Cetuximab and FOLFIRI Therapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>Reimbursement Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of patients with RAS wild type metastatic colorectal cancer.</td>
<td>C18</td>
<td>00328a</td>
<td></td>
</tr>
</tbody>
</table>

*Reimbursement Indicator* (e.g. ODMS, CDS) is not defined, the drug and its detailed indication have not been assessed through the formal HSE reimbursement process.

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 patient's individual clinical circumstances.

Cetuximab is administered once a week. The initial dose is 400 mg/m². All subsequent weekly doses are 250 mg cetuximab/m².

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 the chemotherapy is administered.

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cetuximab</td>
<td>400mg/m²</td>
<td>IV infusion Observe post infusion</td>
<td>²Over 2 hours</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Cetuximab</td>
<td>250mg/m²</td>
<td>IV infusion Observe post infusion</td>
<td>Over 60min</td>
<td>1 and repeat every 7 days</td>
</tr>
<tr>
<td>1</td>
<td>Irinotecan</td>
<td>180mg/m²</td>
<td>IV infusion</td>
<td>500ml glucose 5% over 90mins</td>
<td>Every 14 days</td>
</tr>
<tr>
<td>1</td>
<td>Folinic Acid (Calcium leucovorin)</td>
<td>³400mg/m²</td>
<td>IV infusion</td>
<td>250ml glucose 5% over 2hrs</td>
<td>Every 14 days</td>
</tr>
</tbody>
</table>

Flush line with glucose 5% before administering 5-fluorouracil

| 1   | Fluorouracil (5-FU) | 400mg/m² | IV BOLUS | Slow push through side arm of fast flowing drip | Every 14 days |
| 1   | Fluorouracil | 2400mg/m² | Continuous IV infusion | Over 46h in glucose 5% or 0.9% NaCl | Every 14 days |

³Obtain 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.

²The initial dose should be given slowly and speed of infusion must not exceed 5 mg/min. 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/min. May be administered diluted in 0.9% NaCl or undiluted. Flush the line with 0.9% NaCl at the end of the cetuximab infusion.

³A dose of 200mg/m² 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.

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### NCCP Chemotherapy Regimen

**NCCP Regimen:** Cetuximab and FOLFIRI Therapy

**Published:** 23/10/2017

**Review:** 23/10/2019

**Version number:** 1

**Tumour Group:** Gastrointestinal

**NCCP Regimen Code:** 00328

**ISMO Contributor:** Prof Maccon Keane

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**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 or any of the excipients.
- Patients with mutant RAS mCRC or unknown RAS mCRC status
- Baseline neutrophils < 2 x 10^9/L and/or platelet count < 100 x 10^9/L.
- Severe renal impairment (creatinine clearance < 30ml/min).
- Bilirubin > 3 x ULN.
- Chronic bowel disease and/or bowel obstruction.
- Pregnancy and breast feeding.

**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.

**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.

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Folinic Acid (Calcium Leucovorin) must be administered prior to fluorouracil. It enhances the effects of fluorouracil by increasing fluorouracil binding to the target enzyme thymidylate synthetase.

Patients may suck on ice chips during the bolus injection of fluorouracil to reduce stomatitis.

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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:
- 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 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

<table>
<thead>
<tr>
<th>Dose Level 0</th>
<th>Dose Level -1</th>
<th>Dose Level -2</th>
<th>Dose Level -3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan</td>
<td></td>
<td></td>
<td>Discontinue</td>
</tr>
<tr>
<td>180 mg/m²</td>
<td>150 mg/m²</td>
<td>120 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Folinic Acid (Calcium Leucovorin)</td>
<td></td>
<td></td>
<td>Discontinue</td>
</tr>
<tr>
<td>400 mg/m²</td>
<td>400 mg/m²</td>
<td>400 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Fluorouracil bolus</td>
<td>400 mg/m²</td>
<td>320 mg/m²</td>
<td>260 mg/m²</td>
</tr>
<tr>
<td>Fluorouracil infusion</td>
<td>2400 mg/m²</td>
<td>1900 mg/m²</td>
<td>1500 mg/m²</td>
</tr>
</tbody>
</table>

Note: Folinic acid is delayed or omitted if bolus fluorouracil is delayed or omitted.
Table 2: Dose Modification of FOLFIRI for Haematological Toxicity

<table>
<thead>
<tr>
<th>Prior to a Cycle (DAY 1)</th>
<th>Toxicity</th>
<th>Dose Level for Subsequent Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade</td>
<td>ANC ( \times 10^9/L )</td>
</tr>
<tr>
<td></td>
<td>Grade</td>
<td>ANC ( \times 10^9/L )</td>
</tr>
<tr>
<td>Grade 1.5 ANC ( \geq 1.5 )</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 2.0-1.49 ANC</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 0.5-0.99 ANC</td>
<td>↓ 1 dose level</td>
<td>↓ 1 dose level</td>
</tr>
<tr>
<td>Grade &lt;0.5 ANC</td>
<td>↓ 2 dose levels</td>
<td>↓ 2 dose levels</td>
</tr>
</tbody>
</table>

Grade 4 neutropenia and grade≥2 fever
- If ANC\( \geq 1.5 \) 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

<table>
<thead>
<tr>
<th>Prior to a Cycle (DAY 1)</th>
<th>Toxicity</th>
<th>Dose Level for Subsequent Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade</td>
<td>Platelets ( \times 10^9/L )</td>
</tr>
<tr>
<td></td>
<td>Grade</td>
<td>Platelets ( \times 10^9/L )</td>
</tr>
<tr>
<td>Grade 75 Platelets ( \geq 75 )</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 50-74.9 Platelets</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Grade 10-49.9 Platelets</td>
<td>↓ 1 dose level</td>
<td>↓ 1 dose level</td>
</tr>
<tr>
<td>Grade &lt;10 Platelets</td>
<td>↓ 2 dose levels</td>
<td>↓ 2 dose levels</td>
</tr>
</tbody>
</table>

Renal and Hepatic Impairment:

Table 3: Recommended dose modification in patients with renal or hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>Clinical decision – unlikely to require a reduction.</td>
<td>Unlikely to require a reduction</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>No dose reduction needed, however use with caution as no information in this setting.</td>
<td>Irinotecan is contraindicated in patients with bilirubin levels &gt; 3 x ULN.</td>
</tr>
<tr>
<td>5-FU</td>
<td>Consider dose reduction in severe renal impairment only</td>
<td>Bilirubin (micromol/L)</td>
</tr>
<tr>
<td></td>
<td>&lt;85</td>
<td>&lt;180</td>
</tr>
<tr>
<td></td>
<td>&gt;85 or</td>
<td>&gt;180</td>
</tr>
</tbody>
</table>

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 schedule of cetuximab based on adverse events**

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Discontinue</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion Reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td></td>
<td>Continue slow infusion under close supervision.</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td>Continue slow infusion and immediately administer treatment for symptoms.</td>
</tr>
<tr>
<td>Grade 3 and 4</td>
<td></td>
<td>Stop infusion immediately, treat symptoms vigorously and contraindicate further use of cetuximab</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>Discontinue</td>
<td>No dosage adjustment required. See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse skin reactions.</td>
</tr>
<tr>
<td>Skin reaction grade 1 or 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe skin reaction ≥ grade 3*</td>
<td></td>
<td>Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at 250mg/m².</td>
</tr>
<tr>
<td>First occurrence</td>
<td></td>
<td>Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at 200mg/m².</td>
</tr>
<tr>
<td>Second occurrence</td>
<td></td>
<td>Hold cetuximab treatment for a maximum of 2 weeks. Reinitiate therapy only if reaction has resolved to grade 2 at 150mg/m².</td>
</tr>
<tr>
<td>Third occurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fourth occurrence</td>
<td>Discontinue</td>
<td></td>
</tr>
</tbody>
</table>

* See other supportive care section below
Table 5: Dose modification schedule of FOLFIRI based on adverse events

<table>
<thead>
<tr>
<th>Prior to a Cycle (DAY 1)</th>
<th>Grade of Toxicity</th>
<th>Dose Level for Subsequent Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Grade 2, hold treatment max of 2 weeks</td>
<td>1 and 2</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>&lt; Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the highest grade experienced</td>
<td>3</td>
<td>↓ 1 dose level</td>
</tr>
<tr>
<td>Remains ≥ Grade 2 after 2 weeks, discontinue treatment</td>
<td>4</td>
<td>↓ 2 dose levels</td>
</tr>
<tr>
<td>Stomatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Grade 2, hold treatment max of 2 weeks</td>
<td>1 and 2</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>&lt; Grade 2 within 2 weeks proceed with treatment at the dose level noted across from the highest grade experienced</td>
<td>3</td>
<td>Maintain dose level ↓ 1 dose level</td>
</tr>
<tr>
<td>Remains ≥ Grade 2 after 2 weeks, discontinue treatment</td>
<td>4</td>
<td>Maintain dose level ↓ 2 dose levels</td>
</tr>
</tbody>
</table>

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:
FOLFIRI + Cetuximab – Moderate (Refer to local policy).
Cetuximab alone – Low (Refer to local policy).

PREMEDICATIONS:
- **Cetuximab**
  Patients must receive premedication with an antihistamine and a corticosteroid before 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 250micrograms subcutaneously – see adverse effects below. Atropine should not be used in patients with glaucoma. (See Adverse Effects/Regimen specific complications below).

OTHER SUPPORTIVE CARE:
See local skin care policy for the prevention and treatment of EGFR-inhibitor adverse oral pyridoxine 50mg three times a day when required for the relief of palmar-plantar erythrodynesthesia.
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 (4 mg 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 5 mg/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 preformed 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.

- **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 3 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 (4) 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 fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with fluorouracil, should be carefully monitored during therapy.

- **Dihydropyrimidine dehydrogenase (DPD) deficiency**: Rare, life-threatening toxicities such as stomatitis, mucositis, neutropenia, neurotoxicity and diarrhoea have been reported following administration of fluoropyrimidines (e.g. fluorouracil and capecitabine). Severe unexplained toxicities require investigation prior to continuing with treatment.

- **Palmar Plantar Erythrodysesthesia (PPE)**: This has been reported as an unusual complication of high dose bolus or protracted continuous therapy with 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 fluorouracil regimes.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin.
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• Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydroprimidine dehydrogenase activity.
• Current drug interaction databases should be consulted for more information.

ATC CODE:
Cetuximab - L01XC06
Irinotecan - L01XX19
5-Fluorouracil - L01BC02
Folinic acid - V03AF03

REFERENCES:
2. BCCA Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil and Leucovorin GIFOLFI

Version control

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3/6/16</td>
<td></td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>20/10/2017</td>
<td>Updated with new NCCP regimen template updated dose reductions for all toxicities and dosing in renal and hepatic impairment</td>
<td>Prof Maccon Keane</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.
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1 ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/