Cetuximab (7 days) and FOLFIRI (14 days) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with RAS wild type metastatic colorectal cancer.	C18	00328a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Cetuximab is administered once a week. The initial dose is 400 mg/m^2.
All subsequent weekly doses are 250mg/m^2 cetuximab.
Treatment with FOLFIRI chemotherapy is administered after cetuximab on Day 1 once every 14 days until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Cetuximab	400mg/m^2	IV infusion Observe post infusion[1]	[2]Over 2 hours	1
8	Cetuximab	250mg/m^2	IV infusion Observe post infusion[1]	Over 60 minutes	1 and repeat every 7 days
1	Irinotecan	180mg/m^2	IV infusion	250mL 0.9% NaCl over 90 minutes	Every 14 days
1	Folinic Acid (Calcium leucovorin)	[3]400mg/m^2	IV infusion	250mL 0.9% NaCl over 2 hours	Every 14 days
1	5-Fluorouracil	400mg/m^2	IV BOLUS	Slow push through side arm of fast flowing drip	Every 14 days
1	[4]5-Fluorouracil	2400mg/m^2	Continuous IV infusion	Over 46 hours in 0.9% NaCl	Every 14 days
[1]Obtain vital signs pre-infusion, at 1 hr and post-infusion. 1hr observation period following end of 1st and 2nd cetuximab infusions. If no infusion reactions occur for 2 consecutive doses, then may discontinue observation period and vital signs.					
[2]The initial dose should be given slowly and speed of infusion must not exceed 5 mg/minute. The recommended infusion period is 120 minutes. For the subsequent weekly doses, the recommended infusion period is 60 minutes. The maximum infusion rate must not exceed 10 mg/minute. May be administered diluted in 0.9% NaCl or undiluted. Flush the line with 0.9% NaCl at the end of the cetuximab infusion.					
[3]A dose of 200mg/m^2 of folinic acid may be considered.					
Irinotecan and leucovorin may be infused at the same time by using a y-connector placed immediately before the injection site. Irinotecan and leucovorin should not be combined in the same infusion bag.					
Folinic Acid *(Calcium Leucovorin)* must be administered prior to 5-Fluorouracil. It enhances the effects of 5-Fluorouracil by increasing 5-Fluorouracil binding to the target enzyme thymidylate synthetase.					
[4]See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency.					
Patients may suck on ice chips during the bolus injection of 5-Fluorouracil to reduce stomatitis.					

ELIGIBILITY:

- Indications as above
- Wild type RAS tumours verified by a validated test method
- ECOG 0-2
- Adequate haematological, renal and liver status

CAUTION:

Use with caution in patients with:

- Previous pelvic radiotherapy
- Recent MI
- Uncontrolled angina, hypertension, cardiac arrhythmias, CHF
- In patients with baseline greater than 3 loose bowel movements (BM) per day (in patients without colostomy or ileostomy)

EXCLUSIONS:

- Hypersensitivity to cetuximab, irinotecan, 5-Fluorouracil or any of the excipients.
- Patients with mutant RAS mCRC or unknown RAS mCRC status
- Severe bone marrow failure
- Severe renal impairment
- Bilirubin > 3 x ULN
- Chronic bowel disease and/or bowel obstruction.
- Pregnancy and breast feeding
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, liver and renal profile
- ECG (if patient has compromised cardiac function)
- Complete medical history specifically asking about any previous infusion related reactions (IRR) to another antibody, allergy to red meat or tick bites, or any results of tests for IgE antibodies against cetuximab
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested
    - In patients with moderate or severe renal impairment, blood uracil levels used for dihydropyrimidine dehydrogenase (DPD) phenotyping should be interpreted with caution, as impaired kidney function can lead to increased uracil blood levels. Consequently, there is an increased risk for incorrect diagnosis of DPD deficiency, which may result in under dosing of 5-Fluorouracil or other fluoropyrimidines,

leading to reduced treatment efficacy. Genotype testing for DPD deficiency should be considered for patients with renal impairment.

Regular tests:

- FBC, liver and renal profile prior to each cycle
- Post treatment: monthly electrolytes, magnesium, calcium for 2 months after last cetuximab treatment.
- INR tests if patient is on warfarin as clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Consider a reduced starting dose in patients with identified partial DPD deficiency
  - Initial dose reduction may impact the efficacy of treatment
  - In the absence of serious toxicity, subsequent doses may be increased with careful monitoring
- Any dose modification should be discussed with a Consultant
- Cetuximab or FOLFIRI therapy may be delayed independently of each other and dosing may continue with either component but consideration should be given to the timings of further treatment
- Irinotecan should be administered after appropriate recovery of all adverse events to grade 0 or 1 NCI-CTC grading and when treatment-related diarrhoea is fully resolved
- At the start of a subsequent infusion of therapy, the dose of irinotecan and 5-Fluorouracil, should be decreased according to the worst grade of adverse events observed in the prior infusion
- Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events

The following dose reductions should be used when calculating FOLFIRI dose reductions for patients with toxicities (Table 1).

Table 1: Dose Reduction Levels for All Toxicities

	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2	Discontinue
Folinic Acid *(Calcium Leucovorin)*	400 mg/m^2	400 mg/m^2	400 mg/m^2	Discontinue
5-Fluorouracil bolus	400 mg/m^2	320 mg/m^2	260 mg/m^2	Discontinue
5-Fluorouracil infusion	2400 mg/m^2	1900 mg/m^2	1500mg/m^2	Discontinue

Note: Folinic acid is delayed or omitted if bolus 5-Fluorouracil is delayed or omitted

Table 2: Dose Modification of FOLFIRI for Haematological Toxicity

Prior to a Cycle (DAY 1)	Toxicity		Dose Level for Subsequent Cycles	
	Grade	**ANC ($x\ 10^9$/L)**	**Irinotecan**	**5-Fluorouracil**
• If ANC< 1.5 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks • ANC ≥ 1.5 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest ANC** result of the delayed week(s). • If ANC remains <1.5 after 4 weeks discontinue treatment	1	≥ 1.5	Maintain dose level	Maintain dose level
	2	1.0-1.49	Maintain dose level	Maintain dose level
	3	0.5-0.99	↓ 1 dose level	↓ 1 dose level
	4	<0.5	↓2 dose levels	↓2 dose levels
	Grade 4 neutropenia and grade ≥2 fever		↓2 dose levels	↓2 dose levels
	Grade	**Platelets ($x10^9$/L)**	**Irinotecan**	**5-Fluorouracil**
• If platelets < 75 on Day 1 of cycle, hold treatment, weekly FBC, maximum of 2 weeks • Platelets ≥ 75 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest platelets** result of the delayed week(s). • If platelets remain <75 after 2 weeks, discontinue treatment	1	≥ 75	Maintain dose level	Maintain dose level
	2	50-74.9	Maintain dose level	Maintain dose level
	3	10-49.9	↓ 1 dose level	↓ 1 dose level
	4	<10	↓ 2 dose levels	↓ 2 dose levels
The use of granulocyte colony-stimulating factor (G-CSF) may be considered.				

Renal and Hepatic Impairment:

Table 3: Dose modification of cetuximab, irinotecan and 5-Fluorouracil in renal or hepatic impairment

Drug	Renal impairment	Hepatic impairment			
Cetuximab	Clinical decision – unlikely to require a reduction.	Unlikely to require a reduction			
Irinotecan	No dose reduction needed, however use with caution as no information in this setting.	Irinotecan is contraindicated in patients with bilirubin levels > 3 x ULN.			
5-Fluorouracil	Consider dose reduction in severe renal impairment only	**Bilirubin (micromol/L)**		**AST**	**Dose**
		<85		<180	100%
		>85	or	>180	Contraindicated
		Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2. Increase dose if no toxicity.			

Management of adverse events:

Table 4: Dose modification of cetuximab based on adverse events

Adverse reaction	Recommended dose modification
Infusion Reaction	
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
Interstitial lung disease	Discontinue
Skin reaction grade 1 or 2	No dosage adjustment required. See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions.
Severe skin reaction ≥ grade 3*	
First occurrence	Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at **250**mg/m^2
Second occurrence	Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at **200**mg/m^2
Third occurrence	Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at **150**mg/m^2
Fourth occurrence	Discontinue

* See other supportive care section below

Table 5: Dose modification of FOLFIRI based on adverse events

Prior to a Cycle (DAY 1)	Grade of Toxicity	Dose Level for Subsequent Cycles	
		Irinotecan	5-Fluorouracil
Diarrhoea • ≥ Grade 2, hold treatment max of 2 weeks • < Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the **highest** grade experienced • Remains ≥ Grade 2 after 2 weeks, discontinue treatment	1 and 2	Maintain dose level	Maintain dose level
	3	↓1 dose level	↓ 1 dose level
	4	↓2 dose levels	↓2 dose levels
Stomatitis • ≥ Grade 2, hold treatment max of 2 weeks • < Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the **highest** grade experienced. • Remains ≥ Grade 2 after 2 weeks, discontinue treatment	1 and 2	Maintain dose level	Maintain dose level
	3	Maintain dose level	↓1 dose level
	4	Maintain dose level	↓2 dose levels

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Cetuximab: Low **(Refer to local policy)**
Irinotecan: Moderate **(Refer to local policy)**
5-Fluorouracil: Low **(Refer to local policy)**

PREMEDICATIONS:

- **Cetuximab**

Patients must receive premedication with an antihistamine and a corticosteroid at least one hour prior to receiving cetuximab infusion. This premedication is recommended prior to all subsequent infusions. Patient should be educated about the possibility of delayed infusion-related symptoms

- **Irinotecan**

Prophylactic atropine sulphate 250 micrograms subcutaneously – see adverse effects below.
Atropine should not be used in patients with glaucoma. **(See Adverse Effects/Regimen specific complications below).**

OTHER SUPPORTIVE CARE:

Anti-diarrhoeal treatment **(Refer to local policy).**
Patients should be made aware of the risk of delayed diarrhoea occurring more than 24 hours after the administration of irinotecan and at any time before the next cycle.

- As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate anti-diarrhoeal therapy must be initiated immediately
- The currently recommended anti-diarrhoeal treatment consists of high doses of loperamide (4mg for the first intake and then 2 mg every 2 hours)
- This therapy should continue for 12 hours after the last liquid stool and should not be modified.
- In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours

Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of irinotecan, and advised not to drive or operate machinery if these symptoms occur.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Cetuximab

- **Infusion-related reactions (IRR):**
  - The first dose of cetuximab should be administered slowly and the speed must not exceed 5mg/min whilst all vital signs are closely monitored for at least two hours. If during the first infusion, an infusion-related reaction occurs within the first 15 minutes, the infusion should

be stopped. A careful benefit/risk assessment should be undertaken including consideration whether the patient may have pre-formed IgE antibodies before a subsequent infusion is given
    - If an IRR develops later during the infusion or at a subsequent infusion further management will depend on its severity (Ref Table 4)
    - In cases of mild or moderate infusion-related reaction, the infusion rate may be decreased and maintained at the lower rate in all subsequent infusions
    - Severe infusion-related reactions may occur with symptoms usually occurring during the first infusion and up to 1 hour after the end of the infusion. They may occur several hours after or with subsequent infusions. Patients should be warned of the possibility of such a late onset and instructed to contact their physician if symptoms occur
    - Occurrence of a severe infusion-related reaction requires immediate and permanent discontinuation of cetuximab therapy and may necessitate emergency treatment
    - Special attention is recommended for patients with reduced performance status and pre-existing cardio-pulmonary disease
- **Respiratory disorders:** Interstitial lung disease has been observed with EGFR inhibitors. Treatment should be withheld in the event of onset or worsening respiratory symptoms. If pneumonitis or lung infiltrates are confirmed, treatment should be discontinued**.**
- **Cardiovascular:** An increased frequency of severe and sometimes fatal cardiovascular events and treatment emergent deaths has been observed. When prescribing cetuximab, the cardiovascular and performance status of the patients and concomitant administration of cardiotoxic compounds such as fluoropyrimidines should be taken into account.
- **Skin reactions:** This is the main adverse reaction of cetuximab. Refer to local policy for skin care regime and to Table 4 under Dose Modifications for management of treatment if patient experiences skin reactions.
- **Electrolyte disturbances**: Hypomagnesaemia, hypokalaemia or hypocalcaemia may occur. Electrolyte repletion is recommended, as appropriate.

FOLFIRI

- **Acute cholinergic syndrome:** If acute cholinergic syndrome appears (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation) atropine sulphate (250 micrograms subcutaneously) should be administered unless clinically contraindicated. Caution should be exercised in patients with asthma. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of irinotecan**.**
- **Diarrhoea:** Irinotecan-induced diarrhoea can be life threatening and requires immediate management.
    - Diarrhoea (early onset) - see acute cholinergic syndrome above.
    - Diarrhoea (late onset):
        - Irinotecan-induced diarrhoea can be life threatening and requires immediate management.
        - In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan.
        - Patients with an increased risk of diarrhoea are those who had previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status ≥2 and women.
        - In patients who experience severe diarrhoea, a reduction in dose is recommended for subsequent cycles.
        - The SmPC (7) provides guidelines on when hospitalisation for the management of diarrhoea

is recommended.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Extravasation:** Irinotecan causes pain and tissue necrosis if extravasated**. (Refer to local extravasation guidelines).**
- **Gilbert's Syndrome:** Increases the risk of irinotecan-induced toxicity. A reduced initial dose should be considered for these patients.
- **Respiratory disorders:** Severe pulmonary toxicity has been reported rarely. Patients with risk factors should be monitored for respiratory symptoms before and during irinotecan therapy.
- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with 5-Fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with 5-Fluorouracil, should be carefully monitored during therapy.
- **DPD deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.
- **Hand-foot syndrome, HFS,** also known as palmar-plantar erythrodysaesthesia (PPE) has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-Fluorouracil.

DRUG INTERACTIONS:

- Risk of drug interactions causing decreased concentrations of irinotecan with CYP3A inducers.
- Risk of drug interactions causing increased concentrations of irinotecan with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia.
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of 5-Fluorouracil regimes.
- Concurrent administration of 5-Fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- 5-Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-Fluorouracil-metabolising enzyme DPD. Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect DPD activity.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	03/06/16		Prof Maccon Keane
2	20/10/2017	Updated with new NCCP regimen template updated dose reductions for all toxicities and dosing in renal and hepatic impairment	Prof Maccon Keane
3	16/09/2019	Reviewed. Standardisation of treatment table. Update of exclusion criteria, adverse events and drug interactions.	Prof Maccon Keane
4	09/10/2019	Update of exclusions	Prof Maccon Keane
5	24/08/2020	Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020 Updated Adverse events regarding palmar-plantar erythrodysaesthesia	Prof Maccon Keane
6	09/09/2021	Reviewed. Updated exclusions. Amended emetogenic potential and premedication timing.	Prof Maccon Keane
6a	23/11/2023	Formatting changes and grammatical corrections.	NCCP
6b	25/02/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.