PANITUMUMAB (Vectibix) 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/) (PAN1)

1. Panitumumab in combination with irinotecan based chemotherapy for chemotherapy-naive RAS wild-type metastatic colorectal cancer either 1st line treatment for metastatic colorectal cancer or as 2nd line treatment if treated with 1st line pembrolizumab for MSI-H/dMMR disease. (TA439)

REGIMEN

Day 1	**PANITUMUMAB**	6mg/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

ANTI-EMETICS

Moderately emetogenic day 1
Low emetogenic risk day 2

CONCURRENT MEDICATION REQUIRED

Fluorouracil	Mouth and bowel support eg loperamide, benzydamine mouthwash
Irinotecan	Ensure premedication atropine given 30 minutes prior to treatment

ADMINISTRATION

Panitumumab	The initial dose should be administered over 60 minutes, if tolerated well the subsequent infusions may be administered over 30 to 60 minutes. Doses higher than 1000mg should be infused over 90 minutes.

EXTRAVASATION AND TYPE OF LINE / FILTERS

Fluorouracil – inflammitant
Irinotecan - irritant
Panitumumab - neutral

Administer panitumumab via low protein binding 0.2 or 0.22micron filter
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
DPYD (dihydropyrimidine dehydrogenase) test	baseline
Weight	baseline and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

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).
Panitumumab	Dermatologic related reactions, a pharmacologic effect observed with epidermal growth factor receptor (EGFR) inhibitors, are experienced with nearly all patients. Electrolyte disturbances - hypomagnesaemia, hypokalaemia and hypocalcaemia. Repletion required. Hypersensitivity – reactions may occur more than 24 hours after infusion. Mild or moderate infusion-related reaction the infusion rate should be reduced for the duration of that infusion. Maintain this lower infusion rate in all subsequent infusions. If a severe or life-threatening reaction occurs during an infusion or at any time post-infusion eg bronchospasm, angioedema, hypotension, need for parenteral medication, or anaphylaxis, discontinue permanently. Ocular keratitis and ulcerative keratitis Pulmonary interstitial disease

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS

(not exhaustive list check SPC/BNF/Stockleys)

Fluorouracil	Cimetidine slightly increases exposure to fluorouracil Metronidazole increased toxicity Phenytoin concentration increased Warfarin
Irinotecan	Aprepitant and fosaprepitant increases exposure to irinotecan. Carbamazepine 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

Irinotecan

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

Panitumumab

Ocular

If a diagnosis of ulcerative keratitis is confirmed, treatment should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.

Skin

Occurrence of skin symptom(s) ≥grade 3	Administration of panitumumab	Outcome	Dose regulation
1st occurrence	Withhold 1 or 2 doses	Improved (<grade 3) Not recovered	Continue at 100% original dose. Discontinue
2nd occurrence	Withhold 1 or 2 doses	Improved (<grade 3) Not recovered	Continue at 80% original dose. Discontinue
3rd occurrence	Withhold 1 or 2 doses	Improved (<grade 3) Not recovered	Continue at 60% original dose. Discontinue
4th occurrence	Discontinue		

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

Panitumumab

No dose adjustment is needed.

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.

Panitumumab

No dose adjustment is expected.

REFERENCES

1. CDF list

Assessments

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 6	Ongoing
Clinical assessment	X		Pre cycle		Pre cycle	Alternate cycles or 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
Dihydropyrimidine dehydrogenase (DPYD) deficiency test	X					This test is required for every patient newly 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	X				X	At clinician's discretion. Inform consultant team if not booked by C6
Informed consent	X					Verbal each cycle
Height	X					
Weight recorded	X	X	X	X	X	Every cycle