PANITUMUMAB (Vectibix) IRINOTECAN Modified de Gramont

INDICATION (ICD10) C18, C20

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

For chemotherapy-naive metastatic colorectal cancer where the following criteria are met (TA439):

2. RAS wild-type metastatic colorectal cancer.
3. Not received previous cytotoxic treatment for metastatic disease unless there has been use of previous neoadjuvant combination cytotoxic chemotherapy for potentially resectable metastatic colorectal cancer.
4. Panitumumab in this irinotecan-based combination is being used as either 1st line treatment for metastatic colorectal cancer or as 2nd line treatment if treated with 1st line pembrolizumab for MSI-H/dMMR disease
5. Not received prior treatment with cetuximab or panitumumab unless this was received as part of combination neoadjuvant chemotherapy for potentially resectable metastatic disease. Patients with potentially resectable metastatic disease who have received a neoadjuvant cetuximab/panitumumab-containing combination chemotherapy with the intention of resection if the metastases become resectable, and who do not progress while on treatment with cetuximab/panitumumab but who then become unsuitable for surgery or have unsuccessful surgery, may continue treatment with the same cetuximab/panitumumab-containing combination chemotherapy. Patients who have successful resection(s) after neoadjuvant cetuximab/panitumumab-containing combination chemotherapy for metastatic disease and who did not progress on such chemotherapy may receive cetuximab/panitumumab with subsequent first-line combination chemotherapy if they present later with progression of metastatic disease.
6. Aware that if this patient has BRAF V600 mutation-positive disease, the patient will be ineligible for encorafenib plus cetuximab as a subsequent line of therapy if they receive a cetuximab/panitumumab-containing regimen now as first-line therapy.
7. Aware that from 1st December 2020 an NHS England Best Value framework is in operation for cetuximab and panitumumab in first line colorectal cancer. The choice of this panitumumab - containing regimen is therefore in line with the local application of the Best Value framework for these drugs within my organisation.
8. Panitumumab will be given in combination with irinotecan-based combination chemotherapy.
9. Panitumumab in combination with irinotecan-based chemotherapy will be given until disease progression on this regimen and that panitumumab will be discontinued when this disease progression occurs.If the patient experiences excessive toxicity with irinotecan, panitumumab can be subsequently continued in combination with a fluoropyrimidine alone until disease progression and then will be discontinued.Note: continued use of panitumumab beyond 1st line therapy is not commissioned once disease progression has occurred with 1st line treatment.
10. Where a treatment break of more than 6 weeks beyond the expected cycle length is needed, I will complete a treatment break form to restart treatment, including an indication as appropriate if the patient had an extended break because of COVID 19
11. The use of panitumumab will be as per the Summary of Product Characteristics (SPC).

REGIMEN

Day 1 PANITUMUMAB 6mg/kg in 100ml sodium chloride 0.9% IV infusion over 60** minutes.
Premedication: Atropine 250mcg subcutaneously 30 minutes prior to treatment
IRINOTECAN 180mg/m^2 in 250ml sodium chloride 0.9% (or licensed dose volume) IV infusion over 30 minutes
CALCIUM LEVOFOLINATE 175mg in glucose 5% infusion over 30 minutes
FLUOROURACIL 400mg/m^2 IV bolus
FLUOROURACIL 2400mg/m^2 continuous IV infusion over 46 hours

**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.

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

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 14 days for 6 to 12 cycles

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

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 and LFTs every cycle
Neutrophils x 10^9/L ≥1.5
Platelets x 10^9/L ≥100
Ideally EDTA GFR should be used
Creatinine clearance (GFR) calculated, at the Consultants discretion
Serum creatinine
DPD test
Baseline weight 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. 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. 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

If neutrophils <1.5x10^9/L and/or the platelet count <100x10^9/L delay one week, only treat when neutrophils and platelets are above these limits.
If 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

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.

Bilirubin >85micromol/L	not recommended

Irinotecan

Bilirubin 24-50micromol/L	give 50% dose
Bilirubin >51micromol/L	Clinical decision

Renal impairment

Fluourouracil

CrCl >30ml/min	give 100% dose
CrCl <30ml/min	consider dose reduction

REFERENCES

CDF list