PANITUMUMAB + IRINOTECAN MdG (Folfiri)

For 1st 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
	Irinotecan	180 mg/m^2	IV	Day 1
	Calcium folinate	350mg	IV	Day 1
	5-Fluorouracil	400mg/m^2	IV	Day 1
	5-Fluorouracil	2400mg/m^2	IVI	over 46 hrs, starting Day 1

Other drugs: Pre-emptive management for all patients starting panitumumab:

- Moisturiser e.g. Aveeno applied to face, hands, feet, neck, back and chest twice daily throughout treatment
- advise to limit skin exposure to sun, and to apply sunscreen SPF 15 or higher before going outdoors in sunny weather.
- 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.

Loperamide and ciprofloxacin (250mg po bd x 7 days) should be routinely prescribed with Cycle 1 irinotecan, and patients should be given the information leaflet and counselled to ensure they know how and when to use them.

Primary G-CSF prophylaxis should be considered for patients with additional risk factors – see G-CSF guidelines and / or discuss with Consultant

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.
Irinotecan in 250ml 0.9% sodium chloride over 60 – 90 minutes
Calcium folinate in 250ml 0.9% sodium chloride over 30 minutes
5FU bolus injection over 5 minutes
5FU infusion via central venous catheter and ambulatory infusion device

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 *planned* treatment break.

Main Toxicities: myelosuppression; mucositis; diarrhoea (see Comments); alopecia; infusion-related reactions to panitumumab (see Comments); cholinergic syndrome (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

Extravasation: non-vesicants

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Version: 2	Approved by Lead Chemotherapy Nurse:
Supersedes: Version 1	Date: 7.7.17
Prepared by: S Taylor	Checked by: C Tucker

Regular Investigations:	FBC	Day 1
	U&Es & LFTs	Day 1
	Mg^{2+}	Day 1
	CEA	every 4 weeks
	CT scan	baseline, then every 8 weeks

Comments:

Cholinergic syndrome can be controlled by giving atropine 0.25mg s/c bolus at the time of irinotecan administration. Should the syndrome develop, a further dose of atropine may be given.

Diarrhoea may occur within 30 – 90 minutes of irinotecan infusion, or may be delayed. Once a liquid stool occurs, loperamide 4mg should be taken immediately, followed by one tablet 2 hourly for at least 12 hours, and for 12 hours following the last liquid stool. Patients should be instructed to drink large volumes of water / electrolytes. Concomitant fever or vomiting will require hospitalisation for IV hydration.

If diarrhoea persists for 24 hours despite the loperamide, a prophylactic course of ciprofloxacin 250mg po bd for 7 days should be started. After 48 hours of persistent diarrhoea, the patient should be hospitalised for parenteral support and review of treatment.

Prophylactic ciprofloxacin should also be commenced in patients with neutrophils < 0.5 x 10^9/l, even in the absence of diarrhoea. Patients who develop severe neutropenia are especially at risk of infection if they are also suffering from diarrhoea.

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.[1] Refer to Consultant.

Dose Modifications

Haematological Toxicity:	Neutrophils < 1.5 x 10^9/l or Platelets < 100 x 10^9/l	Delay chemotherapy* for 1 week. Repeat FBC. If recovered, resume treatment.

If more than 1 delay, or 1 delay of ≥ 2 weeks occurs, reduce irinotecan and 5FU (bolus & infusion) doses by 20% for subsequent cycles. If a further delay for myelotoxicity occurs despite a 20% dose reduction, a further 20% dose reduction may be made.

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

Panitumumab Rash:

At the first sign of ***any*** skin toxicity / acneiform eruption, **up to Grade 2** (papular eruption with or without pruritis, covering 10 - 30% of BSA)	• Ensure moisturiser is being used regularly. • Initiate doxycycline 100mg po once daily, to continue throughout while on panitumumab. • Oral antihistamine for relief of any itch. Analgesia may be of benefit.
Grade 2 (intolerable) or Grade 3 acneiform eruption (eruption covering > 30% BSA with or without pruritis, ***or*** < 30% but with extensive super-infection)	• Panitumumab treatment must be interrupted until resolved to ≤ Grade 2. • Increase doxycycline dose to 100mg bd continuous and maintain this dose with all further panitumumab. • Oral antihistamine for relief of any itch. Analgesia may be of benefit. • Once rash resolved, resume panitumumab at: - full dose with 1st occurrence; - 80% dose with 2nd occurrence; - 60% dose with 3rd occurrence.
Grade 3 acneiform eruption not responding to doxycycline 100mg bd	• Switch to erythromycin 500mg po qds
Grade 4 (associated with extensive superinfection requiring IV antibiotics)	• Rarely seen. Discontinue panitumumab permanently. Consult with dermatologist.

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

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.

Diarrhoea: For management of diarrhoea, see "Comments" section.
If diarrhoea from the previous cycle, even if not severe, has not resolved by the time the next cycle is due, delay 1 week. If there is more than 1 delay for this reason, reduce the irinotecan and 5FU (bolus and infusion) doses by 20% for subsequent cycles.
After an episode of severe diarrhoea (Grade 3-4), delay chemotherapy until full recovery, then reduce the irinotecan and 5FU (bolus and infusion) doses by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.

PPE: Treat symptomatically, and initiate pyridoxine 50mg po tds. If PPE continues to be a problem, reduce the 5FU doses (bolus and infusion) by 20% for subsequent cycles.

Renal Impairment: Cockcroft & Gault formula may be used to predict creatinine clearance. If borderline, or if predicted renal function falls by > 30%, an EDTA should be requested.

CrCl (ml/min)	Irinotecan Dose	5 Fluorouracil Dose
< 30	Give 50% dose	Give 80% dose

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	Irinotecan Dose	5 Fluorouracil Dose
Bilirubin 1.5 – 3 x ULN **or** ALP > 5 x ULN	Give 50% dose	Give 100% dose
*Bilirubin > 3 x ULN	Omit irinotecan	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.

References:

Kohne, C et al; J Cancer Res Clin Oncol 2012; 138: 65–72
Price, TJ et al; Lancet 2014; 15 (6) : 569 - 579
Rash advice adapted from HER1/EGFR Inhibitor Rash Management Forum, 2005