## Panitumumab + FOLFOX for the 1st line Treatment of Metastatic Colorectal Cancer

### RUG ADMINISTRATION SCHEDULE

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Diluent and rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Panitumumab</strong></td>
<td>6mg/kg</td>
<td>Intravenous</td>
<td>100mL Sodium Chloride 0.9% at variable rate (see administration notes)</td>
</tr>
<tr>
<td></td>
<td>Glucose 5%</td>
<td>500ml</td>
<td>Infusion</td>
<td>Fast Running for Line Flush</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>8mg</td>
<td>Oral / IV bolus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ondansetron</td>
<td>8mg</td>
<td>Oral / Slow bolus/15 min infusion*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium Leucovorin (folinic acid)</td>
<td>300mg</td>
<td>IV Infusion</td>
<td>250mL Glucose 5% over 2 hours concurrent with oxaliplatin</td>
</tr>
<tr>
<td></td>
<td><strong>Oxaliplatin</strong></td>
<td>85mg/m²</td>
<td>IV Infusion</td>
<td>250mL Glucose 5% over 2 hours concurrent with folinic acid</td>
</tr>
<tr>
<td></td>
<td>Glucose 5%</td>
<td>500ml</td>
<td>Infusion</td>
<td>Line Flush</td>
</tr>
<tr>
<td>Day 3</td>
<td><strong>5 Fluorouracil</strong></td>
<td>400 mg/m²</td>
<td>IV bolus</td>
<td>Over 5 minutes</td>
</tr>
<tr>
<td></td>
<td><strong>5 Fluorouracil</strong></td>
<td>2400 mg/m²</td>
<td>via infusor device</td>
<td>Sodium Chloride 0.9% over 46 hours</td>
</tr>
</tbody>
</table>

Day 3 Attend ward/ clinic for removal of 5-FU infusor device

*Ondansetron IV must be infused over 15 minutes in patients over 65 years of age.

### NUMBER OF DAYS PER CYCLE

14 days until disease progression

### APPROVED INDICATIONS

Panitumumab is recommended, as an option for previously untreated RAS wild-type metastatic colorectal cancer in adults in combination with FOLFOX or FOLFIRI.

### RECOMMENDED TAKE HOME MEDICATION

Ondansetron 8mg twice daily for 2-3 days
Dexamethasone 4mg twice daily for 1-3 days
Metoclopramide 10-20mg three to four times daily as required
Loperamide as required (4mg after first loose stool and 2mg every 2 hours, to a maximum of 16 (2mg) tablets in 24 hours).

*Suggested antiemetic regimen - may vary with local practice. See CINV policy for more details

### INVESTIGATIONS / MONITORING REQUIRED

**Pre-treatment:** Assessment of renal function, FBC, Cardiac history

**Prior to each cycle:** FBC, U&E’s, LFT’s, magnesium & tumour markers as appropriate

FBC on the day of treatment

Where CEA is elevated this should be measured before each cycle (no need to await result before proceeding with treatment).
ASSESSMENT OF RESPONSE
Tumour size and patient symptomatic response to be assessed at appropriate intervals.

REVIEW BY CLINICIAN
Before each cycle as appropriate

NURSE / PHARMACIST LED REVIEW
On cycles where not seen by clinician

ADMINISTRATION NOTES
- Panitumumab must be administered as an intravenous infusion via an infusion pump, using a low protein binding 0.2 or 0.22 micrometre in-line filter.
- The recommended infusion time is approximately 60 minutes. If the first infusion is tolerated, then subsequent infusions may be administered over 30 to 60 minutes. Doses higher than 1,000 mg should be infused over approximately 90 minutes.
- Sodium Chloride 0.9% must be used for line flushing with Panitumumab
- Panitumumab (as with all monoclonal antibodies) can cause infusion reactions. Administration must only take place in facilities with resuscitation facilities.
- In patients experiencing a mild or moderate (CTCAE v 4.0 grades 1 and 2) infusion-related reaction the infusion rate should be reduced for the duration of that infusion. It is recommended to maintain this lower infusion rate in all subsequent infusions.
- Hypersensitivity reactions occurring more than 24 hours after infusion have been reported including a fatal case of angioedema that occurred more than 24 hours after the infusion. Patients should be informed of the possibility of a late onset reaction and instructed to contact their physician if symptoms of a hypersensitivity reaction occur.
- Pulse, Respiration, Blood Pressure and Temperature must be measured during and 1 hour following infusion.

FOLFOX
- Patient requires semi-permanent IV access for this treatment, e.g. PICC line/ Hickman catheter
- Diarrhoea is common, and may require intervention with fluids and electrolytes if severe. If diarrhoea is a problem, give loperamide 2 to 4 mg four times daily as required or codeine phosphate 30mg four times daily and stop 5FU infusion if diarrhoea moderate/severe.
- Note: A variety of calcium folinate doses have been used in clinical trials, e.g. 200mg/m2 with max dose 350mg or Calcium Levofoilate 175mg or Calcium Folinate 350mg. To enable a convenient, cost effective single vial dose, 300mg is recommended.
- Oxaliplatin is incompatible with saline. Must use 5% dextrose as diluent and line flush
- Bronchospasm can occur with oxaliplatin infusion. * If severe laryngeal spasm occurs consider increasing oxaliplatin infusion to 6 hours

Platinum Hypersensitivity
Patients who have previously experienced Grade I or II Platinum Hypersensitivity should be pre-medicated as below:

**45 minutes prior to Oxaliplatin**
- Dexamethasone 20 mg IV in 50 mL NS over 15 minutes (or Hydrocortisone 100mg)

**30 minutes prior to Oxaliplatin**
- Chlorphenamine 10 mg IV and Ranitidine 50 mg IV in 50 mL NS over 20 minutes
Laryngo-Pharyngeal Dysesthesia

As with all platinum based chemotherapy, patients may experience allergic reaction during administration. The following table is intended to help differentiate between Platinum Hypersensitivity and Laryngo-pharyngeal Dysesthesia.

<table>
<thead>
<tr>
<th>Clinical Symptoms</th>
<th>Laryngo-pharyngeal Dysesthesia</th>
<th>Platinum Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>O₂ saturation</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>Present (loss of sensation)</td>
<td>Absent</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Cold induced symptoms</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Normal or Increased</td>
<td>Normal or Decreased</td>
</tr>
</tbody>
</table>

**Treatment**

- Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician’s discretion
- Oxygen, steroids, epinephrine, bronchodilators;
- Fluids and vasopressors if appropriate

**EXTRAVASATION**  See Local Guidelines

**TOXICITIES**

- Peripheral neurotoxicity very common with Oxaliplatin. (dose limiting toxicity)
- Myelosuppression
- Cold induced parathesia
- Nausea and Vomiting
- Allergic reaction
- Diarrhoea
- Stomatitis
- Palmar/Plantar Erythrodysesthesia
- Darkening/discholoration of veins
- Cardiotoxicity - Occasionally patients may experience coronary artery spasm
- Laryngopharyngeal dysesthesia
- Pulmonary toxicity (including interstitial lung disease)
- Infusion reactions to Panitumumab
- Rash / skin reaction to Panitumumab
- Hypomagnesaemia
- Hypokalaemia

**DPD Deficiency and Severe Toxicity Risk**

Dihydropyrimidine dehydrogenase (DPD) plays an important role in the metabolism of fluoropyrimidine drugs 5-fluorouracil (5FU) and capecitabine. Patients with DPD deficiency may be predisposed to experience increased or severe toxicity when receiving 5-FU or capecitabine, and in some cases these events can be fatal.

For all patients having capecitabine or fluorouracil, the risk of severe side effects from capecitabine or 5FU if patients have a deficiency of DPD must be mentioned and patient given a copy of the DPD toxicity information leaflet from cancer research UK.


**DOSE MODIFICATION**

Panitumumab and FOLFOX 1st line MCRC CRP17 CR032-v1.1

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Haematological Toxicity:
- Panitumumab does not normally cause myelosuppression, but is associated with anaemia in more than 10% of patients
- Delay 1 week if ANC < 1.0 and Platelets < 75.
- If delay > 1 week or delay 2 weeks or greater occurs, reduce the 5FU dose (bolus & infusional) and Irinotecan by 20%. Continue at the reduced dose for subsequent cycles unless other toxicity occurs.
- If further delay(s) for bone marrow suppression occur despite a 20% dose reduction, consider a further 20% dose reduction.

Renal function
- Panitumumab is not renally excreted
- If GFR falls to less than 30mls/min Oxaliplatin is contra-indicated

Non-Haematological toxicity

Fluorouracil

<table>
<thead>
<tr>
<th>Non-Haematological Toxicity</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomatitis</td>
<td>Commence Corosyl mouth wash, nystatin suspension</td>
<td>Mouth care + Delay treatment until recovered</td>
<td>Delay chemo until recovered. Restart with a 20% 5FU dose reduction</td>
<td>Delay chemo until recovered. Restart with a 40% 5FU dose reduction</td>
</tr>
<tr>
<td>PPE</td>
<td>No change. Advise emollients as per local practice</td>
<td>Delay treatment until recovered</td>
<td>Delay chemo until recovered. Restart with a 20% 5FU dose reduction</td>
<td>Delay chemo until recovered. Restart with a 40% dose reduction</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Loperamide 4mg initially, then 2mg after each motion</td>
<td>Despite loperamide treatment: delay treatment until recovered. Restart with a 20% 5FU dose reduction</td>
<td>Delay chemo until recovered. Restart with a 20% 5FU dose reduction</td>
<td>Delay chemo until recovered. Delay chemotherapy until recovered. Restart with a 20% dose reduction (Discuss with SpR/Consultant)</td>
</tr>
</tbody>
</table>

Panitumumab - Skin Reactions

<table>
<thead>
<tr>
<th>CTC (v2) definition</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular or popular eruption/erythema without symptoms</td>
<td>Macular or popular eruption/erythema with pruritis or other symptoms; localised desquamation or other lesions covering &lt;50% of body</td>
<td>Symptomatic generalised erythroderma or macular, popular or vesicular eruption or desquamation covering &gt;50% of body</td>
<td></td>
</tr>
<tr>
<td>Topical anti-acne cream (e.g. benzoyl peroxide) for face. Salicylic acid in alcoholic lotion for chest/back</td>
<td>As grade 1 plus menthol in aqueous cream. Oral antihistamine and oral tetracycline (for 3 months)</td>
<td>As grade 2 plus saline compresses if required.</td>
<td></td>
</tr>
</tbody>
</table>

- Systemic or topical steroids for treatment of rash are not generally advised. Patients on tetracyclines should be advised to avoid prolonged exposure to the sun.
- Topical treatments can have a drying effect on the skin. Care should be taken to avoid aggravating xerosis, especially when acne-like rash is fading or becoming scaly. Switch to moisturising creams instead of alcoholic lotion or gel if this occurs.

- Interstitial lung disease
ILD has been observed in 1.3% of patients treated with panitumumab, fatal ILD has been observed in some cases. If patients experience worsening of respiratory symptoms such as dyspnoea, cough and fever, panitumumab must be interrupted and the patient should be promptly investigated. If ILD is confirmed, panitumumab should be discontinued and the patient treated appropriately.

### Panitumumab dose modifications

<table>
<thead>
<tr>
<th>Occurrence of skin symptom(s): ≥ grade 3</th>
<th>Administration of panitumumab</th>
<th>Outcome</th>
<th>Dose regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial occurrence</td>
<td>Withhold 1 or 2 doses &amp; treat as above</td>
<td>Improved (&lt; grade 3)</td>
<td>Restart at 100% of original dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not recovered</td>
<td>Discontinue</td>
</tr>
<tr>
<td>At the second occurrence</td>
<td>Withhold 1 or 2 doses &amp; treat as above</td>
<td>Improved (&lt; grade 3)</td>
<td>Restart at 80% of original dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not recovered</td>
<td>Discontinue</td>
</tr>
<tr>
<td>At the third occurrence</td>
<td>Withhold 1 or 2 doses &amp; treat as above</td>
<td>Improved (&lt; grade 3)</td>
<td>Restart at 60% of original dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not recovered</td>
<td>Discontinue</td>
</tr>
<tr>
<td>At the fourth occurrence</td>
<td>Discontinue</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Oxaliplatin Neurotoxicity:

- Cold related paraesthesia of hands/feet or dyasaesthesia/laryngeal spasm syndrome last a few hours and do not require treatment or dose reduction.
- If severe laryngeal spasm occurs, consider increasing Oxaliplatin infusion to 6 hours
- If symptoms persist for 14 days and/or there is pain, functional loss, omit Oxaliplatin and continue with 5FU/FA until fully recovered, then restart Oxaliplatin at 20% dose reduction.

### TREATMENT LOCATION

Cancer Centre or Cancer Unit

### REFERENCES:

