MODIFIED DE GRAMONT

1. Palliative treatment of inoperable colorectal cancer.
2. Adjuvant use in Stage III and high risk Stage II colorectal cancers, for patients not suitable for oxaliplatin.

Drugs/Dosage:	Calcium folinate (Folinic acid)	350mg	IV	Day 1
	5-Fluorouracil	400mg/m^2	IV	Day 1
	5 Fluorouracil	2400mg/m^2	IVI	over 46 hours

Administration: Calcium folinate in 250ml 0.9% sodium chloride over 30 minutes
5-Fluorouracil (5FU) bolus injection over 5 minutes
5FU infusion via central venous catheter and ambulatory infusion device

Frequency:

Adjuvant use: 2 weekly cycle for 12 cycles

Advanced disease: 2 weekly cycle for 6 cycles, then CT scan and clinical review
After 6 cycles, consider drug holiday in patients who have responded / stable disease, with 6 weekly clinical review and 3 monthly CT scans. Reinitiate treatment if progression seen[2].
N.B. This is Consultant dependent, and other options include a further 3 month block of treatment, or treatment to progression.

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

Anti-emetics: mildly emetogenic

Regular Investigations:	FBC	Day 1
	U&Es	Day 1
	LFTs	4 weekly
	CEA	4 weekly (metastatic crc); 6-8 weekly (adjuvant crc)
	CT scan	after 6 cycles in advanced setting

Comments: Coronary artery spasm is a recognised complication of 5FU although the evidence base regarding aetiology, management & prognosis is not particularly strong. The incidence is estimated to be between 2% and 18%. Coronary artery spasm is more common in patients receiving continuous infusions of 5FU, which 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is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, the 5FU should be withdrawn permanently.[1] Refer to Consultant to discuss.

Reason for Update: platelet count cut-off reviewed	Approved by Consultant: Dr S Essapen
Version: 6	Approved by Lead Chemotherapy Nurse: V Mumford
Supersedes: Version 5	Date: 11.3.14
Prepared by: S Taylor	Checked by: C Tucker

Dose Modifications

Haematological Toxicity:	Neutrophils < 1.5 x 10^9/l or Platelets < 75* x10^9/l	Delay treatment for 1 week. Repeat FBC and, if result within normal range, resume treatment. For patients with recurrent low counts, consider a 20% dose reduction of 5FU for subsequent cycles.

* For palliative use, a higher platelet threshold of 80 - 100 x 10^9/l should be considered if the patient also has other toxicities, or borderline performance status. If in doubt, discuss with Consultant.

Hepatic Impairment[3]: If bilirubin > 3 x ULN, give 50% 5FU dose for subsequent cycles.

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.

Stomatitis[3]: If mouth ulcers develop, treat appropriately and reduce the 5-Fluorouracil doses (bolus and infusion) by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.

Diarrhoea[3]: For diarrhoea occurring between cycles, treat symptomatically. If diarrhoea has not resolved by the time the next cycle is due, delay 1 week. If diarrhoea is a problem despite symptomatic treatment, or if more than 1 delay is required, reduce the 5-Fluorouracil (bolus and infusion) doses by 20% and continue at the lower dose for subsequent cycles unless further toxicity occurs.

PPE[3]: Treat symptomatically, initially with pyridoxine 50mg po tds. If PPE continues to be a problem, reduce the 5-Fluorouracil doses (bolus and infusion) by 20% for subsequent cycles.

References:

Maughan, TS et al (MRC Colorectal Cancer Group); Lancet 2002; 359: 1555 - 1563
[3]MRC Colorectal Cancer Group; FOCUS trial (CR08), Protocol Version 6, Jan 2003
[1]COIN Guidelines Oct 2000
[2]Maughan, TS et al (MRC Colorectal Cancer Group); Lancet 2003; 361: 457 – 464
Tournigand, C et al; JCO 2012; 5645
Andre, T et al; NEJM 2004; 350 (23): 2343 – 2351 (adjuvant)