

## PANITUMUMAB + OXALIPLATIN MdG

For 1<sup>st</sup> line use in RAS wild type metastatic colorectal cancer

Blueteq registration is required before panitumumab treatment may start

Drugs/Dosage:	Panitumumab	6mg/kg	IV	Day 1
	Calcium folinate	350mg	IV	Day 1
	Oxaliplatin	85mg/m <sup>2</sup>	IV	Day 1
	5-Fluorouracil	400mg/m <sup>2</sup>	IV	Day 1
	5-Fluorouracil	2400mg/m <sup>2</sup>	IVI	over 46 hrs, starting Day 1
Other drugs:	Pre-emptive management for all patients starting panitumumab: <ul style="list-style-type: none"> <li>• Moisturiser e.g. Aveeno applied to face, hands, feet, neck, back and chest twice daily throughout treatment</li> <li>• advise to limit skin exposure to sun, and to apply sunscreen SPF 15 or higher before going outdoors in sunny weather.</li> <li>• Doxycycline 100mg od x 14 capsules should also be prescribed routinely with the first panitumumab dose, labelled to be started only at the first appearance of a rash.</li> </ul>			
Administration:	Panitumumab in 100ml sodium chloride 0.9% infused over 60 minutes via a 0.2 micron in-line filter, prior to chemotherapy. If the initial 60 minute infusion is tolerated, subsequent doses may be given over 30 – 60 minutes. Flush with glucose 5% Oxaliplatin in 250ml 5% glucose 5% over 2 hours <i>concurrently with</i> Calcium folinate in 250ml glucose 5% over 2 hours Flush with glucose 5%, and then give 5FU bolus injection over 5 minutes 5FU infusion via central venous catheter and ambulatory infusion device over 46 hours			
Frequency:	2 weekly cycle Duration of treatment is patient- and Consultant-dependent, with options including: treatment to progression; or 3 to 6 month blocks of treatment, followed by a drug holiday or less intensive regimen, for patients who have responded, or have stable disease. N.B. Panitumumab may not continue after a <i>planned</i> treatment break			
Main Toxicities:	myelosuppression;      mucositis;      diarrhoea;      neurotoxicity (see Comments); infusion-related reactions to oxaliplatin or panitumumab (see Comments); coronary artery spasm (see Comments);      palmar/plantar erythema; skin reactions to panitumumab (acne-like rash, dry skin, itching, nail changes);      sore eyes; hypomagnesaemia;      ovarian failure/infertility			
Anti-emetics:	Day 1: highly emetogenic			
Regular Investigations:	FBC	Day 1		
	U&Es & LFTs	Day 1		
	Mg <sup>2+</sup>	Day 1		
	CEA	every 4 weeks		
	CT scan	baseline, then every 8 weeks		

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Prepared by: S Taylor	Checked by: C Tucker

Comments:

**Oxaliplatin & Acute Cold-related Dysaesthesia (CRD):**

Many patients experience transient paraesthesia of hands & feet, and some experience laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion, and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patient should be well advised on precautions to be taken. Does not require treatment or dose reduction.

For laryngopharyngeal dysaesthesia, subsequent infusions should be given over 6 hours. Consideration to infusion of 10mmol of magnesium + 1gram of calcium gluconate in 0.9% sodium chloride 250ml over 1 hour, prior to starting the oxaliplatin, should also be made. NB. The above management may also benefit patients who complain of pain/weakness in arm during peripheral administration, but should **not** be used to try and alleviate CRD or cumulative neuropathy.

**Oxaliplatin & Cumulative dose related peripheral sensory neuropathy:**

Usually occurs after a cumulative dose of 800mg/m<sup>2</sup>. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approx 3 – 5 months to recovery.

**Allergic reactions to oxaliplatin during infusion:** Immediate intervention is to stop the infusion and call for medical help. Treat with IV corticosteroid and antihistamine. After full recovery, the patient may continue with folinic acid and 5FU.

At Consultant discretion, the patient may be re-challenged with oxaliplatin, according to the grade of reaction, as detailed in the separate document "Oxaliplatin Hypersensitivity & desensitisation regimen".

**Allergic reactions to panitumumab** are less likely than with cetuximab.

If the patient experiences a mild or moderate infusion-related reaction, the infusion may be re-initiated at a reduced rate. It is recommended to maintain this lower infusion rate in all subsequent infusions.

A severe allergic reaction requires immediate and permanent discontinuation of panitumumab.

Infusion-related and pulmonary symptoms may also rarely occur several hours after the panitumumab infusion is given. Patients should be warned about this and instructed to contact the hospital if any such symptoms occur.

Low magnesium is to be treated according to local guidelines.

Coronary artery spasm is a recognised complication of 5FU although the evidence base regarding aetiology, management and prognosis is not particularly strong. Coronary artery spasm is more common in patients receiving continuous infusions of 5FU, and is usually reversible on discontinuing the infusion. Should a patient receiving 5FU present with chest pains, stop the 5FU. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, the 5FU should be withdrawn permanently.<sup>1</sup> Refer to Consultant.

**Dose Modifications**

Haematological Toxicity:

Neutrophils < 1.5 x 10<sup>9</sup>/l  
or  
Platelets < 75 x 10<sup>9</sup>/l

Delay chemotherapy\* for 1 week or until FBC recovered. If any Grade 3 or 4 neutropenia (< 1.0 x 10<sup>9</sup>/l) or thrombocytopenia (< 50 x 10<sup>9</sup>/l) observed, reduce oxaliplatin to 65mg/m<sup>2</sup> and reduce 5FU (bolus & infusion) by 20%.

\*Panitumumab is not myelosuppressive and so may be continued during periods of mild myelosuppression, according to clinician preference.

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Renal Impairment: Oxaliplatin may be used at 100% dose in moderate renal impairment (CrCl > 30ml/min), but monitor renal function and dose adjust according to toxicity. Oxaliplatin is contra-indicated in patients with CrCl < 30ml/min.

Panitumumab has not been studied in patients with impaired renal function. However, dose adjustments would not be expected to be required.

Hepatic Impairment:

Liver Function	Oxaliplatin Dose	5 Fluorouracil Dose
*Bilirubin > 3 x ULN	Give 50% dose	Give 50% dose

\*Note that significantly impaired hepatic function may be a sign of disease progression and require cessation of, or change in, treatment. **Always discuss deteriorating organ function with consultant.**

Panitumumab has not been studied in patients with impaired liver function. However, dose adjustments would not be expected to be required.

Panitumumab Rash:

At the first sign of <b>any</b> skin toxicity / acneiform eruption, <b>up to Grade 2</b> (papular eruption with or without pruritis, covering 10 - 30% of BSA)	<ul style="list-style-type: none"> <li>• Ensure moisturiser is being used regularly.</li> <li>• Initiate doxycycline 100mg po once daily, to continue throughout while on panitumumab.</li> <li>• Oral antihistamine for relief of any itch. Analgesia may be of benefit.</li> </ul>
<b>Grade 2 (intolerable) or Grade 3</b> acneiform eruption (eruption covering > 30% BSA with or without pruritis, <b>or</b> < 30% but with extensive super-infection)	<ul style="list-style-type: none"> <li>• Panitumumab treatment must be interrupted until resolved to ≤ Grade 2.</li> <li>• Increase doxycycline dose to 100mg bd continuous and maintain this dose with all further panitumumab.</li> <li>• Oral antihistamine for relief of any itch. Analgesia may be of benefit.</li> <li>• Once rash resolved, resume panitumumab at:               <ul style="list-style-type: none"> <li>- full dose with 1<sup>st</sup> occurrence;</li> <li>- 80% dose with 2<sup>nd</sup> occurrence;</li> <li>- 60% dose with 3<sup>rd</sup> occurrence.</li> </ul> </li> </ul>
<b>Grade 3</b> acneiform eruption not responding to doxycycline 100mg bd	<ul style="list-style-type: none"> <li>• Switch to erythromycin 500mg po qds</li> </ul>
<b>Grade 4</b> (associated with extensive superinfection requiring IV antibiotics)	<ul style="list-style-type: none"> <li>• Rarely seen. Discontinue panitumumab permanently. Consult with dermatologist.</li> </ul>

Topical acne medications are **not** recommended. Use of topical antibiotics is not encouraged, and needs to be discussed with Microbiology first.

Neurological Toxicity:

If neurological symptoms occur, use the following oxaliplatin dose adjustment guidelines: Symptoms lasting > 7 days and troublesome; reduce oxaliplatin dose to 65mg/m<sup>2</sup>. Paraesthesia without functional impairment persisting until next cycle; reduce oxaliplatin dose to 65mg/m<sup>2</sup>. Paraesthesia with functional impairment persisting until the next cycle; oxaliplatin should be discontinued. (Re-initiation may be considered if symptoms resolve)

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- Stomatitis:** For stomatitis occurring between cycles, treat symptomatically. Further chemotherapy must be delayed until fully resolved.  
If mouth ulcers develop, reduce the 5FU doses (bolus and infusion) by 20% for subsequent cycles.  
If further toxicity occurs, reduce the 5FU bolus and infusion by a further 20%, and also reduce the oxaliplatin dose by 20%.
- Diarrhoea:** For diarrhoea occurring between cycles, treat symptomatically. If diarrhoea has not resolved by the time the next cycle is due, delay 1 week.  
For any Grade 3 diarrhoea or stomatitis, reduce subsequent 5FU doses (bolus and infusion) by 20%.  
For any Grade 4 diarrhoea, or repeated Grade 3 after 5FU dose reduction, also reduce the oxaliplatin to 65mg/m<sup>2</sup> for subsequent cycles.
- Palmar/Plantar Erythema:** Treat symptomatically, initially with pyridoxine 50mg po tds. If Grade 3 or 4 PPE occurs, delay further treatment until Grade 0 – 1 and then reduce the 5FU (bolus and infusion) by 20% for subsequent cycles.
- References:** Douillard, JY et al; JCO 2010; 28: 4697 – 4705  
Rash advice adapted from HER1/EGFR Inhibitor Rash Management Forum, 2005

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