FOLFIRINOX (modified)

First-line use in metastatic pancreatic cancer, only for fit patients with PS 0 – 1 and who are not eligible for any clinical trial

Drugs/ Dosage:	Irinotecan	180mg/m^2	IV	Day 1
	Calcium folinate (folinic acid)	350mg	IV	Day 1
	Oxaliplatin	85mg/m^2	IV	Day 1
	5-Fluorouracil	2400mg/m^2	IVI	over 46 hours

Administration: Irinotecan in 250ml sodium chloride 0.9% over 60 – 90 minutes
Flush with glucose 5%
Oxaliplatin in 250ml glucose 5% over 2 hours
concurrently with calcium folinate in 250ml glucose 5% over 2 hours
Flush with glucose 5%
5FU infusion via CVC and ambulatory infusion device over 46 hours

Frequency: 2 weekly cycle for 6 cycles, then CT scan and clinical review
Continue to 12 cycles if response or stable disease.
Continuation beyond 12 cycles in the event of continuing clinical benefit and minimal toxicity may be considered – this is a Consultant only decision

Main Toxicities: myelosuppression; mucositis; diarrhoea; neurotoxicity (see Comments); allergic reactions (see Comments); coronary artery spasm (see Comments); palmar / plantar erythema; ovarian failure/infertility

Anti-emetics: highly emetogenic

Regular Investigations:	FBC	Day 1
	U&Es	Day 1
	Mg^{2+}	Day 1 (ideally, correct any low Mg^{2+} before oxaliplatin given)
	LFTs	4 weekly
	Ca 19-9	4 weekly
	CT scan	after 6 cycles

Comments: Cholinergic syndrome related to irinotecan can be controlled by giving atropine 0.25mg subcutaneously at 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.
N.B. Loperamide and ciprofloxacin must be dispensed to patients on discharge, and patient should be given information leaflet and counselled to ensure they know how and when to use them.

Reason for Update: order of administration reviewed; 5FU bolus removed, and dose modifications adapted accordingly	Approved by Consultant: Dr S Cummins
Version: 4	Approved by Lead Chemotherapy Nurse: P Deery
Supersedes: Version 3	Date: 8.6.16
Prepared by: S Taylor	Checked by: C Tucker

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 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^2. 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".

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 < 75 x 10^9/l — Delay treatment for 1 – 2 weeks. Repeat FBC and, once recovered, resume treatment according to tables below:

	Irinotecan	Oxaliplatin	5FU
1st occurrence of low neutrophils, febrile neutropenia*, or neuts < 0.5 for > 7 days	Give 80% of previous dose	Maintain full dose	Give 80% of previous dose
2nd occurrence of above*	Maintain dose	Reduce to 60mg/m^2	Continue with dose reduction above
3rd occurrence	Stop treatment		
1st occurrence of low platelets	Maintain full dose	Reduce to 60mg/m^2	Reduce to 75% of previous dose
2nd occurrence of low platelets	Give 80% of previous dose	Maintain 60mg/m^2 dose	
3rd occurrence	Stop treatment		

*For any febrile neutropenia or a 2nd episode of low neutrophils, G-CSF prophylaxis should also be initiated with subsequent cycles, starting on Day 5 of each cycle.

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)	Oxaliplatin Dose	Irinotecan Dose	5FU Dose
≥ 30	Give 100% dose	Give 100% dose	Give 100% dose
< 30	Omit oxaliplatin	Give 50% dose	Give 80% dose

Hepatic Impairment:

Liver Function	Oxaliplatin Dose	Irinotecan Dose	5FU Dose
Bilirubin 1. 5 –3 x ULN **or** ALP > 5 x ULN	Give 100% dose	Give 50% dose	Give 100% dose
*Bilirubin > 3x ULN	Give 50% dose	Omit irinotecan	Give 50% dose

*Bilirubin > 3 x ULN: 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**.

Diarrhoea: For management of diarrhoea, see "Comments" section.

If diarrhoea from the previous cycle, even if not severe, has not resolved (without loperamide for at least 24 hours) by the time the next cycle is due, delay 1 week.

Follow the table below for dose reductions in subsequent cycles:

	Irinotecan	Oxaliplatin	5FU
1st occurrence of Grade 3 -4 diarrhoea, or diarrhoea + fever	Give 80% of previous dose	Maintain full dose	Give 80% of previous dose
2nd occurrence of above	Maintain dose	Reduce to 60mg/m^2	Reduce to 75% of previous dose
3rd occurrence	Stop treatment		

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^2.
Paraesthesia without functional impairment persisting until next cycle; reduce oxaliplatin dose to 65mg/m^2.
Paraesthesia with functional impairment persisting until the next cycle; oxaliplatin should be discontinued.

Stomatitis: If mouth ulcers ≥ Grade 2 develop, reduce the 5FU doses (bolus and infusion) by 25% for subsequent cycles unless further toxicity occurs.

Palmar/Plantar Erythema: Treat symptomatically, initially with pyridoxine 50mg po tds. If PPE continues to be a problem (Grade 3 – 4), reduce 5FU bolus and infusion doses by 25% for subsequent cycles.

References:
Conroy T et al; NEJM 2011; 364: 1817 – 1825
De W Marsh, R et al; Cancer Med 2015; 4 (6): 853 - 863
[1]COIN Guidelines Oct 2000