SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Panitumumab & FOLFOX

Colorectal Cancer

PROTOCOL REF: **MPHAPAFXGA**
Version No. 2.0

Approved for use in:

Panitumumab (NICE TA439) is recommended, within its marketing authorisation, as an option for previously untreated, RAS wild-type metastatic colorectal cancer in adults in combination with:

- 5-fluorouracil, folinic acid and oxaliplatin (FOLFOX) or
- 5-fluorouracil, folinic acid and irinotecan (FOLFIRI).

In some instances patients may receive ox-cap or I-cap in place of their FOLFOX or FOLFIRI when patients do not wish to have a line fitted.

Dosage:

Drug	Dosage	Route	Frequency
Panitumumab	6mg/kg	IV	Every 14 days
Oxaliplatin	85mg/m^2	IV	Every 14 days
Calcium Folinate	350mg	IV	Every 14 days
Fluorouracil	400mg/m^2	IV	Every 14 days
Fluorouracil	2400mg/m^2	IV	Every 14 days

To be given for 6 cycles then review, continue until disease progression or unacceptable toxicity

Administration & Counselling Points:

Caution in patients with pre-existing neurotoxicity

Caution in patients with pre-existing heart disease, angina pectoris, arrhythmias or taking high dose aspirin or coumarin anticoagulants

Be aware of infusion related allergic reactions

Teratogenic risk

Emetogenic risk:

Moderate on Day 1, Low on Day 2

Supportive treatments:

Dexamethasone tablets 4mg twice daily for 3 days

Ondansetron 8mg twice a day for 3 days

Metoclopramide 10mg oral tablets, up to 3 times a day or as required

Pliazon cream

Aquamax® cream

Loperamide 4mg initially then 2mg after each loose stool.

Extravasation risk:

Oxaliplatin – Irritant

Fluorouracil – Irritant

Panitumumab - Neutral

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal

Calculate CrCl using Cockroft and Gault formula at baseline and before each cycle and adjust dose according to table.

Creatinine Clearance (mL/min)	Oxaliplatin Dose	Fluorouracil Dose	Panitumumab Dose
≥ 30	Full dose	Full dose	Full dose

	<table><tr><td>< 30</td><td>Omit</td><td>75%</td><td>Use with caution</td></tr></table> If moderate impairment monitor closely and adjust oxaliplatin dose if deterioration or toxicity appears.

Hepatic	<table><tr><th>Liver function</th><th>Oxaliplatin Dose</th><th>Fluorouracil Dose</th><th>Panitumumab Dose</th></tr><tr><td>Bilirubin > 3 x ULN</td><td>100%</td><td>50%</td><td>No dose adjustment needed</td></tr></table> Note that significantly impaired hepatic function might be a sign of disease progression and require cessation or change of treatment. **Always discuss deteriorating organ function with consultant**

Interactions:

Panitumumab
• Monitor for severe diarrhoea, in combination with platinum-based chemotherapy, irinotecan-regimen, bevacizumab
Oxaliplatin
• Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored • Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis
Fluorouracil
• Phenytoin – potentially toxic levels of phenytoin have been reported- monitor carefully • Warfarin and other coumarin anticoagulants – increased bleeding risk, monitor INR carefully, consider switch to LMWH • Sorivudine and analogues – Potentially fatal interaction – avoid completely • Cimetidine, metronidazole and interferon may increase the plasma level of 5-fluorouracil, thereby increasing the toxicity of 5-fluorouracil.

- Fluorouracil enhances the action of other cytostatic drugs and irradiation therapy.
- Avoid live vaccines.
- Alcohol
- Enoxaparin / Dalteparin – monitor for bleeding signs

Treatment schedule:

Day	Drug	Dosage	Route	Diluent and Rate
1	**Dexamethasone** 30 mins before chemotherapy	8mg	PO	
1	**Ondansetron** 30 mins before chemotherapy	16mg	PO	
Flush line with 0.9% sodium chloride before and after panitumumab				
1	**Panitumumab**	6mg/kg	IV	Infuse first dose over 60 minutes* via a 0.2 or 0.22 micrometre in-line filter. Subsequent doses can be infused over 30 to 60 minutes.
Flush line with 5% glucose before and after oxaliplatin				
1	**Oxaliplatin**	85mg/m^2	IV	500mL Glucose 5% infusion over 2 hours
Oxaliplatin and Calcium Folinate given at same time concomitantly				
1	**Calcium Folinate**	350mg	IV	250mL Glucose 5% infusion over 2 hours
1	**Fluorouracil**	400mg/m^2	IV	Bolus over 5 minutes
1-2	**Fluorouracil**	2400mg/m^2	IV	46 hour continuous infusion in Sodium Chloride 0.9%

Main toxicities:

Panitumumab
• Dyspnoea, part of hypersensitivity reaction • Hypersensitivity reaction (delayed effects after 24hours post-infusion) • Skin reactions, cholinergic syndrome, infusion related reactions • Electrolyte disturbances (hypo-Mg, hypo-K, hypo-Ca) • Neutropenia • Cardiovascular • Conjunctivitis / keratitis • Increased diarrhoea, in combination with CAPOX • Increased leucopenia/ neutropenia, in combination with Platinum-based chemo • Increased cardiac ischaemia, myocardial infarction, congestive heart failure • Increased hand-foot syndrome, in combination with fluoropyrimidines
Oxaliplatin
Infusion reactions, neuro toxicity, myelosuppression, mucositis, diarrhoea, nausea and vomiting
Fluorouracil
• Palmar-plantar syndrome • Neutropenia, thrombocytopenia, anaemia, leukopenia • Mucositis, nausea, vomiting, diarrhoea, abdominal pain • Cardiac Ischaemia (coronary artery spasm), ECG abnormalities • Conjunctivitis • Infections, immunosuppression • Bronchospasm, epistaxis • Alopecia • DPD deficiency

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing	Last cycle
Clinical Assessment	X		Pre cycle		Pre cycle	Alternate cycles or team discretion	
SACT Assessment	X	X	X	X	X	Every cycle	Check has OPD
FBC	X	X	X	X	X	Every cycle	X
U&E, calcium, & LFT	X	X	X	X	X	Every cycle	X
CrCl	X	X	X	X	X	Every cycle	X
CEA	X	X	X	X	X	Every cycle	X
Dihydropyrimidine dehydrogenase (DPD) deficiency test	X					This test is required for every patient newly started on capecitabine or fluorouracil for the first time. The result MUST be available before administration of chemotherapy unless clear documentation from the consultant is available to the contrary.	
CT scan (advanced CRC patients)	X					Inform consultant team if not booked	Check has date for CT
Informed Consent	X					Verbal each cycle	
Height	X						
Weight recorded	X	X	X	X	X	Every cycle	X

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed on day 1 if all apply:-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Delay 1 week on day 1 if any apply:-

ANC < 1.0 x 10^9/L	Platelets < 100 x 10^9/L

Lowest count since previous cycle	**Oxaliplatin dose**	**Fluorouracil dose**
Grade 3 / 4 neutropenia (<1.0 x10^9/L) or thrombocytopenia (<50 x 10^9/L)	65mg/m^2 (metastatic)	80% bolus and infusion

If WCC, platelets or ANC (absolute neutrophil count) still below required levels for treatment at week 2:

- delay treatment again and reduce flourouracil and irinotecan doses by 20% for subsequent cycles.
- If a further delay for myelotoxicity occurs despite a 20% reduction a further 20% reduction may be considered. Refer to oncologist.

Note that **panitumumab is not myelosuppressive** and no dose reduction is required

Non- Haematological toxicity:

Panitumumab	
Dermatological	Skin reactions are very common and treatment interruption or discontinuation may be required. • Prophylactic use of oral tetracyclines (6 - 8 weeks), sun screen (SPF > 15 UVA and UVB) and topical application of 1% hydrocortisone cream with moisturiser should be considered. If a patient experiences an intolerable or severe skin reaction (≥ grade 3)

<table>
<tr><td></td><td>
Panitumumab therapy must be interrupted. Treatment may only be resumed if the reaction has resolved to grade 2.
Recommended dose modifications for management of severe skin reactions:
<table>
<tr><th>≥ grade 3 skin reaction</th><th>Panitumumab dose after resolution to ≤ grade 2</th></tr>
<tr><td>1st occurrence</td><td>Resume at full dose</td></tr>
<tr><td>2nd occurrence</td><td>Continue at 80% of original dose</td></tr>
<tr><td>3rd occurrence</td><td>Continue at 60% of original dose</td></tr>
<tr><td>4th occurrence</td><td>Discontinue treatment</td></tr>
</table>
</td></tr>
<tr><td>Ocular</td><td>Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with panitumumab should be interrupted or discontinued.

If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered.</td></tr>
<tr><td>Hypersensitivity reactions including anaphylaxis</td><td>If a severe or life-threatening reaction occurs during an infusion or at any time post-infusion (e.g. presence of bronchospasm, angioedema, hypotension, need for parenteral treatment, or anaphylaxis):
Panitumumab should be permanently discontinued.
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.</td></tr>
</table>

	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.
Pulmonary complications	Cases of interstitial lung disease (ILD), both fatal and non-fatal, have been reported, mainly from the Japanese population. • In the event of acute onset or worsening pulmonary symptoms, panitumumab treatment should be interrupted and a prompt investigation of these symptoms should occur. • If ILD is diagnosed, panitumumab should be **permanently discontinued** and the patient should be treated appropriately. • In patients with a history of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with panitumumab versus the risk of pulmonary complications must be carefully considered.

Oxaliplatin		
Neurotoxicity – see notes below for specific cases	**Neurotoxicity**	**Oxaliplatin dose**
	Grade 1 any duration or grade 2 < 7days but resolving before next cycle	85mg/m^2
	Grade 2 persisting for 7 days or Grade 3 resolved by next cycle	65mg/m^2
	Grade 3 persisting to next cycle or any grade 4	Stop oxaliplatin
Acute cold related dysesthesia (CRD)	Transient paraesthesia of hands and feet as well as laryngopharyngeal dysesthesia (unpleasant sensations in throat) is common. Onset is during or within hours of infusion and it resolves in minutes or days. Symptoms are exacerbated by cold – advise patients on suitable precautions e.g. avoid cold drinks. Should not	

	require dose reduction, but if troublesome then infusion duration can be increased to 6 hours (see note below).
Laryngopharyngeal dysaesthesia	Stop infusion, provide symptomatic treatment. Resume at slower infusion rate. Give subsequent infusions over 6 hours (see note below).
Cumulative dose related sensory neuropathy	Usually occurs after a cumulative dose of 800mg/m^2. Peripheral neuropathy can be a **permanent significant side effect** that can occur during or after treatment is completed. Patients should be informed of this risk. **If this symptom worsens or becomes permanent senior review should be requested.**
Allergic reactions during infusion	Stop the infusion and call for help. Follow trust anaphylaxis policy. Treat with IV corticosteroid and antihistamine. There is no need to stop the capecitabine. Discuss re-challenge with consultant

Whilst the recommended increase in duration of infusion is to 6 hours – where the oncologist and the treating team agree, this can be reduced to 4 hours dependent on the severity of the reaction and the tolerability of the infusion over this time.

Fluorouracil	
Chest pain, coronary artery spasm	Stop fluorouracil, standard angina investigations, stop 5FU immediately, and perform emergency medical assessment. If occurs on the day unit during administration, request for urgent medical review (SpR in CCC-L, and MET team in our chemotherapy hubs) If occurs at home, go to the local A&E. Please inform tumour site consultant after.

<table>
<tr><td>Stomatitis</td><td>If mouth ulcers or > grade 2 symptoms develop treat symptomatically, delay treatment until resolved to grade 1 and reduce fluorouracil doses by 20%. (See table)</td></tr>
<tr><td>Diarrhoea</td><td>
<table>
<tr><th>Grade 0</th><th>Grade 1</th><th>Grade 2</th><th>Grade 3</th><th>Grade 4</th></tr>
<tr><td>None or no change from normal</td><td>Increase of up to 3 bowel movements a day over pre-treatment normal or mild increase in ostomy output</td><td>Increase of up to 4-6 episodes a day or moderate increase in ostomy output or nocturnal movement or moderate cramping</td><td>Increase of up to 7-9 episodes a day or severe increase in ostomy output or incontinence / severe cramping / bloody diarrhoea</td><td>Increase >10 episodes a day or grossly bloody diarrhoea</td></tr>
</table>

Treat diarrhoea between cycles symptomatically.
• If diarrhoea has not resolved by next cycle delay treatment by 1 week.
• If diarrhoea remains troublesome or > 1 week:
- delay is required reduce both fluorouracil bolus and infusion doses by 20% and continue at the lower dose unless further toxicity occurs (See table)</td></tr>
<tr><td>Palmar-Plantar Erythrodysesthesia (PPE)</td><td>Treat symptomatically, delay treatment until resolved to grade 1.
• Reduce fluorouracil doses (bolus and infusion) by 20% for subsequent doses if persistent troublesome PPE. (See table)</td></tr>
</table>

Fluorouracil dose reductions for non haematological toxicity

	Non haematological toxicities (diarrhoea, stomatitis, PPE)			
Grade	0-1	2	3	4
1st occurrence	100%	80%	50%	Stop treatment
2nd occurrence	80%	70%	50%	Stop treatment
3rd occurrence	50%	50%	50%	Stop treatment

References:

1. Oxaliplatin summary of product characteristics accessed 09/09/23 https://www.medicines.org.uk/emc/product/3024
2. BNF available via: https://bnf.nice.org.uk/
3. NICE: CG151 Colorectal cancer: diagnosis and management. Published: 29 January 2020 Last updated: 15 December 2021 Electronic Medicines Compendium Summary of product characteristics for Fluorouracil Fluorouracil injection, 50 mg/ml, solution for injection - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
4. Northern Cancer Alliance, Anti-emetic Guidelines for Chemotherapy Induced Nausea and Vomiting. North of England Cancer Network (northerncanceralliance.nhs.uk)
5. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
6. Cetuximab and panitumumab for previously untreated metastatic colorectal cancer, NICE https://www.nice.org.uk/guidance/ta439
7. Summary of product characteristics, Electronic Medicines Compendium, Vectibix, https://www.medicines.org.uk/emc/product/6178
8. Northern Cancer Alliance, Anti-emetic Guidelines for Chemotherapy Induced Nausea and Vomiting. North of England Cancer Network (northerncanceralliance.nhs.uk)

Circulation/Dissemination

Date added into Q-Pulse	27th February 2024
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
November 2023	2.0	**Joanne McCaughey, Deputy Chief Pharmacist** **Aaron Teoh, Advanced Cancer Pharmacist**	• New format. Flush added • Updated supportive treatments, addition of metoclopramide • Added panitumumab details (main toxicities, non-haematological toxicity)