TRIFLURIDINE-TIPIRACIL (Lonsurf) BEVACIZUMAB

INDICATION (ICD10) C18, C20

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (TRI3)

1. For patients with either metastatic or locally advanced and inoperable colorectal adenocarcinoma cancer who have received 2 or more prior anticancer treatment regimens including fluoropyrimidine with, oxaliplatin and irinotecan-based chemotherapies with or without anti-VEGF agents and/or anti-EGFR-based agents (but no previous trifluridine plus tipiracil). PS 0 or 1. (TA1008)

REGIMEN

Bevacizumab and trifluridine-tipiracil must be started at the same time (no previous trifluridine-tipiracil).

Days 1 to 5 and 8 to 12	**TRIFLURIDINE-TIPIRACIL**	35mg/m^2 (maximum 80mg/dose)	oral	twice daily
Days 1 and 15	**BEVACIZUMAB**	5mg/kg	IV infusion	#ml sodium chloride

diluent volume for dose prescribed as per national standardised product specification

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 28 days until disease progression (formal medical review by end of 2nd 28 day cycle).

ANTI-EMETICS

Low risk days 1 to 12
Minimal risk day 15

CONCURRENT MEDICATION REQUIRED

Bevacizumab	None
Trifluridine-tipiracil	None
GCSF	Consider in patients with recurrent neutropenia, starting between days 13 and 15, duration at consultant's discretion.

ADMINISTRATION

Bevacizumab	The initial dose should be administered over 90 minutes, if tolerated well the second infusion may be administered over 60 minutes. If the 60 minute infusion is well tolerated all subsequent infusions may be administered over 30 minutes.
Trifluridine-tipiracil	One tablet contains Trifluridine 15mg + Tipiracil 6.14mg or Trifluridine 20mg +Tipiracil 8.19mg. Tablets should be taken 12 hours apart. Swallowed with water within 1 hour after completion of the morning and evening meals.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Bevacizumab – neutral

Central or peripheral line

INVESTIGATIONS

Blood results required before SACT administration

FBC, U&E and LFTs Neutrophils ≥1.5x10^9/L (and see dose modifications) Platelets ≥100x10^9/L (and see dose modifications)	baseline and every cycle (day 1) (consider FBC pre-day 15, according to Trust policy)
Serum creatinine (and calculated CrCl)	baseline and every cycle (day 1)
Blood pressure	baseline and before every bevacizumab dose
Urinalysis for proteinuria	baseline and before every bevacizumab dose
Weight	baseline and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Bevacizumab	Arterial thromboembolism Gastrointestinal perforation Haemorrhage Hypertension Wound healing complications
Trifluridine-tipiracil	Bone marrow suppression Diarrhoea Renal and hepatic impairment Stomatitis

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS

(not exhaustive list check SPC/BNF/Stockleys)

Bevacizumab	-
Trifluridine-tipiracil	-

DOSE MODIFICATIONS

If the trifluridine plus tipiracil has to be permanently discontinued then the bevacizumab will also be stopped at the same time.

Trifluridine-tipiracil

Dose level	Dose
Full dose	35mg/m^2
First dose reduction	30mg/m^2
Second dose reduction	25mg/m^2
Third dose reduction	20mg/m^2 (minimum dose 20mg/m^2 twice daily)

Dose escalation is not permitted after it has been reduced.

Haematological

Trifluridine-tipiracil

Neutrophils <0.5×10^9/L	interrupt treatment, resume once ≥1.5×10^9/L
Platelets <50×10^9/L	interrupt treatment, resume once ≥75×10^9/L
Febrile neutropenia	• Interrupt dosing until toxicity resolves to grade 1 or baseline. • When resuming dosing, decrease the dose level by 5mg/m^2 from the previous dose level. • Dose reductions are permitted to a minimum dose of 20mg/m^2 twice daily (or 15mg/m^2 twice daily in severe renal impairment). • Do not increase dose after it has been reduced.
CTCAE grade 4 neutropenia (<0.5x10^9/L) or thrombocytopenia (<25×10^9/L) that results in more than 1 week's delay in start of next cycle	• Interrupt dosing until toxicity resolves to grade 1 or baseline. • When resuming dosing, decrease the dose level by 5mg/m^2 from the previous dose level. • Dose reductions are permitted to a minimum dose of 20mg/m^2 twice daily (or 15mg/m^2 twice daily in severe renal impairment). • Do not increase dose after it has been reduced.

Non-haematological

Bevacizumab

Hypertension

Baseline blood pressure should be <150/100mmHg.

Diastolic increase >20mmHg above baseline or BP rises to >150/100mmHg	Antihypertensive therapy may be required.
Blood pressure >180/110mmHg	It is advised that bevacizumab therapy is withheld until blood pressure controlled.

Proteinuria

Urine dipstick result. 1+ or 2+ on dipstick (0.3–2.9g/L)	Continue with bevacizumab. No additional evaluation required.
3+ on dipstick (3-19g/L)	May have dose of bevacizumab as scheduled, but 24 hour urine to measure 24 hour protein to be done 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.
4+ on dipstick (≥20g/L)	Withhold bevacizumab. 24 hour urine required. Follow 24 hour urine monitoring and guidance as for 3+ on dipstick.

Wound healing
Bevacizumab may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. Therapy should also be withheld for at least 28–60 days before elective surgery.

Trifluridine-tipiracil

CTCAE non-haematologic grade 3 or grade 4 adverse reaction; except for grade 3 nausea and/or vomiting controlled by antiemetic therapy or diarrhoea responsive to antidiarrhoeal medicinal products	• Interrupt dosing until toxicity resolves to grade 1 or baseline. • When resuming dosing, decrease the dose level by 5mg/m^2 from the previous dose level. • Dose reductions are permitted to a minimum dose of 20mg/m^2 twice daily (or 15mg/m^2 twice daily in severe renal impairment). • Do not increase dose after it has been reduced.

Hepatic impairment
Bevacizumab
The safety and efficacy have not been studied in patients with hepatic impairment.

Trifluridine-tipiracil

Bilirubin of >1.5xULN	Not recommended

Renal impairment
Bevacizumab
The safety and efficacy have not been studied in patients with renal impairment.

Trifluridine-tipiracil

CrCl >30ml/min	give 100% dose
CrCl 15-29ml/min	Starting dose of 20mg/m^2 twice daily. One dose reduction to a minimum dose of 15mg/m^2 twice daily is permitted based on individual safety and tolerability. Dose escalation is not permitted after it has been reduced.

REFERENCES
1. SPC

Assessments

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed consent	x				
Clinical assessment	x		Pre-C2		Alternate cycles, or at clinician's discretion
SACT assessment (PS and toxicities)	x	x	x	x	Every cycle
FBC	x	x	x	x	Every cycle
U&E & LFTs (including AST and ALP) & magnesium	x	x	x	x	Every Cycle
CrCl	x	x	x	X	Every cycle
Blood pressure					Every bevacizumab dose
Urinalysis for proteinuria					Every bevacizumab dose
CT scan	x				At baseline, then CT-restaging at 3 cycles, or at clinician's discretion
Weight recorded	x	x	x	x	Every cycle
Height	x	x	x	x	Every cycle