CETUXIMAB (Erbitux) 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 all 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. Cetuximab 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. The patient has 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. Cetuximab will be given in combination with irinotecan-based combination chemotherapy.
9. Cetuximab will be given in a 2-weekly regimen at a dose of 500mg/m².
10. As this dose and schedule of cetuximab is not licensed, this use of cetuximab must be used within the Trust's governance framework.
11. Cetuximab in combination with irinotecan-based chemotherapy will be given until disease progression on this regimen and that cetuximab will be discontinued when this disease progression occurs.If the patient experiences excessive toxicity with irinotecan, cetuximab can be subsequently continued in combination with a fluoropyrimidine alone until disease progression and then will be discontinued.Note: continued use of cetuximab beyond 1st line therapy is not commissioned once disease progression has occurred with 1st line treatment.
12. 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
13. The use of cetuximab will be as per the Summary of Product Characteristics (SPC).

REGIMEN

Day 1 Premedication: Chlorphenamine 10mg IV bolus (and dexamethasone antiemetic) 30-60 minutes prior to treatment
CETUXIMAB 500mg/m^2 in 500ml sodium chloride 0.9% IV infusion
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

NB Cetuximab administer first dose over 120 minutes. If tolerated the second dose and subsequent doses may be given at a rate that does not exceed the maximum rate of 10mg/min. Close monitoring is required during the cetuximab infusion and for at least 1 hour after the end of the infusion (from cycle 2 onwards you can give the other infusions during this observation time)

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

ANTI-EMETICS

Moderately emetogenic day 1
Low emetogenic risk day 2

CONCURRENT MEDICATION REQUIRED

Cetuximab	Ensure premedication chlorphenamine (and dexamethasone from antiemetics) given 30-60 minutes prior to treatment
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

Cetuximab - neutral
Fluorouracil – inflammitant
Irinotecan – irritant

Filter not required
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

Cetuximab	Dyspnoea - as part of a hypersensitivity reaction, or after several weeks of therapy. Older, poor PS or underlying pulmonary disorders may be at increased risk. May be severe and/or long-standing. Hypersensitivity - mild or moderate reaction infusion rate may be decreased. Maintain lower infusion rate for subsequent infusions. Severe - usually during the initial infusion and up to 1 hour after the end of infusion, but may occur after several hours. Requires immediate and permanent discontinuation of cetuximab and may necessitate emergency treatment. Infusion related reactions – If during the 1st infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should be stopped, risk assessment undertaken. If an infusion-related reaction develops later during the infusion or at a subsequent infusion further management will depend on its severity: Grade 1: continue slow infusion under close supervision. Grade 2: continue slow infusion and immediately administer treatment for symptoms. Grade 3 and 4: stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab. Skin reactions - severe skin reaction cetuximab must be interrupted. Treatment may only be resumed, if the reaction has resolved. With the 2nd occurrence of a severe reaction, treatment may be resumed at 75% after interruption. With the 3rd occurrence of a severe reaction, treatment may be resumed at 50% after interruption. If severe skin reactions occur a 4th time or do not resolve during treatment interruption, stop treatment permanently.
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).

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.

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