = regorafenib; SE = standard error; T/T = trifluridine/tipiracil; TTD = time to treatment discontinuation

5.2.12 Subgroup analyses

T/T provided a clinically significant prolongation of OS in all treatment subgroups. Therefore, the company did not perform any subgroup analyses.

ERG comment: Treatment might be effective in all subgroups, but it does not guarantee cost effectiveness in all subgroups. Therefore, the ERG requested subgroup analyses based on the different

subgroups described in RECOURSE and the phase II trial in its clarification letter. The ERG asked for subgroup analyses, based on:

- Tumour status:
  - wild-type KRAS
  - mutant KRAS
- The time between first diagnosis of metastases and randomisation:
  - <18 months
  - ≥18 months
- Geographic region:
  - Europe only
  - United States, Europe and Australia
- Age:
  - <65 year
  - ≥65 year
- Number of prior regimens:
  - 2 and 3
  - ≥4
- ECOG PS:
  - 0
  - 1
- Number of metastatic sites:
  - 1-2
  - 3
- Liver metastases:
  - yes
  - no

NICE, however, decided not to request all these subgroup analyses to be performed by the company. The only analyses requested by NICE was the subgroup analysis based on tumour status (wild-type KRAS, mutant KRAS). The company provided results for these analyses in their response to the clarification letter. Results, based on the cost effectiveness model provided with the clarification letter[9], indicated that the company's probabilistic ICER is £51,881 for the subgroup with mutant KRAS status while it is £45,919 in the subgroup with wild-type KRAS status.

5.2.13 Model validation and face validity check

Face validity

In Section 5.10 of the CS, the company states that "*the de novo cost-effectiveness analysis was validated using a range of experts and methods, detailed in Table 82"* (Table 5.28).[1] No further details were provided concerning the face validity assessment of the model.

Table 5.27: Validation of the de novo cost effectiveness analysis
(Based on Table 82 of the CS[1])

Validation performed by	Nature of validation	Date	Aspects covered
Prof. Martin Hoyle	Full technical review	December 2015	Cost effectiveness model and section 5 of the CS.
Advisory board of health economic (and clinical) experts	Review	January 2016	Complete cost effectiveness model and submission
BresMed	Quality-control check	January 2016	Cost effectiveness model
CS = company submission			

Internal validity
Section 5.10 of the CS contains an overview of persons involved in the validation of the cost effectiveness model (Table 5.27), but no details were provided concerning how the internal validity of the model was assessed.

Cross-validation
No cross-validation of the model results was undertaken, presumably because the review of cost effectiveness studies did not identify any cost effectiveness studies relevant for the current decision problem.

External validity

Comparison with pooled trial data
The company compared the clinical outcomes (OS and PFS) obtained from the model with estimates obtained from the pooled trial data to assess whether the model accurately estimates PFS and OS. Mean PFS estimates from the model were equal to the mean PFS estimates from pooled trial data. Mean OS from the model are however longer than the mean OS obtained from the pooled trial data (for both treatment arms). The difference in OS between T/T and BSC is also larger when mean OS from the cost-effectiveness model are used (3.2 months) instead of the pooled trial data (2.3 months). Differences between modelled PFS and OS estimates and estimates from the pooled trial data are presented in Table 5.28.

Table 5.28: Summary of model results when compared with clinical data
(Based on Table 74 of the CS[1])

Outcome	Clinical trial results (pooled data)	Model result
Overall survival	*Median:* BSC: 5.4 months T/T: 7.3 months Increment: 1.9 months *Mean:* BSC: 6.8 months T/T: 9.1 months Increment: 2.3 months	*Median:* BSC: 5.3 months T/T: 7.4 months Increment: 2.1 months *Mean:* BSC: 7.9 months T/T: 11.1 months Increment: 3.2 months
Progression-free survival	*Median:*	*Median:*

Outcome	Clinical trial results (pooled data)	Model result
	BSC: 1.7 months T/T: 1.9 months Increment: 0.2 months *Mean:* BSC: 1.9 months T/T: 3.7 months Increment: 1.8 months	BSC: 1.6 months T/T: 2.6 months Increment: 1 months *Mean:* BSC: 1.9 months T/T: 3.7 months Increment: 1.8 months
BSC = best supportive care; CS = company submission; T/T, trifluridine/tipiracil		

Comparison with cancer research UK data (CRUK)

Model outcomes were also compared with the CRUK survival estimates for Stage 4 bowel cancer. The five year survival from CRUK was compared with the two year survival of the model. This comparison was deemed suitable by the company because patients in the model already survived *35.2 months on average (i.e. approximately 3 years)* before inclusion in the trial.[1] The five year survival of CRUK was 7-8% and was considered consistent with the two year survival estimated in the model, which was 4% for the BSC group (table 51 of CS[1]).

ERG comment: Assumptions incorporated in the cost effectiveness model were clearly described in the CS. Furthermore, the economic model provided in Excel was transparent. Re-running the model confirmed the outcomes provided by the company in the CS.[1]

Face validity

Since no details were provided on face validation steps undergone during model development, the ERG asked for clarification concerning the validation efforts described in Table 5.28. In its response to the clarification letter, the company explained that the model was entirely reviewed by Professor Hoyle and that he acknowledged that the model was "*appropriate to the NICE decision problem"*. Furthermore, *"The model [was] also fully reviewed by health economic and clinical experts at an advisory board. The findings of the group were that the model was appropriate to the NICE decision problem."*[9] However, no further details were provided on the different steps undergone to assess face validity of the cost-effectiveness model. The ERG was not able to judge whether the face validity of the submitted model was appropriately addressed by the company.

Internal validity

In addition, the company explained in its response to the clarification letter that *"Professor Hoyle was provided with the complete model and conducted a systematic assessment. As part of this assessment he undertook the following: validation of model inputs, parameters, results and sensitivity analyses. In addition he checked the economic model by constructing an independent simplified model"*.[9] This simplified model provided similar results to the submitted model, which eliminated the existence of major errors in the submitted cost-effectiveness model. The ERG agrees with the efforts provided to ensure internal validity.

Cross-validation

Cross-validation was not performed due to the absence of other cost effectiveness assessment for T/T versus BSC in the third treatment line of mCRC. However, a study from Goldstein et al.[59] concerning the cost effectiveness of regorafenib was performed in the same treatment line as the current decision

problem. The ERG asked the company to compare the model structure, utility estimates, resource use estimates, adverse events and outcomes between the BSC arms of the current assessment and Goldstein et al.[59] study. Despites the use of similar utility estimates, outcomes of the studies could not properly be compared because resource use estimates and total LY for the BSC arm were not described in Goldstein et al.[59]

Furthermore, the ERG asked for a comparison of the model structure, utility estimates, resource use estimates, adverse events and outcomes between the BSC arms of ID 794[28] and the current assessment. The company acknowledged the similarities in model structure and AEs profiles between the assessments, but outcomes of the studies were not deemed comparable because patients considered in the assessments are at different disease stages.

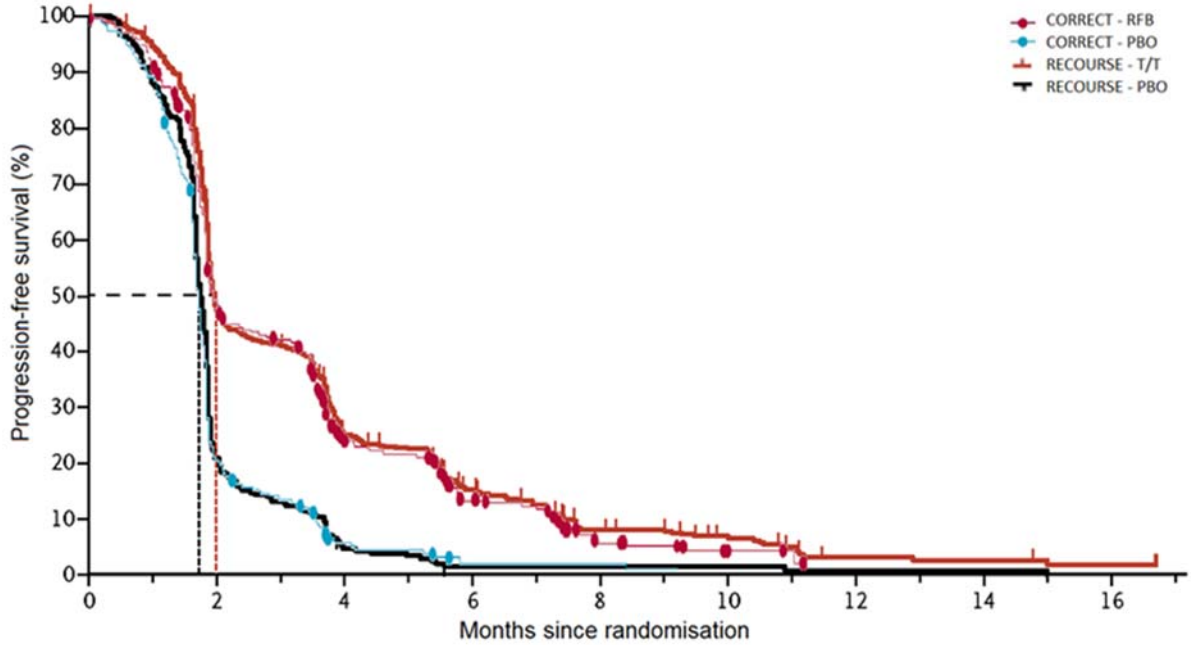
Cross-validation is consequently not thoroughly investigated in the current assessment due to the absence of comparable studies with the current assessment. The ERG agrees the impossibility to present a thorough cross-validation of the current assessment with previous studies.

External validity
The CS contains a comparison of the survival estimates from CRUK and the current assessment. However, the ERG did not consider this comparison to be adequate because the populations from the current assessment and the CRUK were not considered comparable. The ERG consequently asked the company to explain why the external validity of the survival estimates of the model could be assessed through a comparison with data from CRUK. The company responded that they agreed that the CRUK data was not representative of the population from the current decision problem because of the following reasons: *"the data [from the CRUK] and in particular those for mCRC (stage IV) are limited by the fact that they apply to all patients with mCRC irrespective of time since diagnosis of metastatic disease, number of lines of chemotherapy received etc. Therefore the CRUK data are not reflective of the population defined by the decision problem for this appraisal."*[9] This is further justified by the fact that *"The decision problem defines a patient population diagnosed with mCRC who would have received two or more previous lines of chemotherapy (i.e. they have received NICE recommended standard therapies for mCRC and their disease has progressed or when they received the therapy they were found to be intolerant to it). Patients at this line of therapy have much lower survival than those receiving first or second line therapy."*[9] Both parties agreed that a comparison with CRUK data is not suitable for the current decision problem.

The ERG also requested a comparison of survival estimates with a study of Jonker et al.[66] However, the company was not able to conduct this comparison because the study of Jonker et al. focused on *"mCRC patients with high epiregulin (EREG) gene expression plus KRAS wild-type status"* [9], a subgroup which was not considered in the current assessment. Therefore, the results of Jonker et al. and the present assessment would unlikely be comparable, according to the company.

As an alternative, the company provided a comparison of the survival data from the CORRECT and the RECOURSE trials (Figure 5.13). As can be seen, survival curves for the placebo group (BSC) from CORRECT and RECOURSE are almost similar. However, this is not a comparison of the model results with external sources.

Figure 5.13: PFS from the RECOUSE and CORRECT studies – For T/T, PBO and RFB
(Based on Figure 10 of the response to the request for clarification[9])



PBO = placebo; PFS = progression-free survival; RFB = regorafenib; T/T = trifluridine/tipiracil

The ERG was not able to assess whether face validity was properly addressed during model development. Internal validity was correctly assessed through an entire review of the cost effectiveness model. Cross-validation could not be properly performed but trial results seemed comparable to another trial performed in the same treatment line. In conclusion, the ERG think that validation efforts of the cost effectiveness model could have been more intense but were limited by the absence of comparable assessments.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations from Section 5.2, the ERG defined a new base case (see Table 6.1). This base case included multiple adjustments to the original base case by the company presented in the CS.[1] These adjustments were subdivided into three categories (derived from Kaltenthaler et al. 2016[67]):

1. Fixing errors (correcting the model were the company's submitted model was unequivocally wrong)
2. Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
3. Matters of judgement (amending the model were the ERG considers that reasonable alternative assumptions are preferred)

The combination of these corrections/amendments resulted in the ERG base case. Additionally, several explorative sensitivity analyses were performed based on the ERG base case to test uncertainties within the model.

Fixing errors

The ERG identified one error in the model submitted by the Company:

1. the following adverse events rates for BSC (grade ≥ 3) were incorrect in the model (and in table 44 of the CS[67]):
    - Neutropenia
    - Leukopenia
    - Anaemia
    - Thrombocytopenia
    - Increase in alanine aminotransferase level
    - Increase in aspartate aminotransferase level
    - Increase in total bilirubin
    - Increase alkaline phosphatase level
    - Increase in creatinine level

These adverse events were corrected to be in line with the published literature,[2] see Section 5.2.7 for more details.

Fixing violations
The following violations were fixed in the ERG base case to be in line with best practices and the NICE reference case.

2. Keep BSA fixed in PSA (see Section 5.2.11)
3. Correct end-of-life costs to be consistent with the NHS and PSS perspective (see Section 5.2.9)
4. Correct medical oncologist outpatient consultation costs to be consistent with the NHS reference prices (see Section 5.2.9)

Matters of judgement
5. BSA based on observed trial data (parametric estimation; see Section 5.2.9)
6. Updated costs of adverse events (see Section 5.2.9)
7. Use treatment specific post progression treatment costs (see Section 5.2.9)
8. Equal treatment delay (see Section 5.2.9)
9. Use RECOURSE data instead of pooled estimates (see Section 5.2.6)
10. Use unstratified time-to-event models for PFS and OS (see Section 5.2.6)
11. Use utilities derived from the CORRECT study (including AE disutility of 0.01 for being on TT; see Section 5.2.8)

The company and ERG base cases (with PAS) are presented in Table 5.30. Compared with the company base case, the ICER increased by approximately £9,300 to £52,695 in the ERG base case. This difference could largely be attributed to a reduction in incremental QALYs from 0.172 to 0.144. The difference between the results of the company and the ERG base case are mainly caused by the following changes in the model:

- Fixing errors with adverse events for BSC
- Use of RECOURSE data instead of pooled estimates
- Use of CORRECT utilities[30] only (i.e. not averaging with utilities from the TA176 CS report[32]).

Giving that the pooled analyses might be preferred or might not differ substantially compared with more sophisticated pooling techniques, despite the lack of justification for/use of naïve pooling (i.e.

not stratifying by trial), Table 5.29 presents ERG base case using the pooled evidence. In this analyses, pooled evidence is used for OS, PFS, AE, BSA and dose reductions.

Table 5.29: Company and ERG base case (with PAS) – probabilistic results

	T/T		BSC				
	QALYs	**Costs**	**QALYs**	**Costs**	**ΔCosts**	**ΔQALY**	**ICER**
Company base case*	0.593	£17,783	0.420	£10,299	0.172	£7,484	£43,427
ERG base case	0.542	£17,167	0.398	£9,605	0.144	£7,562	£52,695
ERG base case pooled	0.561	£17,197	0.407	£9,584	0.154	£7,613	£49,392

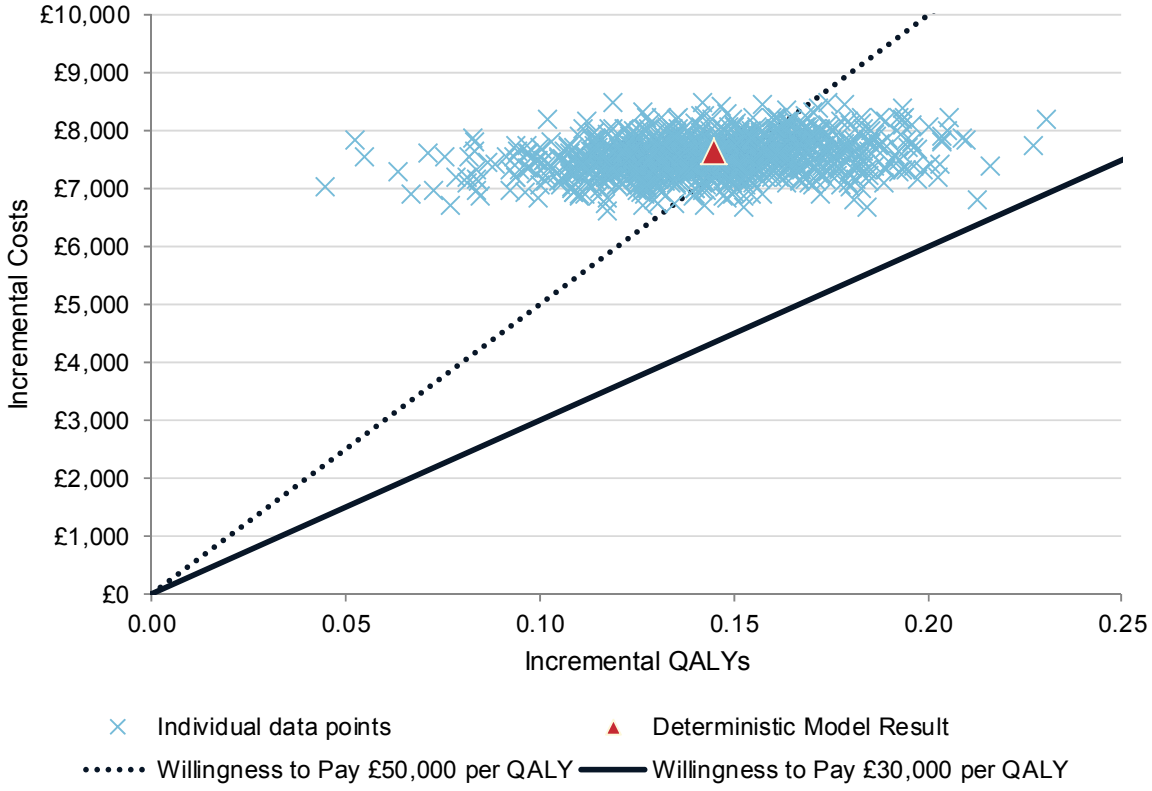
* Calculated by the ERG

BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; T/T = trifluridine/tipiracil

5.3.1 Probabilistic sensitivity analyses (ERG base case)

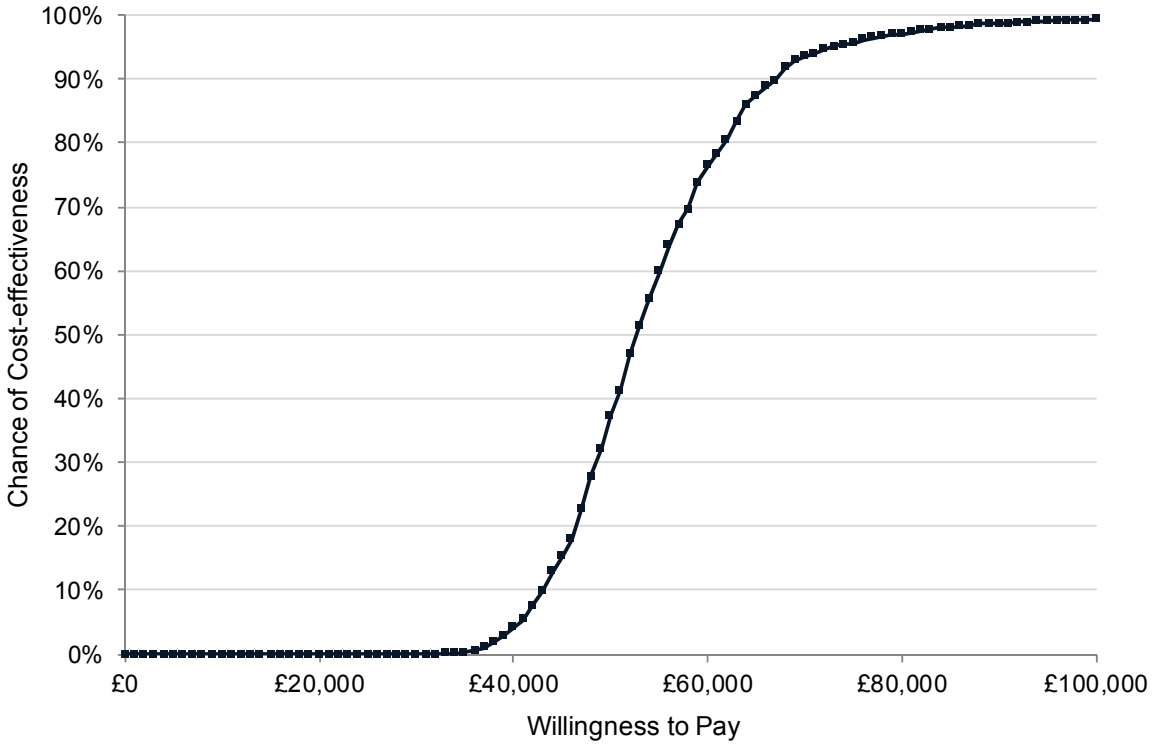
A PSA was performed to capture the uncertainty in the estimation of input parameters in the new ERG base case. Figure 5.14 presents the cost effectiveness plane and Figure 5.15 shows the cost effectiveness acceptability curves (CEACs). The probability that T/T is cost effective is smaller in the ERG base case compared to the company's base case (0% versus 0% and 37% versus 77% for thresholds of £30,000 and £50,000, respectively).

Figure 5.14: Cost effectiveness plane for all treatment options (QALYs; ERG base case)



ERG = Evidence Review Group; QALY = quality-adjusted life year

Figure 5.15: Cost effectiveness acceptability curves (ERG base case)



ERG = Evidence Review Group

5.3.2 Additional exploratory and subgroup analyses performed by the ERG base case

Additional exploratory sensitivity analyses were performed by the ERG to examine the potential impact of various alternative assumptions on the cost effectiveness estimates. These analyses were performed based on the ERG base case and illustrated that using the UK general population BSA estimates and an alternative source for resource use had a moderate impact on the results. These two analyses increased the ERG base case ICER of £52,695 to £53,776 and £54,739, respectively (Table 6.2).

Subgroup analyses based on KRAS status (Table 6.3) indicated that the ICER for the KRAS wild-type and KRAS mutant subgroups would be £53,042 and £50,721 respectively.

5.4 Conclusions of the cost effectiveness section

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a reasonable extent. Reviewing the overall evidence, the ERG confirmed that there was no existing cost effectiveness model for T/T for the current indication.

In terms of population, there is uncertainty regarding the generalisability of the RECOURSE trial population to the population for whom T/T is considered in the UK. More specifically, following the licence it may be possible that patients not represented in the trial receive this medication. Additionally, as the definition of BSC was unclear, i.e. there is currently no internationally accepted definition of BSC, it is unclear whether BSC considered in the evidence, and hence in the model, is representative for BSC in the UK.

The company model follows a logical structure with respect to the nature of the disease. One of the main strengths of the CS (including the economic model) is the clarity and transparency. The cost

effectiveness results were generally robust under the one-way sensitivity and scenario analyses conducted. The model was most sensitive to changes in utility scores and selection of OS and PFS curves. Major uncertainties identified by the ERG were: whether or not to use the naïve pooling provided by the company, averaging of utilities from various sources, estimation of resource use (mainly based on expert opinion) and estimation of BSA.

The company base case ICER (probabilistic) was £43,427 (with PAS). The ERG had a total of 11 adjustments/corrections which lead to the ERG base case ICER of £52,695 (with PAS). This included fixing errors, fixing violations and matters of judgement. The most influential adjustments/corrections were 1) fixing errors with adverse events for BSC; 2) use of RECOURSE data instead of pooled estimates and; 3) use of CORRECT utilities[30] only. Fixing errors concerning adverse events rates was an issue that was unequivocally wrong in the economic model submitted by the company. Moreover, the ERG preference to use the data from the RECOURSE trial only, instead of the pooled evidence (including the phase II trial) was mainly due to the lack of justification for/use of naïve pooling by the company (i.e. not stratifying by trial) and the potential bias incurred by this adjustment was unknown (both the direction and magnitude). Nevertheless, as this is a matter of judgement and the pooled analysis might be preferred or might not differ substantially compared with more sophisticated pooling techniques, the ERG presented a pooled base case (based on pooled data of the phase II and RECOURSE trials) wherein the ICER decreased with £3,303 to £49,392. Finally, the ERG preferred to use the utilities from the CORRECT study[30] only, instead of averaging these with utility values from the CS of TA176.[32] The ERG doubts whether TA176[32] is an appropriate source for health state utilities for the present decision problem.

Exploratory sensitivity analyses illustrated that using the UK general population BSA estimates and an alternative source for resource use had a moderate impact on the ICER (£53,776 and £54,739, respectively). Subgroup analyses based on KRAS status indicated that the ICER for the KRAS wild-type and KRAS mutant subgroups would be £53,042 and £50,721, respectively.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In Section 5.3 the ERG base case was presented, which was based on various changes compared to the company base case. Tables 6.1 and 6.2 show how each individual change impacts the ICER plus the combined effect of all changes simultaneously. The analyses numbers in Table 6.1 correspond to the analyses numbers reported in Section 5.3. Moreover, the exploratory sensitivity and subgroup analyses are presented in Tables 6.2 and 6.3 (both conditional on the ERG base case). Appendix 3 and the economic model sent by the ERG contains technical details on the analyses performed by the ERG.

Table 6.1: ERG base case, incorporating corrections and amendments identified by the ERG (with PAS) – probabilistic results

	T/T		BSC				
	QALYs	**Costs**	**QALYs**	**Costs**	**ΔCosts**	**ΔQALY**	**ICER**
Company base case*	0.593	£17,783	0.420	£10,299	0.172	£7,484	£43,427
1-4 Fixing errors and violations	0.593	£17,494	0.421	£9,679	0.172	£7,815	£45,335
5 BSA based on observed trial data	0.593	£17,634	0.422	£10,116	0.170	£7,517	£44,120
6 Updated costs of adverse events	0.592	£18,479	0.420	£10,892	0.172	£7,587	£43,986
7 Use treatment specific post progression treatment costs	0.593	£17,642	0.422	£10,120	0.171	£7,523	£43,997
8 Equal treatment delay	0.592	£17,772	0.422	£10,241	0.170	£7,531	£44,271
9 Use RECOURSE data instead of pooled estimates	0.573	£17,320	0.416	£10,139	0.157	£7,181	£45,784
10 Use unstratified time-to-event models	0.588	£17,257	0.427	£10,259	0.161	£6,999	£43,446
11 Use CORRECT utilities	0.568	£17,754	0.401	£10,262	0.167	£7,493	£44,851
ERG base case	**0.542**	**£17,167**	**0.398**	**£9,605**	**0.144**	**£7,562**	**£52,695**
ERG base case (pooled)	**0.561**	**£17,197**	**0.407**	**£9,584**	**0.154**	**£7,613**	**£49,392**

* Calculated by the ERG

BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; QALY = quality-adjusted life year; T/T = trifluridine/tipiracil

Table 6.2: Exploratory sensitivity analyses based on ERG base case (with PAS) – probabilistic results

	T/T		BSC				
	QALYs	**Costs**	**QALYs**	**Costs**	**ΔCosts**	**ΔQALY**	**ICER**
ERG base case	0.542	£17,167	0.398	£9,605	0.144	£7,562	£52,695
Incorporating costs of additional AE	0.542	£17,340	0.397	£9,715	0.145	£7,625	£52,545
Use time on treatment instead of PFS	0.544	£17,510	0.398	£9,913	0.146	£7,597	£52,146
Alternative source for medical resource use (Hoyle et al. 2013[62]; table 4)	0.544	£17,162	0.397	£9,097	0.147	£8,065	£54,739
Alternative AE disutility for being on TT	0.545	£17,169	0.398	£9,616	0.147	£7,553	£51,358
Use BSA from the UK	0.543	£17,556	0.397	£9,733	0.145	£7,823	£53,776

* Calculated by the ERG

AE = adverse event; BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; PFS = progression-free survival; QALY = quality-adjusted life year; T/T = trifluridine/tipiracil; UK = United Kingdom

Table 6.3: Subgroup analyses based on ERG base case (with PAS) – probabilistic results

	T/T		BSC				
	QALYs	**Costs**	**QALYs**	**Costs**	**ΔCosts**	**ΔQALY**	**ICER**
KRAS wild-type	0.544	£17,281	0.398	£9,509	0.147	£7,771	£53,042
KRAS mutant	0.542	£16,925	0.397	£9,581	0.145	£7,344	£50,721

* Calculated by the ERG

BSC = best supportive care; ERG = Evidence Review Group; ICER = incremental cost-effectiveness ratio; KRAS = Kirsten rat sarcoma viral oncogene homolog; PAS = patient access scheme; QALY = quality-adjusted life year; T/T = trifluridine/tipiracil

7 END OF LIFE

According to Section 4.13.1 of the CS, T/T fulfils the criteria for end of life care.[1] The relevant table from the submission is reproduced below.

Table 7.1: Summary of the decision problem
(Based on Table 47 of the CS[1])

<table>
<tr><th>Criterion</th><th>Data available</th></tr>
<tr><td>The treatment is indicated for patients with a short life expectancy, normally less than 24 months</td><td>1. Final appraisal determination NICE TA242[7], section 4.4.19.
“For metastatic colorectal cancer that has progressed after first-line treatment, the Committee agreed that the technologies fulfil the first criterion related to life expectancy, because estimates of life expectancy from people randomised to best supportive care in the second-line setting were less than 12 months”
2. Hoyle et al. 2013[62]
Describes the cost-effectiveness analysis of cetuximab, cetuximab plus irinotecan, and panitumumab for third and further lines of treatment for KRAS wild-type patients with mCRC. This reports a mean OS for BSC of 0.51 years (6.2 months)
3. Mean OS (RECOURSE)[2]
The mean OS in the BSC arm was 0.64 years (7.7 months)
4. Mean OS pooled analysis (RECOURSE and Yoshino)[2, 3]
The mean OS in the BSC arm was 0.66 years (7.9 months)</td></tr>
<tr><td>There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment</td><td>The estimates of OS are based on mature survival data. The proportion of patients who had died in the RECOURSE and phase II trials were 89.0% and 72.9%, respectively.
1. Mean OS - Pooled analysis
<table>
<tr><th></th><th>Days</th><th>Months</th></tr>
<tr><td>Trifluridine/tipiracil</td><td>338</td><td>11.1</td></tr>
<tr><td>BSC</td><td>240</td><td>7.9</td></tr>
<tr><td>Incremental</td><td>98</td><td>3.2</td></tr>
</table>
2. Mean OS (RECOURSE)
<table>
<tr><th></th><th>Days</th><th>Months</th></tr>
<tr><td>Trifluridine/tipiracil</td><td>326</td><td>10.7</td></tr>
<tr><td>BSC</td><td>234</td><td>7.7</td></tr>
<tr><td>Incremental</td><td>92</td><td>3.0</td></tr>
</table></td></tr>
<tr><td>The treatment is licensed or otherwise indicated for small patient populations</td><td>1. Section 3.4.2 and section 6.1[1]
Based on the epidemiological data that are available for mCRC and expert clinical opinion, it is estimated that approximately 2,600 patients may receive further active therapy at third line or beyond (i.e. where trifluridine/tipiracil may be considered). Currently, this treatment comprises capecitabine, chemotherapy re-challenge or clinical trials
2. Market research
Pharmacor (Decision Resources Group) determined that the number of patients in the UK with mCRC (KRAS wild-type and KRAS mutation-positive) who would be treated at third line or beyond was 2,490. Further</td></tr>
</table>

Criterion	Data available
	details of the survey are available in appendix 5.[23]

BSC = Best supportive care; KRAS = Kirsten rat sarcoma viral oncogene homolog; mCRC = Metastatic colorectal cancer; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS = overall survival; TA = Technology Appraisal

ERG comment: The company provided evidence from various sources to support that the submission fulfils end of life criteria.

1. The first criterion of a short life expectancy includes the RECOURSE trial where survival was 7.7 months in the best supportive care arm. The ERG considers this criterion to have been met.
2. Evidence for the second criterion (an extension to life of at least three months compared to current NHS treatment) is taken from the pooled estimate of the included trials (phase II trial and RECOURSE) and for RECOURSE alone. If the more relevant figure from the RECOURSE trial is used the criterion is just met as overall incremental survival is three months exactly. The ERG notes that the pooled mean result using the actual trial data shows a mean increase in overall survival of 2.3 months (T/T: 9.1 months; BSC: 6.8 months).
3. The third criterion of a small patient population is taken from a survey by Pharmacor (see Appendix 5 of the CS for details[23]) of the number of patients in the UK with mCRC (KRAS wild-type and KRAS mutation-positive) who would be treated at third line or beyond and from the company's estimates based on a previous technology assessment[10] and expert opinion. The ERG agrees that the population to be treated is likely to be small but it is noted that the figure of 2,600 patients to be treated might be an underestimate given that the CS does not include Wales in its estimates of the incidence of mCRC.

8 OVERALL CONCLUSIONS

8.1 Statement of principal findings

The CS was based on two randomised trials (phase II trial and RECOURSE) of trifluridine/tipiracil (T/T) compared to best supportive care (BSC) alone for patients with advanced/metastatic colorectal cancer (mCRC) receiving treatment at the third line or beyond. No indirect or mixed treatment comparisons were presented The ERG agreed that the randomised trials were appropriately selected using systematic review methods and were both of high quality. Although both trials ensured consistency on medications excluded from BSC, the nature of BSC provided could vary between trial centres. The nature of BSC provided might also differ from that provided in England and Wales and this is drawn to the attention of the committee.

The phase II trial included 172 participants from Japan while RECOURSE was a multinational trial including 800 participants. RECOURSE included 394 participants from Europe (nine from the United Kingdom (UK)). The company conducted analyses demonstrating that the effect of T/T did not vary according to geographical location and as a result, the trials were pooled. There is a lack of information on methods of pooling the two included randomised trials but overall it was considered acceptable from the point of view of clinical effectiveness that the trials were pooled.

The ERG further notes that there is an under-representation of non-white, non-Asian populations across the trial (approximately 1% of RECOURSE are listed as 'black'). Considering further the issue of applicability of the trials, the population in RECOURSE is a more treated population than might be expected in practice in England and Wales. Patients were required to have received chemotherapy with fluoropyrimidine, oxaliplatin, irinotecan and bevacuzimab. Bevacuzimab is not currently available in England and Wales. A small number in the phase II trial had not received bevacuzimab (22%) but the phase II trial included fewer participants than RECOURSE. Those who did not receive bevacizumab, and are thus appropriate to the England and Wales population, represent a small percentage of the trial populations (approximately 4%). The company states that T/T might be expected to work better in a less treated population based on clinical advice. This appears to be reasonable.

The included trials do not directly assess health-related quality of life as specified in the NICE scope. Although based on the pooled result there is a benefit to patients of the median increase in overall survival of 2.3 months (T/T: 9.1 months, BSC: 6.8 months), the quality of life experienced can only be inferred from effects of disease control and occurrence of adverse events. Regarding median progression-free survival (PFS), the pooled results showed an increase of 0.2 months (T/T: 1.9 months, BSC: 1.7 months). In terms of disease control, a greater proportion of T/ T patients in both trials had stable disease (42.9% vs. 10.5% in the phase II trial and 42.4% vs. 15.9% in RECOURSE). However numbers achieving partial response or complete response were very small overall. Rates of adverse events and serious adverse events were similar between T/T and BSC for the RECOURSE trial.[25] In both trials 'treatment-related AEs' were found to be [redacted]. In RECOURSE, more patients in the BSC arm were reported to [redacted][25], [redacted].[24]

The CS provides evidence from various sources to support that the submission fulfils end of life criteria. The first criterion of a short life expectancy includes the RECOURSE trial where survival was 7.7 months in the best supportive care arm. Evidence for the second criterion (an extension to life

of at least three months compared to current National Health Service (NHS) treatment) is taken from the survival modelling calculations for the pooled estimate OS for both included trials (incremental survival: 3.2 months) and for RECOURSE alone (incremental survival: 3.0 months). The third criterion of a small patient population is taken from a survey of the number of patients in the UK with mCRC who would be treated at third line or beyond and from the company's estimates based on a previous technology assessment (approx. 2,600 patients) as well as expert opinion (2,490 patients).

The company base case ICER (probabilistic) was £43,427 (with PAS). The ERG had a total of 11 adjustments/corrections which lead to the ERG base case ICER of £52,695 (with PAS). This included fixing errors, fixing violations and matters of judgement. The most influential adjustments/corrections were 1) fixing errors with adverse events for BSC; 2) use of RECOURSE data instead of pooled estimates and; 3) use of CORRECT utilities[30] only. Fixing error concerning adverse events rates was an issue that was unequivocally wrong in the economic model submitted by the company. Moreover, the ERG preference to use the data from the RECOURSE trial only, instead of the pooled evidence (including the phase II trial) was mainly due the lack of justification for/use of naïve pooling (i.e. not stratifying by trial) and the potential bias incurred by this adjustment was unknown (both the direction and magnitude). Nevertheless, as this is a matter of judgement and the pooled analysis might be preferred or might not differ substantially compared with more sophisticated pooling techniques, the ERG presented a pooled base case (based on pooled data of the phase II and RECOURSE trials) wherein the ICER decreased by £3,303 to £49,392. Finally, the ERG preferred to use the utilities from the CORRECT study[30] only, instead of averaging these with utility values from the CS of TA176.[32] The ERG doubts whether TA176[32] is an appropriate source for health state utilities for the present decision problem.

Exploratory sensitivity analyses illustrated that using the UK general population BSA estimates and an alternative source for resource use had a moderate impact on the ICER (£53,776 and £54,739, respectively). Subgroup analyses based on KRAS status indicated that the ICER for the KRAS wild-type and KRAS mutant subgroups would be £53,042 and £50,721 respectively.

8.2 Strengths and limitations of the assessment

The company's submission contained a well-conducted systematic review which addressed the scope issued by NICE. Searches were carried out in line with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4. The CS and response to clarification provided sufficient details for the ERG to appraise the searches. The review identified two methodologically sound randomised controlled trials. The main trial, RECOURSE, was a large, multinational trial. The trials assessed the outcomes outlined by NICE with the exception of quality of life. Overall, the CS is well presented, transparent and in line with the final scope.

Considering the population, there is uncertainty regarding the generalisability of the RECOURSE trial population to the population for whom T/T is considered in the UK. More specifically, following the licence it may be possible that patients not represented in the trial receive this medication. Additionally, as the definition of BSC was unclear, i.e. there is currently no internationally accepted definition of BSC, it is unclear whether BSC considered in the evidence and hence in the model is representative for BSC in the UK.

The ERG believes incorrect search strategies for HRQoL were reported in the Appendix of the CS. The company response to the ERG clarification letter was that the reported search strategies were correct. However, the results reported in the CS suggest that separate HRQoL searches were

conducted, and that four studies with HRQoL data met the inclusion criteria of the review. Without full details of the HRQoL search strategies the ERG was unable to assess their quality.

Most uncertainty in the health economic model was related to the estimation of progression free survival and overall survival as well as the utility values. Additional uncertainties identified by the ERG included whether or not to use the naïve pooling provided by the company, averaging of utilities from various sources, estimation of resource use (mainly based on expert opinion) and estimation of BSA. Using mainly expert opinion for resource use (instead of empirical data) was considered by the ERG as one of the main weaknesses is. This uncertainty might have an impact on the ICER as examined in the exploratory sensitivity analyses.

8.3 Suggested research priorities

Given the paucity of robust evidence on health-related quality of life in metastatic colorectal cancer, especially beyond first line, further research is warranted in this area. Additionally, the estimation of resource use (mainly based on expert opinion) was an area of uncertainty in the cost effectiveness model.

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Appendix 1: Further critique of searches in the company submission

Clinical effectiveness

- CAS Registry numbers for the interventions were not included in the search strategies.
- There was no animal/human limit included in either the MEDLINE or Embase search strategy. This would probably have had little impact on the results because of the number of facets already combined in the strategy, and particularly the inclusion of both the precise 'advanced/metastatic' facet and 'RCT/observational studies' filter.
- The RCT search filter includes 'Review of reported cases.pt.' and 'Review, multicase.pt.': neither term identifies any records; neither term is included in the SIGN RCT filter[21] from which this is derived; and neither term is actually a publication type (pt) in MEDLINE (Ovid).
- Reporting the exact date span of the database searches would have been more transparent than using 'to present' for MEDLINE. This would allow others to replicate the search more accurately. In the list of databases given in the main CS for each of the 3 searches conducted, the date span was given as '1980 to present' for Embase, but it was then reported more specifically with the search strategies in the appendices: Embase 1980 to 2015 Week 43; Searched on 26th October 2015.
- The Cochrane Library database issue numbers were not reported. Further, the results from the Cochrane Library search would have been better reported per database rather than as a total.
- The company did not supply website addresses or details of the search strategy or search terms used for the conference searches. There are a number of ASCO and ISPOR meetings each year, and it was not clear which were searched. It would not be possible to reproduce the conference proceedings searches reported in the CS.
- There were no searches for unpublished and ongoing trials via Trials registers, e.g. ClinicalTrials.gov and ICTRP.

Cost effectiveness

- In the MEDLINE search strategy it appears that search line #26 was inadvertently combined with search line #25. Search line #25 comprises search terms for economic evaluation, whilst the facet which includes line #26 was comprised of search terms for 'models': these facets were then combined using Boolean AND. Search line #26 consisted of a set of acronyms for economic analyses (CEA, CBA, CUA, etc.) and should have been included in that facet of search terms (search line #24). In the Embase search strategy the corresponding search lines were line #33 (economic evaluation) and #32 (economic analyses acronyms).
- There were redundant search terms where hyphenated phrases have been replicated: the databases searched do not recognise hyphens, and so the same results are achieved with or without hyphens. e.g., 'cost benefit analysis' retrieves the same as 'cost-benefit analysis'.
- The Cochrane Library database issue number (NHS EED and HTA) were not reported. Further, the results from the Cochrane Library search would have been better reported per database rather than as a total.
- The cost-effectiveness facet of terms used in the Cochrane Library was inappropriate. NHS EED only consists of economic evaluations, and so this facet of terms was redundant.

Measurement and valuation of health effects

- Appendix 10 refers to the search strategy for section 5.4.3. This should be section 5.4.2.

Appendix 2: Summary list of cost effectiveness evaluation

Question(s)	*Response (Y, N or NS)*	*Comments*
Is there a clear statement of the decision problem?	Y	In the executive summary
Is the objective of the evaluation and model specified and consistent with the stated decision problem?	Y	
Is the primary decision-maker specified?	Y	
Is the perspective of the model stated clearly?	Y	
Are the model inputs consistent with the stated perspective?	N	Some of the end of life costs are not consistent with the perspective
Has the scope of the model been stated and justified?	Y	
Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Y	
Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	
Are the sources of data used to develop the structure of the model specified?	Y	
Are the causal relationships described by the model structure justified appropriately?	Y	
Are the structural assumptions transparent and justified?	Y	
Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	
Is there a clear definition of the options under evaluation?	N	A clear definition of BSC is missing
Have all feasible and practical options been evaluated?	Y	
Is there justification for the exclusion of feasible options?	Y	Regorafenib, the only other licensed product in the same disease stage as T/T, is not considered in the base case as it is not recommended for use in the NHS (by NICE or the CDF).
Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	Y	
Is the time horizon of the model sufficient to reflect all important differences between options?	Y	

Question(s)	*Response (Y, N or NS)*	*Comments*
Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	Y	
Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	
Is the cycle length defined and justified in terms of the natural history of disease?	Y	
Are the data identification methods transparent and appropriate given the objectives of the model?	Partly	Unclear how health state utility values, not identified in the systematic review, were selected.
Where choices have been made between data sources, are these justified appropriately?	Partly	See above. In addition, it is unclear why the study by Siena et al (i.e. the CORRECT study)[29, 30] was preferred as the source for HRQoL data above the study by Chang et al.[31] which might potentially be consistent with the NICE reference case.
Has particular attention been paid to identifying data for the important parameters in the model?	Partly	Systematic search have been performed to identify relevant cost-effectiveness and health-related quality of life studies. However, a broader search objective and strategy (e.g. including other interventions than T/T only in the cost effectiveness review) would potentially identify cost-effectiveness studies relevant for informing the model produced by the company. For instance, the studies by Goldstein et al.,[59] Starling et al.,[60], Shiroiwa et al.,[61] and Hoyle et al.,[62] which were identified by the company but eventually excluded (see Table 2 of Appendix 6 of the CS[1]), might have been relevant for informing the model.
Has the quality of the data been assessed appropriately?	Partly	It is unclear how the quality of the data from ID794[28] is assessed.
Where expert opinion has been used, are the methods described and justified?	N	Methods for estimating resource use based on expert opinion were not described.
Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Partly	The selection of a stratified or non-stratified time-to-event model based on AIC is methodologically incorrect.
Is the choice of baseline data described and justified?	Y	
Are transition probabilities calculated appropriately?	Y	
Has a half-cycle correction been applied to both cost and outcome?	N	No half-cycle correction is required given the short (daily) cycle length.

Question(s)	*Response (Y, N or NS)*	*Comments*
If not, has this omission been justified?	Y	
If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Unclear	Pooling methods are not described
Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Y	
Have alternative extrapolation assumptions been explored through sensitivity analysis?	Y	
Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Y	"It is noted that the long-term plausibility of the log-logistic distribution should be justified given that the curves typically predict long tails, which may not be clinically justified in some disease areas. However, Kaplan-Meier data are mature (with approximately 10% (T/T) and 5% (BSC) of patients still alive at the end of each curve); therefore, even if this is the case, OS would not be vastly over-predicted."
Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	N	
Are the costs incorporated into the model justified?	Partly	Rationale / justification for assumptions / expert opinion regarding resource use are unclear.
Has the source for all costs been described?	Y	
Have discount rates been described and justified given the target decision-maker?	Y	
Are the utilities incorporated into the model appropriate?	N	Unclear why the utilities identified in the literature review were averaged with utilities from an alternative sources (not identified in the literature review) which does not seem to be applicable.
Is the source for the utility weights referenced?	Y	
Are the methods of derivation for the utility weights justified?	Y	
Have all data incorporated into the model been described and referenced in sufficient detail?	Y	
Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices	Y	

Question(s)	*Response (Y, N or NS)*	*Comments*
appropriate)?		
Is the process of data incorporation transparent?	Y	
If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	N	Triangular distributions are not justified (particularly for post-progression treatment costs)
If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	N	BSA is incorporated in the probabilistic sensitivity analyses, this is more likely a reflection of first order uncertainty (i.e. variability). Moreover, reference prices, which are typically fixed are varied in the probabilistic sensitivity analyses.
Have the four principal types of uncertainty been addressed?	Partly	Patient heterogeneity was not considered.
If not, has the omission of particular forms of uncertainty been justified?	N	The justification provided: "Subgroup analysis is not considered in the de novo analysis, given the size of the patient population and that, in RECOURSE, trifluridine/tipiracil was associated with a clinically relevant prolongation in OS in all treatment subgroups" is flawed since the finding that T/T is associated with clinically relevant prolongation in OS in most treatment subgroups does not indicate that it is cost-effective in all subgroups.
Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Y	
Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	N	
Has heterogeneity been dealt with by running the model separately for different subgroups?	N	
Are the methods of assessment of parameter uncertainty appropriate?	Partly	BSA and reference prices are incorporated in the probabilistic sensitivity analyses.
If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	N	Arbitrary ranges of +/- 20% of the mean are used.
Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Partly	Although the cost-effectiveness analysis was validated (see table 82 of the CS[1]), a detailed description of the validation process is missing.
Are any counterintuitive results from the model explained and justified?	N	Higher post-progression drug costs for BSC compared with T/T (see table 78 of the CS[1]) seems counterintuitive given that the post-progression drug costs are equal for both comparators and T/T

Question(s)	*Response (Y, N or NS)*	*Comments*
		has more life year in the post-progression health state. After inspecting the model, the ERG noticed that this difference was driven by the discounting of costs.
If the model has been calibrated against independent data, have any differences been explained and justified?	N	The differences between the model estimates and the data from Cancer Research UK have not been explained and justified.
Have the results of the model been compared with those of previous models and any differences in results explained?	N	Despite, the model results, in particular for BSC, could be cross validated with other economic models considering ≥3rd line treatment for mCRC. BSC cross validation might have been possible using Goldstein et al.,[59] Starling et al.,[60], Shiroiwa et al.,[61] and/or Hoyle et al.[62]
AIC = Akaike information criterion; BSC = best supportive care; BSA = body surface area; CDF = Cancer Drugs Fund; CS = company submission; ERG = Evidence Review Group; HRQoL = health-related quality of life; mCRC = metastatic colorectal cancer; N = No; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NS = not specified; OS = overall survival; T/T = trifluridine/tipiracil; UK = United Kingdom; Y = Yes		

Appendix 3: Details and deterministic ICER of ERG analyses (for validation purposes)

#		Adjusted cell(s)	Deter-ministic ICER
	Fixing errors		
1	AE in updated model (BSC)	Adverse EventsQ39:R47	£45,808
	Fixing violations		
2	Keep BSA fixed in PSA	ParametersO32:O33	£44,032
3	Correct EOL costs	ListsI54	£44,059
4	Correct Medical oncologist outpatient consultation costs	CostsF98	£44,066
1-4	Fixing errors + violations combined		£45,870
	Matters of judgement		
5	BSA based on observed trial data	DosingJ18	£44,194
6	Update costs of adverse events	Adverse EventsI30:J42 & Adverse EventsAC21:AF42	£44,658
7	Use treatment specific post progression treatment costs	CostsF80	£44,385
8	Equal treatment delay (using TT value)	Survival and ProgressionI42 & Survival and ProgressionI35	£44,407
9	Use RECOURSE data instead of pooled estimates	ControlsG15	£45,748
10	Use unstratified time-to-event models for PFS and OS	Survival and ProgressionI18 & Survival and ProgressionI21	£43,935
11	Use CORRECT utilities (including AE disutility of 0.01 for being on TT)	UtilitiesF13	£45,509
	ERG base case		£52,648
	ERG Pooled analyses	CostsF56:58 & DosingJ19 & Adverse EventsM17 & ControlsG15	£49,963
	Exploratory sensitivity analyses (conditional on ERG base case)		
	Incorporating costs of additional AE	Adverse EventsM18	£52,545
	Use time on treatment instead of PFS	TTDG13	£52,967
	Alternative source for medical resource use (Hoyle et al 2013[62]; Table 4)	Resource useI18 & CostsF97	£56,709
	Alternative AE disutility for being on TT (see ERG report)	'Adverse EventsAH22:AI46 & UtilitiesD22 & PF - IntS14	£52,090
	Use BSA from the UK	DosingJ18	£54,442

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Trifluridine with tipiracil hydrochloride for treating metastatic colorectal cancer after standard therapy [ID876]

You are asked to check the ERG report from Kleijnen Systematic Reviews to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE the end of 18 May using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Discussion of availability of HRQoL data

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 9 of the report, within the section regarding the critique of the decision problem in the company's submission, the ERG state: *"Furthermore, the Evidence Review Group (ERG) noted that on 25 February 2016, a positive summary of opinion was issued by the European Medicines Agency (EMA). However, health-related quality of life (HRQoL) data were not collected in either of the two clinical trials presented in the CS."* Though this is true, the lack of HRQoL data should not be discussed as a potential issue relating to the decision problem, as it refers to the clinical data available. Additionally, this should not be stated following the EMA summary of opinion, as it suggests that the two statements are related.	Though the statement itself is factually accurate, we would ask for it to be removed, given that the lack of HRQoL present in the two clinical trials is already discussed in further detail within the "Summary of cost effectiveness submitted evidence by the company" section. We ask this for the following reasons: • Use of the statement following discussion regarding the positive summary of opinion by the EMA suggests that the opinion should be taken with caution due to the lack of HRQoL data within the trials – this is misleading, as the decision was made by the EMA in consideration of the trial data available. • Discussion regarding the lack of HRQoL data within the clinical trials should be discussed in association with the steps taken to account for this – as discussed in the "Summary of cost effectiveness submitted evidence by the company" section. • The lack of HRQoL data available within the clinical trials does not violate the NICE case, as Section 5.8 states *"If not available in the relevant clinical trials, EQ-5D data*	Amending this error will not affect model results, but will promote understanding that although HRQoL data are not available from clinical trials, this does not mean the evidence submitted is non-conformant to the decision problem. NICE guidance suggests that EQ-5D utilities should be used where available, which the evidence submitted adheres to.	Not a factual error It should be noted that the paragraph with the statement on health-related quality of life data not being collected, is embedded in a wider statement, i.e. "The decision problem in the company submission (CS) is in line with the final scope issued by the National Institute for Health and Care Excellence (NICE). Furthermore, the Evidence Review Group (ERG) noted that on 25 February 2016, a positive summary of opinion was issued by the European Medicines Agency (EMA). However, health-related quality of life (HRQoL) data were not collected in either of the two clinical trials presented in the CS." As stated by the company the statement on HRQoL data is true and is hard to see how it can be read out of context.

	can be sourced from the literature."		

Issue 2 Discussion of clinical evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 9 of the report, within the section regarding the summary of clinical effectiveness evidence submitted by the company, the ERG state: *"The pooled mean increase in OS was 2.3 months (T/T: 9.1 months, BSC: 6.8 months)."* This statement is misleading, and contains incorrect data mistakenly presented. In addition, these data are also presented on the following pages: Page 11 paragraph 7 Page 48 paragraph 1 Page 51 paragraph 3 Page 51 paragraph 4 which states *"median survival of 2.3 months (pooled)"* Median is a typographical error Page 98 paragraph 3 and table 5.28 Page 109 bullet point 2	This statement is misleading, as the outcome should be stated as the restricted mean i.e. assuming all patients were dead at the end of follow up. The restricted mean is calculated as the integral of the Kaplan-Meier curve (i.e. the area under the curve), and is therefore subject to a number of caveats relating to the calculation of the Kaplan-Meier curve itself (e.g. censoring). This issue was flagged within the CS on page 170 which states: *"At the end of the Kaplan-Meier curves, all patients were assumed to die."* The Kaplan-Meier curve was not considered to be the optimal measure of expected survival outcomes for patients within the model, and therefore parametric curve fits were applied in the model base case. Furthermore, these figures were based on data that were replaced shortly ahead of submission. We apologise for this oversight, and request that the following numbers be considered in line with those produced by the model previously submitted. **Table 1: Summary of model results compared with clinical data *(Revision of Table 74)*** **Outcome** | **Clinical trial** | **Model result**	The statement is misleading, and implies that mean survival outcomes are the same as restricted mean survival outcomes. It is essential that all references to these data, which occur repeatedly throughout the document are appropriately presented clearly as the restricted mean to avoid any confusion. Addressing this error will aid understanding of the evidence presented.	Page 51, paragraph 4: "median" was replaced with "mean" For all other comments: Not a factual error The ERG report is based on and in line with the information provided in the company submission.

Page 110 paragraph 4	<table><tr><th></th><th>results (pooled data)</th><th></th></tr><tr><td>Overall survival</td><td>*Median:* BSC: 5.4 months T/T: 7.3 months *Mean:* BSC: 7.2 months T/T: 9.6 months</td><td>*Median:* BSC: 5.3 months T/T: 7.4 months *Mean:* BSC: 7.9 months T/T: 11.1 months</td></tr><tr><td>Progression-free survival</td><td>*Median:* BSC: 1.7 months T/T: 1.9 months *Mean:* BSC: 1.9 months T/T: 3.7 months</td><td>*Median:* BSC: 1.6 months T/T: 2.6 months *Mean:* BSC: 1.9 months T/T: 3.7 months</td></tr><tr><td colspan="3">**Key:** BSC, best supportive care; T/T, trifluridine/tipiracil.</td></tr></table> These numbers therefore provide a pooled restricted mean increase in OS of 2.4 months. In conclusion, we would ask for this statement, along with all others considering this quantity, to be reflective of the information above. In particular, we would ask that the statement in question be amended to the following: *"Based on the pooled trial data, an estimate of the restricted mean OS was calculated to be 2.4 months (T/T: 9.6 months, BSC: 7.2 months). This estimate was made with the caveat that at the end of follow up, all patients were expected to have died."*		
Additionally, the ERG also state:	The statement regarding the use of non-randomised trials is misleading, as these data were not used to	The statement is potentially misleading, as it implies that	Not a factual error

"Two non-randomised trials were presented in the CS." This statement is true, but the ERG do not comment further that these data were not used to inform the model. This is potentially misleading.	inform the model. Data from the clinical trials were deemed sufficient for use within the model. Consequently, we would ask that the statement be amended to the following: *"Two non-randomised trials were identified in the CS, but were not used to inform the de novo economic model."*	non-randomised evidence was used within the economic analysis. Addressing this error will aid understanding of the evidence presented.	The statement is part of the "Summary of clinical effectiveness evidence submitted by the company". The subsequent section "Summary of the ERG's critique of clinical effectiveness evidence submitted" clearly states that the two non-randomised trials were not assessed by the ERG.
On page 10 of the report, the ERG state: *"The populations described in the NICE final scope, including patients with mCRC for whom standard therapies are 'unsuitable', seems approximately similar to the population described by the company, following the anticipated licence, but differs slightly from populations in the trials, which were used to inform the model. Consequently, following the licence it may be possible that patients not represented in the trials receive this medication. This includes patients "for whom standard therapies are unsuitable". It remains unclear in which direction this discrepancy would influence the outcomes."* The licence for the product has been	The anticipated licence for trifluridine/tipiracil (as presented on page 22 of the CS) states: *"Trifluridine/tipiracil is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF (vascular endothelial growth factor) agents and anti-EGFR (epidermal growth factor receptor) agents."* The phrase *"for whom standard therapies are unsuitable"* alludes to patients who are either intolerant to standard therapies or not considered candidates for standard therapies at this line of therapy, not at previous lines of therapy. It is expected that the majority of patients will have received the majority of the therapies listed in the license above. The licence has been written such that trifluridine/tipiracil is only considered for patients that have no other possible treatment options.	The licence was misinterpreted, as the eligibility for treatment applies to the current line the patient is expected to undergo, and does not necessarily relate to prior treatments. The study population considers patients pre-treated with a variety of systemic anti-cancer agents, but not all patients have received all available therapies in both the trials.	Not a factual error The ERG feels that the text of the report is a fair representation of the company submission.

misinterpreted in this statement.	Furthermore, on page 11 of the report, the ERG state: *"Patients were further required* [within the clinical trials] *to have received prior chemotherapy with bevacizumab. However under NICE guidance patients in England would not be able to routinely receive bevacizumab prior to treatment with T/T. The company's interpretation in conjunction with clinical advice was that tumours in patients who had received fewer treatments were likely to be less resistant to additional therapy. This implies that the evidence for T/T presented might underestimate response in a UK population. This is an assumption, but it appears to be fair."* In consideration of this statement, it appears likely that patients who have not received the same prior lines of therapy as per the trial populations may be less resistant to additional therapy. Consequently, we would ask that the statement be amended to the following: *"… patients not represented in the trials receive this medication. This includes patients "for whom standard therapies are unsuitable" i.e. there are no other recommended treatments for a patient at this line. It remains unclear…"*		
On page 11 of the report, the ERG state: *"For the second criterion (extension of life) to be met, NICE usually expects to see "at least an additional 3 months, compared with current NHS treatment". As stated before,*	As previously discussed, this estimate is based on the restricted mean and an incorrect data cut, results of which were inadvertently supplied in Table 74 of the CS. Furthermore, in consideration of the "End of life" criteria, we ask that the report should state the best estimate of survival outcomes, namely the output	Amending the statement to consider the modelled estimate of mean survival avoids issues relating to the use of the restricted mean, and is therefore more representative of expected	Not a factual error As discussed for issue 2. It should be noted that table 7.1 of the ERG report presents the relevant results.

pooled estimates showed smaller differences in mean (OS: 2.3 months; PFS: 1.8 months) and median (OS: 1.9 months; PFS: 0.2 months) survival when comparing T/T to BSC (no confidence intervals available).” We would like to re-iterate how this statement is misleading, based on consideration of an incorrect data cut previously provided and does not consider the long-term efficacy of treatment with trifluridine/tipiracil (i.e. does not consider extrapolated survival curves).	from the economic model using parametric survival curve fitting. Consequently, we would ask that the statement be amended to the following: *“Regarding the CS fulfilling end of life criteria, the ERG believes that the first criterion (short life expectancy) has been met. For the second criterion (extension of life) to be met, NICE usually expects to see “at least an additional 3 months, compared with current NHS treatment”. The results from the de novo economic model demonstrate an estimated increase in mean survival of 3.2 months when comparing T/T to BSC (11.1 versus 7.9 months, respectively). The relevant population will be small but it should be highlighted that the figures presented might be an underestimate as they do not include Wales.”*	outcomes following treatment with trifluridine/tipiracil.	

Issue 3 Discussion surrounding pooled data

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On pages 13 and 63 of the report, the ERG state: *“…the ERG prefers using a more conservative assumption in its base case analysis by using RECOURSE data only. However, since there are no fundamental arguments which prevent the two trials from being pooled, besides the lack of clarity of the methodology, the ERG also presents its base case analysis based on the pooled effectiveness estimates from both trials.”* This statement suggests that whilst there is no	The latter statement should be amended to suggest the ERGs concern with using pooled data whilst not discounting it. Consequently, we would ask that the statement be amended to the following: *“The ERG examined the log-cumulative hazard plots from RECOURSE data only, due to*	The opinion of the ERG regarding the use of pooled data should be consistent, and we would therefore propose this amendment in the interest of clarity.	Not a factual error The two statements cited from the ERG report are consistent, i.e. pooling is not suitable as a result of the lack of clarity regarding the methodology.

evidence to consider pooled data to be inappropriate, the ERG prefer the use of data from RECOURSE only. This statement however is contradicted in the report. On page 66, the ERG state: *"The ERG examined the log-cumulative hazard plots from RECOURSE data only because pooling was not deemed suitable in the current assessment based on above-mentioned arguments."* This contradicts the previous statement which suggests that pooled analysis may still be appropriate. We would consider the latter statement to be misleading, as the pooled analysis was not originally considered to be unsuitable.	*the aforementioned concerns relating to the methodology used for pooling."* We would consider this amendment to be more in line with the stated concerns in previous sections of the document.		

Issue 4 Distribution of body surface area

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 84 of the report, the ERG state: *"According to the ERG, the non-parametrised distribution of BSA from RECOURSE is a reasonable estimate of BSA to calculate drug costs."* The ERG do not clarify why using the non-parameterised distribution of BSA is more reasonable than the log-normal fit presented in the company base-case. Further to this, on page 59 of the report, the ERG state: *"The PSA included BSA scenarios, where BSA was not varied stochastically."* BSA was varied stochastically when the log-	We would consider the need to change the base case setting relating to the distribution of BSA should be done so with logical rationale, and would ask the ERG to amend the statement on page 84 to include reasoning as to why this was deemed more appropriate. Additionally, we would ask the ERG to clarify on page 59 that the static distribution of observed BSA does not vary stochastically. The log-normal fit was chosen in order to allow for stochastic variation in BSA (should this be deemed appropriate), in order to assess the variability in drug cost dependent on this parameter.	The current wording of the document suggests we varied the distribution regarding BSA without logical reasoning. The distribution was varied to capture the uncertainty relating to BSA, which in consideration of available data and its influence on model results, we would consider as parameter uncertainty. Although the ERGs opinion is valid, we feel that this is misleading, given that we are aware that BSA informs active drug cost, and	We agree that the text in Table 5.3 on page 58 of the ERG report is incorrect. The correct text is: "BSA was included in the PSA as a stochastic parameter."

normal distribution fit is applied (as per the base case settings), as it was deemed important to consider given that the cost of treatment relies on this assumption. Whilst we appreciate the ERG consider the variation of BSA to be *"incorrect as variance in BSA is an indication of patient variability and not of parameter uncertainty"*, we would ask that the statement made should clarify whether this refers to the model supplied to the ERG, or the model post-ERG changes. In the first case, the statement above may require amendment as BSA was varied stochastically in the original base case, but was not in the ERG base case.	Consequently, we would ask that the statement be amended to the following: *"The PSA included BSA scenarios, where BSA was not varied stochastically when the observed trial data setting is used. The distribution of BSA was varied however when a log-normal fit was considered, as the company considered this appropriate given its influence on drug costs."*	therefore intentionally explored the uncertainty around these parameters in detail through a range of sources.	
On page 13 of the report, the ERG state: *"According to the ERG, the non-parametrised distribution of BSA from RECOURSE is more reasonable estimate of BSA to calculate drug costs. As this most likely results in an underestimation of T/T costs, the BSA based on the UK population (which most likely results in an overestimation of T/T costs) is considered in an exploratory sensitivity analysis."* We agree that BSA based on the UK population is likely to overestimate T/T costs, however would ask the ERG to consider stating more clearly the caveats associated with using this model setting, as currently this statement is potentially misleading.	We would consider additional information regarding the two possible sources of BSA data to be very important in promoting understanding. Consequently, we would ask that the statement be amended to the following: *"According to the ERG, the non-parametrised distribution of BSA from RECOURSE is more reasonable estimate of BSA to calculate drug costs. As this most likely results in an underestimation of T/T costs, the BSA based on the UK general population (i.e. a non-mCRC specific population which therefore most likely results in an overestimation of T/T costs) is considered in an exploratory sensitivity analysis."*	Page 13 of the report states: *"The CS reported that advisory board clinicians agreed with the use of a lower estimate of BSA as compared with the UK general population since mCRC patients would be expected to lose weight."* We consider it important to state further reasoning as to why this is the case (i.e. potentially non-reflective of the disease area), but agree that use of these data may be considered as an overestimation of T/T costs.	Not a factual error

Issue 5 Minor/Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In paragraph 4 of section 2.2 of the report on page 18, the ERG state: *"This is correct as regorafenib is not licensed"* This statement is incorrect, as regorafenib is licensed.	Regorafenib is licensed for the treatment of patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy. Consequently, we would ask that the statement be amended to the following: *"Regorafenib is licensed in the UK for the treatment of mCRC, however, it is not recommended by NICE due to a non-submission (TA334 – terminated appraisal)"*	Factual accuracy	Changes were made accordingly (page 19)
In paragraph 4 of section 3.2 of the report on page 22, the ERG state: "*An average course of treatment is 2 days…"* This statement is incorrect, as the average course of treatment is 28 days.	The average course of treatment of trifluridine/tipiracil is 28 days, as specified in the summary of product characteristics. Consequently, we would ask that the statement be amended to the following: "*An average course of treatment is 28 days…"*	Factual accuracy	This was corrected and the text on page 22 now reads: "The company stated that trifluridine/tipiracil is marketed as an oral tablet with dosing based on body surface area at a recommended starting dose of 35mg/m^2 followed by individual adjustments for safety and tolerability. An average course of treatment is 28 days with management in secondary care either as a chemotherapy day case or outpatient setting (Sections 2.3.1 and 2.4.1 of the CS)."