BEVACIZUMAB CAPECITABINE

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/) (BEV11) (BEV12)

1. Bevacizumab with FIRST LINE fluoropyrimidine-based chemotherapy for metastatic or locally advanced and inoperable colorectal cancer and has not received any previous systemic therapy for this indication. Patients may have received neoadjuvant systemic therapy for non-metastatic disease and/or adjuvant chemotherapy after surgery and has a documented presence of microsatellite stability (MSI-S) or DNA mismatch repair proficiency (pMMR) confirmed by validated testing, OR immunotherapy is not being used as first line therapy due to its unsuitability for this patient. The primary reason for the patient NOT receiving either cetuximab or panitumumab alongside first line chemotherapy is has a right sided primary tumour, the tumour has a mutant RAS status or the RAS test result not yet reported and the decision to proceed without knowing RAS status has been discussed with the patient during the consenting process or cetuximab or panitumumab are not suitable for this patient due to pre-existing medical conditions or sensitivities.
2. Bevacizumab with SECOND LINE fluoropyrimidine-based chemotherapy for metastatic or locally advanced and inoperable colorectal cancer and has received ONE prior line of systemic therapy for this indication and has a documented presence of microsatellite stability (MSI-S) or DNA mismatch repair proficiency (pMMR) confirmed by validated testing, OR the patient received immunotherapy as their first line treatment, OR immunotherapy is not being used as second line therapy due to its unsuitability for this patient. The tumour is either BRAF V600E mutation NEGATIVE, or the patient received cetuximab/panitumumab as part of first line therapy, or the patient is not suitable for 2nd line treatment with encorafenib in combination with cetuximab as per form ENC2.

REGIMEN

Day 1	**BEVACIZUMAB**	7.5mg/kg	IV infusion	#ml sodium chloride 0.9%
Days 1 to 14	**CAPECITABINE**	1250mg/m^2 (2500mg/m^2/day)	oral	twice daily

diluent and diluent volume for dose prescribed as per national standardised product specification

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 21 days until disease progression

ANTI-EMETICS

Low risk days 1 to 14

CONCURRENT MEDICATION REQUIRED

Bevacizumab	None
Capecitabine	Mouth and bowel support to be considered eg benzydamine mouthwash, loperamide. A pack of loperamide should usually be supplied with cycle 1.

ADMINISTRATION

Bevacizumab	None
Capecitabine	should be taken 12 hours apart. Swallowed with water within 30 minutes after a meal, or dissolve in 200ml luke warm water, stir thoroughly (squash may be added if unpalatable).

EXTRAVASATION AND TYPE OF LINE / FILTERS

Bevacizumab - neutral

Filter not required
Central or peripheral line

INVESTIGATIONS

Blood results required before SACT administration

FBC, U&E and LFTs Neutrophils ≥1.5x10^9/L Platelets ≥100x10^9/L	baseline and every cycle
EDTA GFR or calculated CrCl at consultant's discretion.	baseline and every cycle
Serum creatinine	baseline and every cycle
Blood pressure	baseline and before every bevacizumab dose
Urinalysis for proteinuria	baseline and before every bevacizumab dose
DPYD (dihydropyrimidine dehydrogenase) test	baseline if no previous result / treatment with a fluoropyrimidine
Weight	baseline and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Bevacizumab	Arterial thromboembolism Gastrointestinal perforation Haemorrhage Hypertension Wound healing complications
Capecitabine	Palmar plantar (handfoot syndrome) causing red palms and soles – treat with pyridoxine 50mg tds. Diarrhoea – treat with loperamide or codeine. Cardiotoxicity – monitor cardiac function. To minimise risk of anthracycline induced cardiac failure signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue. All patients should be told to report any cardiac symptoms immediately and should be told to stop the medication immediately if any suspicion of cardiac problems. Stomatitis.

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS (not exhaustive list check SPC/BNF/Stockleys)

Bevacizumab	-
Capecitabine	Brivudine and analogues should be avoided Warfarin and caution with all oral anticoagulants Phenytoin Allopurinol

DOSE MODIFICATIONS

DPYD variant identified follow national or local DPD dose modification guidelines.

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.

Capecitabine
Dose limiting toxicities include diarrhoea, abdominal pain, nausea, stomatitis and handfoot syndrome. Toxicity can be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction).
Once the dose has been reduced it should not be increased at a later time.
When capecitabine is stopped for toxicity, the doses are omitted and not delayed.

Toxicity grades	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 2 - 1st appearance	Interrupt until resolved to grade 0-1	100%
Grade 2 - 2nd appearance	Interrupt until resolved to grade 0-1	75%
Grade 2 - 3rd appearance	Interrupt until resolved to grade 0-1	50%
Grade 2 - 4th appearance	Discontinue treatment permanently	Not applicable
Grade 3 - 1st appearance	Interrupt until resolved to grade 0-1	75%
Grade 3 - 2nd appearance	Interrupt until resolved to grade 0-1	50%
Grade 3 - 3rd appearance	Discontinue treatment permanently	Not applicable
Grade 4 - 1st appearance	Discontinue permanently OR if physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
Grade 4 - 2nd appearance	Discontinue treatment permanently	Not applicable

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

Capecitabine

Treatment related bilirubin of >3xULN or ALT/AST >2.5xULN	Interrupt capecitabine Treatment may be resumed when bilirubin decreases to <3xULN or hepatic aminotransferases decrease to <2.5xULN.

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

Capecitabine

CrCl >50ml/min	give 100% dose
CrCl 30-50ml/min	give 75% dose
CrCl <30ml/min	contraindicated

REFERENCES
1. CDF list

Assessments

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing	Last cycle
Clinical assessment	X		Pre cycle		Pre/post cycle 4	Alternate cycles or team discretion	
SACT assessment (PS and toxicities)	X	X	X	X	X	Every cycle	Check has OPD
FBC	X	X	X	X	X	Every cycle	X
U&E, calcium, & LFT	X	X	X	X	X	Every cycle	X
CrCl	X	X	X	X	X	Every cycle	X
Blood pressure	X	X	X	X	X	Every cycle	X
Urine protein	X	X	X	X	X	Every cycle	X
CEA (Advanced patients only)	X	X	X	X	X	Every cycle	X
Dihydropyrimidine dehydrogenase (DPYD) deficiency test	X					Essential for all patient to be started on capecitabine or fluorouracil. The result MUST be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary.	
CT scan (Advanced patients only)	X					Inform consultant team if not booked	Check has date for CT
Informed consent	X					Verbal each cycle	
Height	X						
Weight recorded	X	X	X	X	X	Every cycle	X