Thames Valley Cancer Alliance

NHS

BEVACIZUIMAB IRINOTECAN Modified de Gramont

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. (BEV11)
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. (BEV12)

REGIMEN

Day 1	**BEVACIZUMAB**	5mg/kg	IV infusion	#ml sodium chloride 0.9%
	Premedication 30 minutes prior to irinotecan: Atropine 250mcg subcutaneously			
	IRINOTECAN	180mg/m^2	IV infusion	#ml diluent over 30 minutes
	CALCIUM FOLINATE	350mg	IV infusion	250ml glucose 5% over 30 minutes
	FLUOROURACIL	400mg/m^2	IV bolus	
	FLUOROURACIL	2400mg/m^2	IV infusion	continuous over 46 hours

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

NB Calcium folinate (calcium leucovorin) is not the same as calcium levofolinate.
Calcium levofolinate is a single isomer of folinic acid and the dose is generally half that of calcium folinate.

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 14 days until disease progression.
BEV11 Note – Patients who move to 2nd line fluoropyrimidine based chemotherapy may continue to receive bevacizumab with this 2nd line chemotherapy via form BEV12.
BEV12 Note – Patients who move to 3rd line treatment may continue to receive bevacizumab with trifluridine plus tipiracil if this is the most appropriate third line regimen, and the patient meets all of the criteria on form TRI3.

ANTI-EMETICS
Moderately emetogenic day 1
Low emetogenic risk day 2

CONCURRENT MEDICATION REQUIRED

Bevacizumab	None
Fluorouracil	Mouth and bowel support eg loperamide, benzydamine mouthwash
Irinotecan	Ensure premedication atropine given 30 minutes prior to treatment

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.

EXTRAVASATION AND TYPE OF LINE / FILTERS
Bevacizumab - neutral
Fluorouracil – inflammitant
Irinotecan – irritant

Filter not required
Central line (single lumen)

INVESTIGATIONS
Blood results required before SACT administration

FBC, U&E including Mg^{++} and LFTs Neutrophils ≥1.5x10^9/L (1.0-1.5x10^9/L retest and if on an upward trend then can go ahead, if no access to retest then contact Dr) Platelets ≥75x10^9/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

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MAIN TOXICITES AND ADVERSE REACTIONS

Bevacizumab	Arterial thromboembolism Gastrointestinal perforation Haemorrhage Hypertension Wound healing complications
Fluorouracil	Palmar plantar (handfoot syndrome) causing red palms and soles – treat with pyridoxine 50mg tds Diarrhoea – treat with loperamide or codeine

	Cardiotoxicity – monitor cardiac function (consider ECG at baseline). Special attention is advisable in treating patients with a history of heart disease, arrhythmias or angina pectoris or those who develop chest pain during treatment with fluorouracil. Stomatitis.
Irinotecan	Acute cholinergic syndrome (including diarrhea and delayed diarrhoea, abdominal pain, hypotension, dizziness, malaise, increased salivation). Drink large volumes of fluid containing electrolytes and an appropriate antidiarrhoeal therapy - loperamide 4mg initially then 2mg every 2 hours, continuing for 12 hours after the last liquid stool (maximum of 48 hours in total).

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

Bevacizumab	-
Fluorouracil	Cimetidine slightly increases exposure to fluorouracil. Metronidazole increased toxicity. Phenytoin concentration increased. Warfarin.
Irinotecan	Aprepitant and fosaprepitant increases exposure to irinotecan. Carbamazepine and St John's wort decreases exposure to irinotecan, avoid. Enzalutamide, mitotane, phenobarbitone, phenytoin, primidone and rifampicin decreases exposure to irinotecan, avoid.

DOSE MODIFICATIONS
Haematological

Neutrophils <1.5x10^9/L and/or platelet count <100x10^9/L	delay one week, only treat when neutrophils and platelets are above these limits.
Grade 4 neutropenia	consider giving 50% irinotecan and fluorouracil in palliative disease or GCSF support for non-palliative disease.
If >1 delay or 1 delay ≥2 weeks give 80% irinotecan and fluorouracil for future cycles. A further dose reduction may be made at the clinician's discretion	

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.

Irinotecan
If patients suffer from severe diarrhoea, which required IV rehydration or neutropenic fever, consider reduction in subsequent cycles, discuss with SpR or Consultant.

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

Fluorouracil

Significantly impaired hepatic function eg bilirubin >50micromol/L may be a sign of disease progression and require cessation of, or change in, treatment. Always discuss deteriorating liver function with consultant.	
If hepatic function is impaired, the recommended dose can be reduced to give 50% to 70% dose, but no need for dose adjustment is expected in mild and moderate (without renal impairment).	
Bilirubin >85micromol/L	not recommended

Irinotecan

Bilirubin 24-50micromol/L	give 50% dose
Bilirubin >51micromol/L	not recommended

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

Fluourouracil

If renal function is impaired, the recommended dose can be reduced to give 50% to 70% dose, but no need for dose adjustment is expected.

Irinotecan
Not recommended in renal impairment, use with caution.

REFERENCES
1. CDF list

Assessments

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Clinical assessment	X		Pre cycle		Pre cycle	Every 6 weeks, alternate cycles or at team discretion
SACT assessment (PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E, calcium, magnesium & LFT	X	X	X	X	X	Every cycle
CrCl	X	X	X	X	X	Every cycle
Blood pressure	X	X	X	X	X	Every cycle
Urine protein	X	X	X	X	X	Every cycle
Dihydropyrimidine dehydrogenase (DPYD) deficiency test	X					This test is normally only required if a patient has not had capecitabine or fluorouracil in the past. However a consultant may still request this test if capecitabine or fluorouracil was not tolerated previously. The result MUST be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary. DPD deficiency may lead to life threatening toxicity.
CT scan	X					At cycle 6, Inform consultant team if not booked
Informed consent	X					Verbal each cycle

Height	X					
Weight recorded	X	X	X	X	X	Every cycle