CETUXIMAB (Erbitux) 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/) (CET1)

1. Cetuximab in combination with irinotecan based chemotherapy for chemotherapy-naive RAS wild-type metastatic colorectal cancer 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. (TA439)

REGIMEN

Day 1	**Premedication** 30-60 minutes prior to cetuximab: Chlorphenamine 10mg IV bolus Dexamethasone 8mg IV bolus (also part of antiemetics)			
	CETUXIMAB	500mg/m^2	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

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

ADMINISTRATION

Cetuximab	Administer first dose over 120 minutes (maximum rate 5mg/min). 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 other infusions may b started during this observation time).

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 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

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 Infusion related reactions Skin 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).

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 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
Cetuximab
Infusion reactions

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.

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
Cetuximab
No dose adjustment required.

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
Cetuximab
No dose adjustment required.

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
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