Somerset, Wiltshire, Avon and Gloucestershire Cancer Alliance

Bevacizumab & Lonsurf (Colorectal)

Please note this protocol has been produced in a new format that is currently being piloted. Any feedback on this new format should be sent to SSGMeetings@uhbw.nhs.uk

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Indication

Trifluridine-tipiracil (Lonsurf) with bevacizumab for treating metastatic colorectal cancer after 2 lines of systemic treatment(including fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapies, antivascular endothelial growth factor or anti-epidermal growth factor receptor treatments).

(NICE TA1008)

Response Rates

Phase 3 SUNLIGHT trial
Trifluridine-tipiracil (Lonsurf) plus bevacizumab (n=246) vs trifluridine-tipiracil (Lonsurf) alone (n=246)
Median OS: Lonsurf plus bevacizumab = 10.8 months vs Lonsurf alone = 7.5 months
Median PFS: Lonsurf plus bevacizumab = 5.6 months vs Lonsurf alone = 2.4 months

Regimen details

Day	Drug	Dose	Route
1-5 & 8-12	Trifluridine-Tipiracil (Lonsurf)	35mg/m^2 BD	Oral
1 & 15	Bevacizumab	5mg/kg	IV infusion

Trifluridine-tipiracil may be continued as single agent in the event of bevacizumab toxicity requiring discontinuation. Bevacizumab monotherapy is not permitted.

Cycle frequency
28 days

Number of cycles
Until disease progression or unacceptable toxicity.

Pre-medication
Nil

Supportive medication
Loperamide if required.
Antiemetics if required.
Topical emollients to prevent PPE
Proton pump inhibitor if required.
Antihypertensives may be required to manage hypertension commonly observed with bevacizumab therapy.
Consider GCSF (e.g. days 13-17) as per local policy.

Emetogenicity
This regimen has low emetic potential.

Administration
Bevacizumab is administered as an intravenous infusion in sodium chloride 0.9% to a final concentration of between 1.4 to 16.5mg/mL. Doses up to 1650mg are administered in 100mL sodium chloride 0.9%, doses greater than 1650mg are administered in 250mL sodium chloride 0.9%.

The first infusion must be given over 90 minutes. If tolerated, the next infusion can be given over 60 minutes; if this is also tolerated, subsequent infusions can be given over 30 minutes.

Bevacizumab should not be initiated for at least 28 days following major surgery or until the wound is fully healed. For elective surgery, bevacizumab should be withheld for 28 days following surgery. For minor surgery (including port placement) bevacizumab should be withheld for 7 days following surgery.

Trifluridine/Tipiracil is available as two strengths of tablet:
15 mg tablet containing 15 mg /6.14 mg of trifluridine and tipiracil (as hydrochloride)
20mg tablet containing 20 mg /8.19 mg of trifluridine and tipiracil (as hydrochloride)

Dosing is based on the trifluridine dose and is rounded to the nearest 5mg. The dose must not exceed 80mg BD.

Tablets should be taken twice a day within 1 hour of morning and evening meals. The doses should be swallowed whole with a glass of water. It may be easier for patients to take the tablets Monday-Friday for ease of remembering treatment days, although this is not essential.

Doses should be prescribed as per the following table:

Body surface area (m^2)	**Dose (mg)**	**Tablets per dose**	
		15mg	**20mg**
≤ 1.07	35mg BD	1	1
1.07-1.22	40mg BD	0	2
1.23-1.37	45mg BD	3	0
1.38-1.52	50mg BD	2	1
1.53-1.68	55mg BD	1	2
1.69-1.83	60mg BD	0	3
1.84-1.98	65mg BD	3	1
1.99-2.14	70mg BD	2	2
2.15-2.29	75mg BD	1	3
≥2.30	80mg BD	0	4

Extravasation

Bevacizumab is neutral (Group 1)

Mandatory investigations – pre first cycle

Investigation	**Validity period**
FBC	14 days
U&E (including creatinine)	14 days
LFT	14 days
Blood pressure (BP)	Baseline
Proteinuria (dipstick)	On day 1

Additional investigations advised pre-first cycle

- ECG +/- echocardiogram if significant cardiac history.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Blood pressure	Before each bevacizumab dose (more frequently if hypertension)
Proteinuria (dipstick)	Before each bevacizumab dose*

* If 3+ on dipstick perform 24 hour urinalysis and delay bevacizumab until <2g/24 hours.

Additional investigations advised pre subsequent cycles

- Repeat ECG +/- echocardiogram as clinically indicated

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer must be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.5 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine clearance (CrCl)	> 30 mL/min
Bilirubin	≤ 1.5 x ULN
Proteinuria	1+ or 2+ on dipstick, <2g/24 hours on urinalysis
Blood pressure	<140/90mmHg

Dose modifications

Trifluridine-tipiracil: A maximum of 3 dose reductions are permitted to a minimum dose of 20mg/m^2 BD. See SPC for BSA based dose banding tables at the different dose reduction levels.

Dose level	Dose
Full dose	35mg/m^2 BD
First dose reduction	30mg/m^2 BD
Second dose reduction	25mg/m^2 BD
Third dose reduction	20mg/m^2 BD

Once the dose has been reduced it should not be re-escalated. If trifluridine-tipiracil is discontinued, bevacizumab must also be discontinued.

Bevacizumab: Dose reduction is not recommended; doses should be withheld, or treatment discontinued.

Bevacizumab should not be administered alone in the case of delay or omission of trifluridine-tipiracil dosing, the entire cycle should be delayed and bevacizumab restarted at the same time as trifluridine-tipiracil.

Haematological toxicity

To commence a new cycle, neutrophils should be ≥ 1.5 x 10^9/L and platelets should be ≥ 75 x 10^9/L.

During a cycle, trifluridine-tipiracil and bevacizumab should be withheld and recommenced as per the table below:

Haematological parameter	Interruption criteria	Resumption criteria
Neutrophils	< 0.5 x 10^9/L	≥ 1.5 x 10^9/L
Platelets	< 50 x 10^9/L	≥ 75 x 10^9/L

If febrile neutropenia or grade 4 neutropenia (< 0.5 x 10^9/L) or thrombocytopenia (< 25 x 10^9/L) resulting in more than 1 week's delay to start of next treatment:
- withhold trifluridine-tipiracil and bevacizumab until resolves to ≤ grade 1 or baseline
- resume dosing when neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L at next dose reduction level

Renal impairment

Trifluridine-tipiracil: No dose adjustment in mild to moderate renal impairment (CrCl ≥ 30ml/min). For patients with severe renal impairment (CrCl 15-29ml/min) a starting dose of 20mg/m^2 twice daily is recommended with a further dose reduction to 15mg/m^2 twice daily permitted if required due to toxicity. Administration in end stage renal disease (CrCl < 15ml/min) is not recommended.
Bevacizumab: There is no data regarding administration of bevacizumab in patients with renal impairment and dose modification should not be required.

Hepatic impairment

Trifluridine-tipiracil: no dose modification in mild hepatic impairment. Trifluridine-tipiracil is not recommended in moderate-severe hepatic impairment (bilirubin > 1.5 x ULN) as limited data suggests higher incidence of G3 and 4 hyperbilirubinaemia in patients with moderate-severe hepatic impairment at baseline.

Bevacizumab: There is no data regarding administration of bevacizumab in patients with hepatic impairment and dose modification should not be required.

Dose reductions for other toxicities

Any other ≥ grade 3 toxicity (except grade 3 nausea and/or vomiting controlled by anti-emetics or diarrhoea controlled by anti-diarrhoeals):
- withhold treatment with both agents until resolves to ≤ grade 1 or baseline
- resume treatment with trifluridine-tipiracil 5mg/m^2 BD dose reduction (to a minimum dose of 20mg/m^2 BD)
- the dose should not be increased following a dose reduction

Side Effects

SUNLIGHT study:

Toxicity		Any grade (%)	Grade 3 or 4 (%)
Haematological	Neutropenia	62.2	43.1
	Anaemia	28.9	6.1
	Thrombocytopenia	17.1	2.8
Non-haematological	Nausea	37.0	1.6
	Asthenia	24.4	4.1
	Fatigue	21.5	1.2
	Diarrhoea	20.7	0.8
	Decreased appetite	20.3	0.8
	Vomiting	18.7	0.8
	Abdominal pain	11.8	2.0
	Constipation	11.0	0
	Stomatitis	11.0	0.4
	Hypertension	10.2	5.7

Specific drug related side effects:

Bevacizumab

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Hypertension	Hypersensitivity reactions	Hypertensive encephalopathy
Thromboembolism	Haemorrhage	Posterior reversible encephalopathy syndrome (PRES)
Wound healing complications	GI perforation	
Proteinuria	Fistula	Renal thrombotic microangiopathy
Fatigue	Congestive heart failure	Osteonecrosis of the jaw

Bevacizumab toxicity management

Toxicity	Definition	Action
Infusion related reactions	Grade ≤ 2	**90 minute infusion**: premedication prior to next dose and give over 90 minutes (if tolerated may reduce infusion duration for future cycles with premedication) **60 minute infusion**: all subsequent doses should be given over 90 minutes with premedication. **30 minute infusion**: all subsequent doses should be given over 60 minutes with premedication.
	Grade >2	Discontinue bevacizumab
Hypertension	Grade 1 Increase of >20 mmHg (diastolic) or >140/90 mmHg (previously within normal limits) asymptomatic and transient (<24 hours)	Recheck 1 hour later: - if <140/90 mmHg – administer as normal - if 140/90 mmHg - 150/100 mmHg –administer and recheck BP 48 hours later (commence antihypertensives if BP remains >140/90 mmHg). - if >150/100 mmHg – omit and recheck BP 48 hours later(commence antihypertensives if BP remains >140/90 mmHg).
	Grade 2 Recurrent or persistent (> 24 hours) increase by 20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits	Withhold bevacizumab. Commence antihypertensive medication. Once BP <140/90 mmHg restart treatment.
	Grade 3 ≥160/100mmHg	Withhold bevacizumab. If persistent, escalate antihypertensive treatment If hypertension cannot be controlled permanently discontinue treatment.
	Grade 4 Hypertensive crisis	Permanently discontinue bevacizumab.
Proteinuria	1+ or 2+	Continue bevacizumab.
	3+	Continue bevacizumab, with 24 hour urinalysis prior to next cycle, then: - if <2g continue treatment with 24 hour urinalysis prior to each dose. If falls to <1g return to dipstick analysis. - if ≥2g withhold until repeat urinalysis <2g then restart treatment with 24 hour urinalysis prior to each dose.
	4+	Withhold bevacizumab. 24 hour urinalysis. Then treat as above.
	Nephrotic syndrome	Permanently discontinue bevacizumab

Trifluridine-tipiracil

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Anaemia	Infections, neutropenic sepsis	Electrolyte disturbances
Neutropenia	Dysgeusia	Arthralgia, myalgia
Thrombocytopenia	Stomatitis	QT prolongation
Decreased appetite	Dyspepsia	
Diarrhoea	Dry skin, pruritis, rash	
Nausea, vomiting	Deranged LFTs	
	Proteinuria	

Additional information

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

Bevacizumab should be used with caution in patients with:
- Untreated central nervous system metastases
- History or risk factors for thromboembolic events
- Significant cardiac risk factors for development of congestive heart failure

Significant drug interactions – for full details consult product literature/ reference texts

Trifluridine-tipiracil:
Medicinal products that interact with nucleoside transporters CNT1, ENT1 and ENT2: use with caution, increased risk of toxicity.
Inhibitors of OCT2 or MATE1: use with caution, increased risk of toxicity.
Human thymidine kinase substrates, e.g., zidovudine: use with caution may reduce efficacy of trifluridine /tipiracil. If using antiviral medicinal products that are human thymidine kinase substrates, monitor for possible decreased efficacy of the antiviral medicinal product, and consider switching to an alternative antiviral medicinal product that is not a human thymidine kinase substrate, such as lamivudine, zalcitabine, didanosine and abacavir.
Hormonal contraceptives: it is unknown whether trifluridine /tipiracil may reduce the effectiveness of hormonal contraceptives. Therefore, women using hormonal contraceptive must also use a barrier contraceptive method.

Bevacizumab: No documented significant reactions.

References

- National Institute for Health and Care Excellence. NICE Technology Appraisal Guidance 1008 accessed 1 Feb 2017 via www.nice.org.uk
- Summary of Product Characteristics Lonsurf (Servier) accessed 07 Nov 2024 via www.medicines.org.uk
- Summary of Product Characteristics Bevacizumab (Roche) accessed 07 Nov 2024 via www.medicines.org.uk
- Prager GW et al. Trifluridine-tipiracil and bevacizumab in Refractory Metastatic Colorectal Cancer. N Engl J Med 2023;388:1657-1667.

Version	Issue date	Review date	Revision	Written/Checked/Authorised
1	Nov 2024	Nov 2027	New protocol	Written/reviewed: Dr T Strawson-Smith (Consultant Oncologist, UHBW NHS Trust) Checked: Kate Gregory (Lead Pharmacist for SACT protocols, SWAG Cancer Alliance) Authorised: Dr J Braybrooke (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)
1.1	Jan 2026	Nov 2027	Minor adjustments to wording to clarify need to hold bevacizumab treatment if trifluridine-tipiracil treatment is delayed/omitted	Updated by: Kate Gregory (Lead Pharmacist for SACT Protocols, SWAG Cancer Aliiance)

Schedule of investigations and treatment plan

Activity	Pre-tx	Cycle 1 D1	Cycle 1 D15	Cycle 2 D1	Cycle 2 D15	Cycle 3 D1	Cycle 3 D15	Ongoing
Informed consent	x							
Clinical assessment	x	x		x		x		Prior to each cycle
FBC	x	x		x		x		Prior to D1 of each cycle
U&E &LFTs	x	x		x		x		Prior to D1 of each cycle
CrCl	x	x		x		x		Prior to D1 of each cycle
Imaging as per guidance	x							Repeat as clinically indicated
ECG+/-ECHO (if indicated)	x							If clinically indicated
Blood pressure	x	x	x	x	x	x	x	Prior to each bevacizumab administration (consider regular home monitoring if hypertension)
Urine dipstick	x	x	x	x	x	x	x	Prior to each bevacizumab administration
Weight recorded	x			x		x		Prior to D1 of each cycle
Height recorded	x							Repeat if necessary