Indication	For the treatment of metastatic or locally advanced and inoperable colorectal cancer in patients who have received 2 or more prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies with or without anti-VEGF agents and/or anti-EGFR-based agents, if disease reoccurrence is within 6 months of the last dose of neo-adjuvant or adjuvant treatment this can be classed as a prior line for metastatic or locally advanced and inoperable disease. NB: The regimens of either FOLFIRINOX or FOLFOXIRI can be counted as 2 chemotherapy regimens. NB: patients must not have received prior trifluridine plus tipiracil.
Treatment Intent	Palliative
Frequency and number of cycles	Repeat every 28 days. Continue until disease progression or unmanageable toxicity or patient choice. NB: If the trifluridine plus tipiracil has to be permanently discontinued then the bevacizumab will also be stopped at the same time. A formal medical review as to whether treatment should continue or not should occur no later than by the end of the 2nd cycle of therapy.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor for proteinuria by dipstick urinalysis and check blood pressure prior to starting and before each cycle. • Report to consultant if BP >/= 140/90. Reference should be made to KMCC guidelines for bevacizumab induced hypertension. See table 4 for guidance on proteinuria. • FBC, U&Es, LFTs Day 1 of every cycle. Neutrophils should be >/=1.5 and platelets >/=100. • **Management of toxicity and dose modifications** • **Trifluridine-tipiracil:** (see table 3 and also table 2 for patients with severe renal impairment) o Neutrophils 0.5 – 1.49 or Platelets 50-100. Delay treatment until recovered, then restart treatment at same dose and inform the treating consultant. o Neutrophils < 0.5 or platelets <50. Delay treatment until recovered. If the delay is more than 1 week, or febrile neutropenia observed, or non-haematological Grade 3 or Grade 4 adverse reaction (except for Grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhoea responsive to antidiarrhoeals) dose reduce as follows, o Interrupt dosing until toxicity resolves to Grade 1 or baseline. o When resuming dosing, decrease the dose level by 5mg/m^2/dose from the previous dose level. o A maximum of 3 dose reductions are permitted to a minimum dose of 20mg/m^2 (or 15 mg/m^2/dose twice daily in severe renal impairment) twice daily. Dose level reduction is to 30mg/m^2 bd, 25mg/m^2 bd and 20mg/m^2 bd as appropriate. o Dose escalation is not permitted after it has been reduced.

	• **Bevacizumab:** Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended. If trifluridine plus tipiracil is delayed, bevacizumab should also be delayed. If the trifluridine plus tipiracil has to be permanently discontinued then the bevacizumab will also be stopped at the same time. • **Renal Impairment:** o **Trifluridine-tipiracil**: No dose adjustment in mild or moderate renal impairment (30-89ml/min). In severe renal impairment (15-29ml/min) a starting dose of 20 mg/m^2 is recommended. One dose reduction to a minimum dose of 15 mg/m^2 twice daily is permitted (see table 2). Dose escalation is not permitted after it has been reduced. Not recommended in end stage renal disease (CrCl<15ml/min). o **Bevacizumab**: no dose recommendation. • **Hepatic Impairment:** o **Trifluridine-tipiracil:** No dose adjustment in mild hepatic impairment. Not recommended in moderate or severe hepatic impairment (total bilirubin > 1.5 x ULN) as a higher incidence of Grade 3 or 4 hyperbilirubinaemia is observed in patients with baseline moderate hepatic impairment (limited data). o **Bevacizumab:** no dose recommendation. • **Bevacizumab infusion-related reactions:** If a patient experiences a mild infusion-related reaction, give the next infusion over 60 - 90 minutes +/- chlorphenamine cover. If this is tolerated, reduce the infusion time for the next doses in a step-wise fashion to a minimum of 30 minutes, and maintain that infusion time for all remaining doses. • **Bevacizumab specific monitoring and guidance:** o Bevacizumab may adversely affect wound healing. Do not give bevacizumab if patient has undergone major surgery within the last 28 days. Treatment should be stopped at least 28 days prior to elective surgery. o Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation with bevacizumab. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation. It is recommended an OGD is undertaken in patients at high risk of variceal bleeding and that all sizes of varices be assessed and treated as per local standard of care prior to treatment. o Patients may be at increased risk for the development of fistulae when treated with bevacizumab. o Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with bevacizumab. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. o Caution should be exercised when bevacizumab and intravenous bisphosphonates are administered simultaneously or sequentially, as cases of osteonecrosis of the jaw have been reported. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with bevacizumab. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible. o Any suspected thrombosis and/or haemorrhage d/w consultant. o Patients with a history of arterial thromboembolism, diabetes or >65 years old should be treated with caution. Patients with thromboembolic reactions </= Grade 3 need to be closely monitored. o Bevacizumab should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism (refer to SPC for management).

	• **Common drug/food interactions (for comprehensive list refer to BNF/SPC):**
	  ○ Antivirals which are human thymidine kinase substrates (e.g. zidovudine) may have a reduced anti-viral effect with trifluridine-tipiracil.
	  ○ Caution when bevacizumab is used with drugs known to cause bleeding, concurrent use may increase risk.
	• **Driving and using machinery**: There may be a minor influence on the ability to drive and use machines. Fatigue, dizziness or malaise may occur during treatment.
	• **For oral self-administration**: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Macmillan information sheet.

References	KMCC protocol COL-044 V1 CDF V1.368 accessed online

NB For funding information, refer to CDF and NICE Drugs Funding List

Repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1 and 15	**BEVACIZUMAB**	**5mg/kg**	IV	15mins*	In a total of 100mls sodium chloride 0.9% Flush line with sodium chloride 0.9%
	If a patient experiences a mild infusion-related reaction, give the next infusion over 60 - 90 minutes +/- chlorphenamine cover. If this is tolerated, reduce the infusion time for the next doses in a step-wise fashion to a minimum of 30 minutes, and maintain that infusion time for all remaining doses. *unlicensed rate of infusion				

TTO	Drug	Dose	Route	Directions
Day 1	**TRIFLURIDINE & TIPIRACIL** **(Lonsurf®)**	**35mg/m² (Max.80mg/dose)**	PO	BD on Days 1 to 5 and Days 8 to 12 Swallow whole with water within one hour after completion of morning and evening meals. Available as 15mg (+ 6.14 mg tipiracil) and 20mg (+ 8.19 mg tipiracil) trifluridine tablets. See table 1 for starting dose calculation. If doses are missed or withheld, they should be omitted.
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 days continuously. (dispense on cycle 1 then only if required)
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.

Table 1 – Trifluridine & tipiracil - Starting dose calculation according to BSA

Starting dose	BSA (m^2)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg/6.14 mg	20 mg/8.19 mg	
35 mg/m^2	< 1.07	35	1	1	70
	1.07 - 1.22	40	0	2	80
	1.23 - 1.37	45	3	0	90
	1.38 - 1.52	50	2	1	100
	1.53 - 1.68	55	1	2	110
	1.69 - 1.83	60	0	3	120
	1.84 - 1.98	65	3	1	130
	1.99 - 2.14	70	2	2	140
	2.15 - 2.29	75	1	3	150
	≥ 2.30	80	0	4	160

Table 2 – Trifluridine & tipiracil – starting dose and dose reduction in patients with severe renal impairment according to BSA

Reduced dose	BSA (m^2)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg/6.14 mg	20 mg/8.19 mg	
Starting dose					
20 mg/m^2	< 1.14	20	0	1	40
	1.14 – 1.34	25[a]	2[a]	1[a]	50[a]
	1.35 – 1.59	30	2	0	60
	1.60 – 1.94	35	1	1	70
	1.95 – 2.09	40	0	2	80
	2.10 – 2.34	45	3	0	90
	≥ 2.35	50	2	1	100
Dose reduction: From 20 mg/m^2 to 15 mg/m^2					
15 mg/m^2	< 1.15	15	1	0	30
	1.15 – 1.49	20	0	1	40
	1.50 – 1.84	25[a]	2[a]	1[a]	50[a]
	1.85 – 2.09	30	2	0	60
	2.10 – 2.34	35	1	1	70
	≥ 2.35	40	0	2	80

Table 3 – Trifluridine & tipiracil dose reductions according to BSA

Reduced dose	BSA (m^2)	Dose in mg (2x daily)	Tablets per dose (2x daily)		Total daily dose (mg)
			15 mg/6.14 mg	20 mg/8.19 mg	
Level 1 dose reduction: From 35 mg/m² to 30 mg/m²					
30 mg/m²	< 1.09	30	2	0	60
	1.09 - 1.24	35	1	1	70
	1.25 - 1.39	40	0	2	80
	1.40 - 1.54	45	3	0	90
	1.55 - 1.69	50	2	1	100
	1.70 - 1.94	55	1	2	110
	1.95 - 2.09	60	0	3	120
	2.10 - 2.28	65	3	1	130
	≥ 2.29	70	2	2	140
Level 2 dose reduction: From 30 mg/m² to 25 mg/m²					
25 mg/m²	< 1.10	25[a]	2[a]	1[a]	50[a]
	1.10 - 1.29	30	2	0	60
	1.30 - 1.49	35	1	1	70
	1.50 - 1.69	40	0	2	80
	1.70 - 1.89	45	3	0	90
	1.90 - 2.09	50	2	1	100
	2.10 - 2.29	55	1	2	110
	≥ 2.30	60	0	3	120
Level 3 dose reduction: From 25 mg/m² to 20 mg/m²					
20 mg/m²	< 1.14	20	0	1	40
	1.14 – 1.34	25[a]	2[a]	1[a]	50[a]
	1.35 – 1.59	30	2	0	60
	1.60 – 1.94	35	1	1	70
	1.95 – 2.09	40	0	2	80
	2.10 – 2.34	45	3	0	90
	≥ 2.35	50	2	1	100

[a] At a total daily dose of 50 mg, patients should take 1 x 20 mg/8.19 mg tablet in the morning and 2 x 15 mg/6.14 mg tablets in the evening.

Table 4: Proteinuria – management of bevacizumab

1+ or 2+ on dipstick (0.3 – 2.9g/L)	3+ on dipstick (3 - 19g/L):	4+ on dipstick (≥20g/L)
Continue with bevacizumab. No additional evaluation required	May have dose of bevacizumab as scheduled, but will need 24-hour urine collection to measure protein a few days before next cycle due. If 24hr protein result < 2g, continue with bevacizumab. With continued proteinuria monitoring via 24-hour urine before each dose. If the 24-hour protein level falls to < 1g/24hr, return to dipstick analysis. If >/=2g, withhold bevacizumab until repeat 24-hour urine collection shows < 2g protein. Then re-introduce bevacizumab, with continued proteinuria monitoring via 24-hour urine.	**Withhold bevacizumab**. 24-hour urine collection required. Follow 24-hour urine monitoring and guidance as for 3+ on dipstick.