North West London Cancer Network

HEPATO PANCREATICO BILIARY
(Including Neuroendocrine and GISTs)
Section by: Dr Harpreet Wasan, Dr Rohini Sharma and Dr Alexandra Taylor
Version: HPB Regimens v5.2 NWLCN 20Oct11
Section last updated: 19th September 2011 Section last corrected: 20th October 2011
Approved by GI Oncology Lead Clinician Dr H Wasan Date:
Approved by NWLCN HPB Tumour Group: Professor N Habib Date:
Review Date: September 2012

I N D E X

HEPATO PANCREATICO BILIARY
(Including Neuroendocrine and GISTs)
Section by: Dr Harpreet Wasan, Dr Rohini Sharma and Dr Alexandra Taylor
Version: HPB Regimens v5.2 NWLCN 20Oct11
Section last updated: 19th September 2011 *Section last corrected: 20th October 2011*
Approved by GI Oncology Lead Clinician *September 2011*
Approved by WLCN HPB Tumour Group: *September 2011*
Review Date: September 2012

Tumour Markers

Diagnosis	Tumour Markers
Cholangiocarcinoma	CA19-9, CEA (CA125)
Duodenal cancer	CA19-9, CEA
Gall Bladder	CA19-9, CEA
Pancreas	CA19-9, CEA (CA125)
Hepatocellular	Alpha fetoprotein (αFP)
Neuro endocrine	5HIAA, Fasting GI peptide screen CGa, NSE, alpha fetoprotein (αFP)

If tumour markers not elevated at baseline not necessary to repeat with every cycle.

Chemotherapy Alone (No radiotherapy)

5-Fluorouracil Single Agent Regimens +/- Folinic Acid

Folinic acid refers to the mixed race mix D and L isomers
Calcium levofolinate refers to L-folinic acid isomer only.

1. **DeGramont – Modified (**MdG via CVAD CTIS: 734, via NS CTIS: 1219)

Folinic Acid	350mg	IV over 2 hours	Day 1
5 Fluorouracil	400mg/m^2	IV bolus	Day 1
5 Fluorouracil	2800mg/m^2	IV over 46 hours	Days 1 to 2

Interval between cycles: Repeat every 14 days
Number of cycles: HPB: 6-12 cycles/3-6 months
Tests before starting course of chemo: FBC, U&Es, LFTs. INR if hepatocellular cancer diagnosis. Tumour markers in table on page 3.
Tests to OK/Confirm each cycle of chemo**:** FBC, U&Es, LFTs. INR if hepatocellular cancer diagnosis
Supportive drugs with each cycle: Low risk antiemetics as per NWLCN guidelines or as per local policy
Chlorhexidine mouthwash 10mls QDS.
Loperamide if required 2-4mg QDS prn. (Max 16mg/24hours).
Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate

Additional information:

DeGramont Regimens

May 2005: all DeGramont regimens for upper GI standardised to the "modified" version either via a CVAD/infusor or via peripheral line/litre infusion bags.

Administration notes:

If 5FU administered using an ambulatory infusion pump via a central venous access device (CVAD) refer to relevant protocol for care of CVAD. Joint care with the community nursing services should be arranged in advance to support the patient and to assist with disconnecting the chemotherapy and flushing the CVAD. Written community nursing referral should be completed and the patient should be discharged with a home spillage kit, sharps container and a small supply of equipment to flush the line and dress the entry site of the CVAD.

Dose modifications: See DeGramont-modified table below

References: DeGramont et al. J. Clin Oncol 1997 15:808-15
Annals Oncol 1998;9(4):47 Seymour MT et al

Table: DeGramont – Modified

NB. Palliative patients will require greater dose reductions than stated below based on individual patient parameters. Discuss with consultant.

Side-Effect: MdG	**Dose Modification** (Source: Focus (CR08) Trial/2000)
Haematology (CR08) Neutrophils $x10^9/L$ and Platelets $x10^9/L$ ≥ 1.5 and ≥ 100 <1.5 or <100	Full dose. Delay until recovery. Only treat when neutrophils and platelets are above these limits If more than 1 delay, or one delay of ∃2 weeks occurs then restart with: 5FU: 20% dose reduction (bolus and infusion). Continue with this reduced dose unless further toxicity occurs. If further delays for myelotoxicity occur despite the 20% dose reduction, discuss with consultant
Renal function GFR below 30ml/min	Unclear guidance. Discuss with consultant
Hepatic function	Unclear guidance. Discuss with consultant
Stomatitis (Focus)	If mouth ulcers occur despite routine chlorhexidine mouthwash: 5FU: 20% dose reduction (bolus and infusion). Continue with this reduced dose unless further toxicity occurs.
Diarrhoea (Focus)	Between cycles – treat symptomatically loperamide 2-4mg QDS PRN and/or codeine phosphate 30-60mg QDS PRN Not resolved by next cycle: Delay 1 week/until recovered If diarrhoea still a problem • Despite symptomatic treatment • Or more than one delay is required Then dose reduce 5FU: 20% dose reduction (bolus and infusion). Continue with this reduced dose unless further toxicity occurs.

Side-Effect: MdG	**Dose Modification** (Source: Focus (CR08) Trial/2000)
Hand-Foot Syndrome (Focus/Focus 2) ≥Grade 2	Stop 5FU until recovered then restart with 5FU 20% dose reduction (bolus and infusion) for subsequent cycles. Phase III randomised controlled trials show no benefit from pyridoxine for prevention or treatment of 5FU induced hand/foot syndrome. Pyridoxine is not recommended
DPD Deficiency (Focus)	1-3% of patients have markedly exaggerated 5FU toxicity due to reduced 5FU catabolism. Discuss with consultant.
Cardiotoxicity (Focus)	Uncommon. 5FU may provoke angina or MI in patients with ischaemic heart disease. Seek specialist opinion on upgraded anti-anginal medication and consider dose reduction or alternative non 5FU treatment.
Neurotoxicity (Focus)	Uncommon – Cerebellar Consider alternative non 5FU treatment

2. **Lokich/5FU-300 Contin** (CTIS: 221)

5-Fluorouracil 300mg/m^2/day IV continuous infusion for 12 weeks

Continuous infusion for 12 weeks , 1 cycle = 3 weeks. Repeat tests every 21 days

Interval between cycles: Continuous infusion for 12 to 24 weeks (4 to 8 cycles of 21 days)
Number of cycles: HPB: 12-24 weeks
Tests before starting course of chemo: FBC, U&Es, LFTs. Tumour markers in table on page 3.
Tests to OK/Confirm each cycle of chemo: FBC, U&Es, LFTs
Supportive drugs with each cycle: Low risk antiemetics as per NWLCN guidelines or as per local policy
Chlorhexidine mouthwash 10mls QDS
Loperamide 2mg QDS PRN (max 16mg/24hours)
Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
Additional Information:
Administration notes: See page 4
Dose modifications: Table: Lokich page 6
References: Lokich et al. J.Clin Oncol 1989 7:425-32
J. Clin Oncol 2001. Webb et al (ECF)

Table: Lokich

NB. Palliative patients will require greater dose reductions than stated below based on individual patient parameters. Discuss with consultant.

Side-effect: Lokich	**Dose Modification** (Source: CR06 Trial)
Haematology WBC <2.0x10^9/L OR Platelets <75x 10^9/L	Interrupt infusion for 1 week (or until recovery Resume with 5FU: reduce dose by 50mg/m^2/ day
Renal function GFR below 30ml/min	Unclear guidance. Discuss with consultant
Hepatic function	Unclear guidance. Discuss with consultant
Stomatitis (CR06)	Routine mouthcare with chlorhexidine. If still a problem: stop chemo until recovery then Restart with 5FU: Reduce by 50mg/m^2/day
Diarrhoea (CR06)	Give loperamide 2-4mg QDS or codeine phosphate 30-60mg QDS If still a problem: stop chemo until recovery then: Restart with 5FU: Reduce by 50mg/m^2/day
Hand/Foot Syndrome ≥Grade 2	Stop chemo until recovered then restart with: 5FU dose reduced by 50mg/m^2/day. Phase III randomised controlled trials show no benefit from pyridoxine for prevention or treatment of 5FU induced hand/foot syndrome. Pyridoxine is not recommended
DPD Deficiency	1-3% of patients have markedly exaggerated 5FU toxicity due to reduced 5FU catabolism. Discuss with consultant.
Cardiotoxicity	Uncommon. 5FU may provoke angina or MI in patients with ischaemic heart disease. Seek specialist opinion on upgraded anti-anginal medication and consider dose reduction or alternative non 5FU treatment.
Neurotoxicity	Uncommon – Cerebellar Consider alternative non 5FU treatment

3. **MAYO Adaptations:**

5FU425/FA20 5 day (CTIS: 739) **or 5FU 370/FA20 5day** (CTIS: 659)

Folinic Acid	20mg/m^2	IV bolus	Days 1 to 5
5 Fluorouracil	dose determined by age see below		
Dose under 70 years			
And ECOG ≤1	425mg/m^2	IV bolus	Days 1 to 5
Dose over 70 years and/or			
ECOG ≥2	370mg/m^2	IV bolus	Days 1 to 5

Interval between cycles: Repeat every 28 days

Number of cycles: HPB: 6 cycles/6 months

Tests before starting course of chemo: FBC, U&Es, LFTs, tumour markers indicated in table on page 3. INR if hepatocellular cancer

Tests to OK/Confirm each cycle of chemo: FBC, U&Es, LFTs. INR if hepatocellular cancer

Supportive drugs with each cycle: Low risk antiemetics as per NWLCN guidelines or as per local policy
Chlorhexidine mouthwash 10mls QDS
Loperamide 2-4mg QDS PRN (max 16mg/day)
Ice chips 5 minutes before and for 30 minutes after injection (if tolerated) to reduce mucositis (Focus)

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information:

Administration notes:

Suck ice cubes or ice lollies 5 minutes before and for 30 minutes after injection (if tolerated) of 5FU may reduce the incidence of stomatitis.

Dose Modifications: See MAYO table page 8

Reference: J. Clin Oncol 1997 15:246-250. O'Connell et al

Table: MAYO (Ref. QUASAR protocol UKCCCR 1998)

Radical treatment only:

For combination of Haematological/non Haematological toxicity

- Wait until FULL recovery ie. neutrophils ≥1.5 x10^9/L and platelets ≥100 x10^9/L and/or any persistent mucositis and diarrhoea have resolved
- If within 2 weeks restart chemo using dose modifications below
- If FULL recovery takes more than 2 weeks discuss with consultant

Haematological Toxicity			**Non Haematological Toxicity On day of chemo or during previous cycle** (Diarrhoea or mucositis)			
Neutrophils x10^9/L		Platelets x10^9/L	**CTC Grade**			
			0-1	**2**	**3**	**4**
≥ 1.5	And	≥100	Full dose	Full dose	Delay until recovery to toxicity ≤grade 2 then give 50% dose reduction	Do not give
≥1.0-1.5*	And/or	50-99 Discuss with consultant as in some cases may go ahead with neutrophils 1.0 to 1.5 provided platelets ≥100	Delay until haematological recovery then give full dose	Delay until haematological recovery then give 20% dose reduction	Delay until full haematological and non-haematological recovery to toxicity grade ≤2 then give 50% dose reduction	Do not give
0.5-0.99	Or	25-49	Delay until full haematological recovery then give 20% dose reduction	Delay until haematological recovery then give 30% dose reduction	Delay until full haematological and non-haematological recovery to toxicity ≤ grade 2 then give 50% dose reduction	Do not give
<0.5	Or	<25	Delay until haematological recovery then give 50% dose reduction	Delay until haematological recovery then give 50% dose reduction	Delay until full haematological and non-haematological recovery to toxicity ≤ grade 2 then give 50% dose reduction	Do not give

Do not dose reduce Folinic Acid

Side-Effect: MAYO	**Dose Modification** (Source:Quasar/FOCUS trials)
Haematology	See table above
Renal function GFR below 30ml/min	Unclear guidance. Discuss with consultant
Hepatic function	Unclear guidance. Discuss with consultant
Stomatitis	Routine mouthcare with chlorhexidine. Ensure ice chips are being used. If still a problem reduce dose according to table page 8
Diarrhoea	Give loperamide 2-4mg oral QDS PRN (max 16mg/24hours) or codeine phosphate 30-60mg oral QDS PRN. If still a problem reduce dose according to table page 8
Hand and Foot Syndrome	Reduce dose according to table page 8 Phase III randomised controlled trials show no benefit from pyridoxine for prevention or treatment of 5FU induced hand/foot syndrome. Pyridoxine is not recommended
DPD Deficiency (Focus)	1-3% of patients have markedly exaggerated 5FU toxicity due to reduced 5FU catabolism. Discuss with consultant.
Cardiotoxicity (FOCUS)	Uncommon. 5FU may provoke angina or MI in patients with ischaemic heart disease. Seek specialist opinion on upgraded anti-anginal medication and consider dose reduction or alternative non 5FU treatment.
Neurotoxicity (Focus)	Uncommon – Cerebellar Consider alternative non 5FU treatment

5-Fluorouracil - Cisplatin Combination Chemotherapy

4. **ECF via CVAD** (CTIS: 270**)**

Epirubicin	50mg/m^2	IV bolus	Day 1
Prehydrations			Day 1
Cisplatin	60mg/m^2	IV over 2 hours	Day 1
Post hydrations			Day 1
5-Fluorouracil	200mg/m^2/ day	IV continuous infusion starting 4 hours before cisplatin on first cycle	Days 1 to 21

Interval between cycles: Repeat every 21 days
Number of cycles: HPB Metastatic/palliative: 4-8 cycles
Tests before starting course of chemo: FBC, U&Es, Mg, LFTs, Crcl (calculated). Do EDTA if <60mls/min, tumour markers in table on Page 3.
Cardiac assessment: patients with a history of ischaemic heart disease and abnormal ECG should have pre-treatment evaluation of cardiac function with MUGA scan or equivalent. If left ventricular ejection fraction is less than 50% prior to treatment then omit epirubicin (MAGIC).
Tests to OK/Confirm each cycle of chemo: FBC, U&Es, Mg, LFTs. Crcl (calculated). Do EDTA if rising serum creatinine,
Supportive drugs with each cycle: Very high risk antiemetics as per NWLCN guidelines or as per local policy
Chlorhexidine mouthwash 10mls QDS.
Loperamide 2-4mg QDS orally PRN (max 16mg/24hours)
Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information:

Administration notes:

Epirubicin: Vesicant, administer according to WLCN protocol

Cisplatin:

Weigh patient before and after cisplatin infusion or monitor urine output. If weight gain >1.5kg or symptomatic of fluid retention; inform doctor, patient may require diuretics. Inpatients should be on a fluid-balance chart and weighed daily. Average urine output of at least 100ml/hr is expected during and for 6 hours after cisplatin infusion. Outpatients should be encouraged to drink 3 litres of fluid within the following 24 hours.

5-Fluorouracil:

If 5FU administered using an ambulatory infusion pump via a central venous access device (CVAD), refer to relevant protocol for care of CVAD. Joint care with the community nursing services should be arranged in advance to support the patient and to assist with disconnecting the chemotherapy and flushing the CVAD. Written community nursing referrals should be completed and the patient should be discharged with a home spillage kit, sharps container and a small supply of equipment to flush the line and dress the entry site of the CVAD.

Dose modifications: Table: ECF below
Reference: Br J. Cancer 1999:80:269-72. Waters et al
EJC 2003:1(5) suppl; Cunningham et al

Table: ECF
NB. Palliative patients will require greater dose reductions than above based on individual patient parameters. Discuss with consultant.

Side-effect: ECF			**Dose Modification** (Source:REAL 2 Trial/)		
Haematology (REAL 2) Neutrophils x 10^9/L		Platelets x 10^9/L	**Cisplatin**	**5FU**	**Epirubicin**
≥1.0	and	≥75	Full dose	Full dose	Full dose
0.5-0.9	or	50-74	Delay until recovery then full dose	Stop 5FU until recovery then full dose	Delay until recovery then give epirubicin 25% dose reduction
< 0.5	or	25-49	Delay until recovery then full dose	Stop 5FU until recovery then full dose	Delay until recovery then give epirubicin 50% dose reduction
Any	or	<25	Delay until recovery then full dose	Stop 5FU until recovery then full dose	Omit on subsequent cycles
Neutropenic fever (REAL 2)					
Grade 3 infection/fever with neutropenia (ANC <1) at any time			Full dose on subsequent cycles	Full dose on subsequent cycles	Epirubicin 25% dose reduction on subsequent cycles
Grade 4 infection/fever with neutropenia (ANC <1) at any time			Full dose on subsequent cycles	Full dose on subsequent cycles	Epirubicin 50% dose reduction on subsequent cycles

Side-effect: ECF		**Dose Modification** (Source:REAL 2 Trial/)		
Renal Function (Cisplatin standardised Mar-09 based on ABC02)		**Cisplatin**	**5FU**	**Epirubicin**
Crcl (EDTA)	≥60mls/min	Full dose	Full dose	Full dose
	50-59mls/min	25% dose reduction	Full dose	Full dose
	40-49mls/min	50% dose reduction	Full dose	Full dose
	30-39mls/min	Do not give. Discuss carboplatin with consultant	Full dose	Full dose
	<30mls/min	Do not give	Discuss with consultant	Discuss with consultant
Hepatic Function (Real 2) Bilirubin Transaminases (ref. 1)	>1.5 x ULN 2xULN	Omit epirubicin until bilirubin returns to below this level. Consider epirubicin dose reduction. Discuss with consultant		
Stomatitis (Real 2)				
	Grade 1	Consider topical treatments eg. Difflam mouthwash or sucralfate 1g/5mls mouthwash QDS		
	Grade 2	As grade 1 plus stop 5FU until recovery. Restart at 150mg/m^2/ day (or 50mg/m^2/day reduction)		
	Grade 3	As grade 1 plus stop 5FU until recovery. Restart at 100mg/m^2/ day (or 100mg/m^2/day reduction)		
	Grade 4	As grade 1 plus stop 5FU until recovery. Restart at 50mg/m^2/ day		
Diarrhoea (Real 2)				
	Grade 1	Commence loperamide 2-4mg QDS prn oral (max 16mg/24hrs) or codeine phosphate 30-60mg oral QDS		
	Grade 2	As grade 1 plus stop 5FU until recovery. Restart at 150mg/m^2/ day (or 50mg/m^2/day reduction)		
	Grade 3	As grade 1 plus stop 5FU until recovery. Restart at 100mg/m^2/ day (or 100mg/m^2/day reduction)		
	Grade 4	As grade 1 plus stop 5FU until recovery. Restart at 50mg/m^2/ day		
Hand-Foot Syndrome				
	Grade 1	Full dose 5FU		
	Grade 2	Stop 5FU until recovery. Restart at 150mg/m^2/ day (or 50mg/m^2/day reduction)		
	Grade 3	Stop 5FU until recovery. Restart at 100mg/m^2/ day (or 100mg/m^2/day reduction)		
	Grade 4	Stop 5FU until recovery. Restart at 50mg/m^2/ day		
		Phase III randomised controlled trials show no benefit from pyridoxine for prevention or treatment of 5FU induced hand/foot syndrome. Pyridoxine is not recommended		

Side-effect: ECF	**Dose Modification** (Source:REAL 2 Trial/)
Neurotoxicity (Real 2) ≥Grade 2 CTC neurotoxicity or new functional deterioration in hearing, new tinnitus or significant high frequency hearing loss on audiogram	Stop cisplatin. Consider carboplatin AUC5 instead.
Cardiotoxicity (Real 2)	Any patient who develops unexplained cardiac failure while on treatment should undergo evaluation of cardiac function with MUGA or ECG. If left ventricular function is less than lower limit of normal range then: Do not give epirubicin. Uncommonly, 5FU may provoke angina or MI in patients with ischaemic heart disease. Seek specialist opinion on upgraded anti-anginal medication and consider dose reduction or alternative non 5FU treatment.
DPD Deficiency (Focus)	1-3% of patients have markedly exaggerated 5FU toxicity due to reduced 5FU catabolism. Discuss with consultant

5. **CF: CISP60-5FU Contin** (CTIS: 1221)

Prehydrations			Day 1
Cisplatin	60mg/m^2	IV over 2 hours	Day 1
Post hydrations			Day 1
5-Fluorouracil	200mg/m^2/ day	IV continuous infusion starting 4 hours before cisplatin on first cycle	Days 1 to 21

Interval between cycles: Repeat every 21 days
Number of cycles: Upper GI Palliative ECF alternative where epirubicin contraindicated: 2-6 cycles
Tests before starting course of chemo: FBC, U&Es, Mg, LFTs, Crcl (calculated). Do EDTA if <60mls/min, tumour markers indicated in table on page 3.
Tests to OK/Confirm each cycle of chemo: FBC, U&Es, Mg, LFTs. Crcl (calculated). Do EDTA if rising serum creatinine.
Supportive drugs with each cycle: Very high risk antiemetics as per NWLCN guidelines or as per local policy
Chlorhexidine mouthwash 10mls QDS.
Loperamide 2-4mg QDS orally PRN (max 16mg/day)
Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
Additional information:
Administration notes: See ECF page 10
Dose modifications: See table page 14
Reference:

Table: CISP60-5FU Contin

Side-Effect: CISP60-5FU Contin	**Dose Modification** (Real 2)
Haematology Neutrophils x10^9/L ≥1.0 and Platelets x10^9/L ≥75	Full dose Do not give below these levels. Delay until recovery and discuss with consultant
Renal Function (Cisplatin standardised Mar-09 based on ABC02) Crcl (EDTA) ≥60mls/min 50-59mls/min 40-59mls/min 30-39mls/min <30mls/min	Full dose all drugs Cisplatin: 25% dose reduction 5FU: Full dose Cisplatin: 50% dose reduction 5FU: Full dose Cisplatin: Do not give. Discuss carboplatin with consultant 5FU: Full dose Do not give. Discuss with consultant
Stomatitis (Real 2) Grade 1 Grade 2 Grade 3 Grade 4	Consider topical treatments eg. Difflam mouthwash or sucralfate 1g/5mls mouthwash QDS As grade 1 plus, stop 5FU until recovery. Restart at 150mg/m^2/ day (or 50mg/m^2/day reduction) As grade 1 plus, stop 5FU until recovery. Restart at 100mg/m^2/ day (or 100mg/m^2/day reduction) As grade 1 plus, stop 5FU until recovery. Restart at 50mg/m^2/ day
Diarrhoea (Real 2) Grade 1 Grade 2 Grade 3 Grade 4	Commence loperamide 2-4mg QDS prn oral (max 16mg/24hrs) or codeine phosphate 30-60mg oral QDS As grade 1 plus, stop 5FU until recovery. Restart at 150mg/m^2/ day (or 50mg/m^2/day reduction) As grade 1 plus, stop 5FU until recovery. Restart at 100mg/m^2/ day (or 100mg/m^2/day reduction) As grade 1 plus, stop 5FU until recovery. Restart at 50mg/m^2/ day
Hand-Foot Syndrome (Real 2) Grade 1 Grade 2 Grade 3 Grade 4	5FU full dose Stop 5FU until recovery. Restart at 150mg/m^2/ day (or 50mg/m^2/day reduction) Stop 5FU until recovery. Restart at 100mg/m^2/ day (or 100mg/m^2/day reduction) As grade 1 plus, stop 5FU until recovery. Restart at 50mg/m^2/ day Phase III randomised controlled trials show no benefit from pyridoxine for prevention or treatment of 5FU induced hand/foot syndrome. Pyridoxine is not recommended
DPD Deficiency	1-3% of patients have markedly exaggerated 5FU toxicity due to reduced 5FU catabolism. Discuss with consultant.
Cardiotoxicity	Uncommon. 5FU may provoke angina or MI in patients with ischaemic heart disease. Seek specialist opinion on

Side-Effect: CISP60-5FU Contin	Dose Modification (Real 2)
	upgraded anti-anginal medication and consider dose reduction or alternative non 5FU treatment.
Neurotoxicity ≥Grade 2 or new functional deterioration in hearing, new tinnitus or significant high frequency loss on audiogram	Stop cisplatin Consider alternative with consultant

6. **MdG-CISP60** (Modified DeGramont-Cisplatin-60) (CTIS:)

Prehydrations			Day 1
Cisplatin	60mg/m^2	IV over 1 hour	Day 1
Folinic acid	350mg	IV over 2 hours	Day 1
5 Fluorouracil	400mg/m^2	IV bolus	Day 1
5 Fluorouracil	2400mg/m^2	IV over 46 hours	Days 1-2

Interval between cycles: Repeat every 14 days
Number of cycles: HPB: 6-12 cycles/3-6 months
Tests before starting course of chemo: FBC, U&Es, Mg, LFTs, Crcl (calculated). Do EDTA if < 60mls/min. INR if hepatocellular cancer diagnosis. Tumour markers indicated in table on page 3.
Tests to OK/Confirm each cycle of chemo**:** FBC, U&Es, LFTs, Crcl (calculated). Do EDTA if rising serum creatinine. INR if hepatocellular cancer diagnosis
Supportive drugs with each cycle: Very high risk antiemetics as per NWLCN guidelines or as per local policy
Chlorhexidine mouthwash 10mls QDS.
Loperamide if required 2-4mg QDS prn. (Max 16mg/24hours).
Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
Additional information:
Administration notes: See ECF page 10
Dose modifications: See DeGramont-modified table page 16
References: DeGramont et al. J. Clin Oncol 1997 15:808-15
Annals Oncol 1998;9(4):47 Seymour MT et al

Table: DeGramont – Modified/Cisplatin

NB. Palliative patients will require greater dose reductions than stated below based on individual patient parameters. Discuss with consultant.

Side-Effect: MdG-Cisplatin	**Dose Modification** (Source: Focus (CR08) Trial/2000)
Haematology (CR08) Neutrophils $x10^9$/L and Platelets $x10^9$/L	
≥1.5 and ≥100	Full dose.
<1.5 or <100	Delay until recovery. Only treat when WBC/neutrophils and platelets are above these limits If more than 1 delay, or one delay of ∃2 weeks occurs then restart with: 5FU: 20% dose reduction (bolus and infusion). Continue with this reduced dose unless further toxicity occurs. If further delays for myelotoxicity occur despite the 20% dose reduction, discuss with consultant
Renal function Crcl (Cisplatin standardised Mar-09 based on ABC02)	
≥60mls	All drugs full dose
50-59mls/min	Cisplatin: 25% dose reduction 5FU: Full dose
40-49mls/min	Cisplatin: 50% dose reduction 5FU: Full dose
30-39mls/min	Cisplatin: Do not give. Discuss carboplatin with consultant 5FU: Full dose
<30mls/min	Discuss with consultant
Hepatic function	Unclear guidance. Discuss with consultant
Stomatitis (Focus)	If mouth ulcers occur despite routine chlorhexidine mouthwash: 5FU: 20% dose reduction (bolus and infusion). Continue with this reduced dose unless further toxicity occurs.
Diarrhoea (Focus)	Between cycles – treat symptomatically loperamide 2-4mg QDS PRN and/or codeine phosphate 30-60mg QDS PRN Not resolved by next cycle: Delay 1 week/until recovered If diarrhoea still a problem • Despite symptomatic treatment • Or more than one delay is required Then dose reduce 5FU: 20% dose reduction (bolus and infusion). Continue with this reduced dose unless further toxicity occurs.
Hand-Foot Syndrome ≥Grade 2	Stop 5FU until recovered then restart with 5FU dose reduced by 20% (bolus and infusion) for subsequent cycles Phase III randomised controlled trials show no benefit from pyridoxine for prevention or treatment of 5FU induced hand/foot syndrome. Pyridoxine is not recommended

Side-Effect: MdG-Cisplatin	Dose Modification (Source: Focus (CR08) Trial/2000)
DPD Deficiency (Focus)	1-3% of patients have markedly exaggerated 5FU toxicity due to reduced 5FU catabolism. Discuss with consultant.
Cardiotoxicity (Focus)	Uncommon. 5FU may provoke angina or MI in patients with ischaemic heart disease. Seek specialist opinion on upgraded anti-anginal medication and consider dose reduction or alternative non 5FU treatment.
Neurotoxicity (Focus)	Uncommon – Cerebellar Consider alternative non 5FU treatment

Capecitabine Combinations

Capecitabine is NOT licensed as single agent for any upper GI/HPB indications, but is used in combination in ECX regimen. NOTE that capecitabine has both liver toxicity and liver interactions as well as being renally cleared so should be used with care in the ECX combination. Capecitabine has local approval at some sites for single agent use as sensitising agent with concurrent radiotherapy. See page 59

7. **ECX** (CTIS: 1027)

Epirubicin	50mg/m^2	IV bolus	Day 1
Prehydrations			Day 1
Cisplatin	60mg/m^2	IV over 2 hours	Day 1
Post hydrations			Day 1
Capecitabine	625mg/m^2 ie. total 1250mg/m^2/day	Orally twice daily after meals with water	Days 1 to 21

Capecitabine 625mg/m^2 BD Dose Table (SPC)

Body Surface Area (m^2)	Dose 625mg/m^2 BD		
	Dose per administration (mg)	Number of 150mg and/or 500mg tablets per administration (each administration to be given morning and evening)	
		150mg	500mg
≤ 1.38	800	2	1
1.39 – 1.52	950	3	1
1.53 – 1.66	1000	-	2
1.67 – 1.78	1000	-	2
1.79 – 1.92	1150	1	2
1.93 – 2.06	1300	2	2
2.07 – 2.18	1300	2	2
≥ 2.19	1450	3	2

Interval between cycles: Repeat every 21 days
Number of cycles: HPB: 4-8 cycles
Tests before starting course of chemo: FBC, U&Es, Mg, LFTs, Crcl (calculated). Do EDTA if <60mls/min, tumour markers in table on page 3. Cardiac assessment: patients with a history of ischaemic heart disease and abnormal ECG should have pre-treatment evaluation of cardiac function with MUGA scan or equivalent. If left

ventricular ejection fraction is less than 50% prior to treatment then omit epirubicin.

Tests to OK/Confirm each cycle of chemo: FBC, U&Es, Mg, LFTs. Crcl (calculated). Do EDTA if rising serum creatinine

Supportive drugs with each cycle: Very high risk antiemetics as per NWLCN guidelines or as per local policy
Chlorhexidine mouthwash 10mls QDS.
Loperamide 2-4mg QDS orally PRN. (Max 16mg/day)

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
Patient must attend nurse capecitabine counselling clinic, for cycle 1 and 2 of ECX. Take capecitabine after meals and with water.

Additional information:

Administration notes:

Cisplatin:

Weigh patient before and after cisplatin infusion or monitor urine output. If weight gain >1.5kg or symptomatic of fluid retention; inform doctor, patient may require diuretics. Inpatients should be on a fluid-balance chart and weighed daily. Average urine output of at least 100ml/hr is expected during and for 6 hours after cisplatin infusion. Outpatients should be encouraged to drink 3 litres of fluid within the following 24 hours.

5 Fluorouracil:

If 5FU administered using an ambulatory infusion pump via a central venous access device (CVAD), refer to relevant protocol for care of CVAD. Joint care with the community nursing services should be arranged in advance to support the patient and to assist with disconnecting the chemotherapy and flushing the CVAD. Written community nursing referrals should be completed and the patient should be discharged with a home spillage kit, sharps container and a small supply of equipment to flush the line and dress the entry site of the CVAD.

Capecitabine

Patients must receive specific capecitabine counselling prior to treatment from a capecitabine trained nurse/pharmacist as per local policy. Patients must be given written and verbal information on capecitabine including how to take the tablets, when to stop (ie. In the event of toxicity and after 14 days), and whom to contact when side effects occur. Written information should be sent to the patient's GP. Capecitabine tablets should be taken with water 30 minutes after food and approximately 12 hours apart. Capecitabine interacts with warfarin and phenytoin and therefore patients on these drugs must have their blood levels monitored more regularly. Capecitabine is contraindicated with allopurinol.

Dose modifications: Table ECX page 19

Reference: ASCO Abstract REAL 2

Table: ECX

NB. Palliative patients will require greater dose reductions than above based on individual patient parameters. Discuss with consultant.

Side-effects: ECX			**Dose Modifications** (Source REAL 2)		
Haematology (REAL 2) Neutrophils x 10^9/L		Platelets x 10^9/L	**Cisplatin**	**Capecitabine**	**Epirubicin**
≥ 1.0	and	≥ 75	Full dose	Full dose	Full dose
0.5-0.9	or	50-74	Delay until recovered then full dose	Stop capecitabine until recovery then full dose	Delay until recovery then give epirubicin 25% dose reduction
< 0.5	or	25-49	Delay until recovery then full dose	Stop capecitabine until recovery then full dose	Delay until recovery then give epirubicin 50% dose reduction
Any	and	<25	Delay until recovery then full dose	Stop capecitabine until recovery then full dose	Do not give
Neutropenic fever OR Grade 3 infection/fever with neutropenia (ANC <1) at any time			Full dose on subsequent cycles	Full dose on subsequent cycles	Epirubicin: 25% dose reduction on subsequent cycles
Grade 4 infection/fever with neutropenia (ANC <1) at any time			Full dose on subsequent cycles	Full dose on subsequent cycles	Epirubicin: 50% dose reduction on subsequent cycles
Renal function GFR (REAL2/SPC) (Cisplatin standardised Mar-09 based on ABC02)					
≥ 60mls/min			Full dose	Full dose	Full dose
50-59 mls/min			Cisplatin 25% dose reduction	Full dose	Full dose
40-49mls/min			Cisplatin 50% dose reduction	Capecitabine SPC recommends no dose adjustment of starting dose for 1250mg/m^2/day, but recommends careful monitoring and prompt treatment interruption if patient develops a grade 2, 3 or 4 adverse event and dose adjustments as per SPC table on page 21	Full dose
30-39mls/min			Do not give	Discuss with consultant	Full dose
≤30mls/min			Do not give	Do not give	Do not give

Side-effects: ECX	**Dose Modifications** (Source REAL 2)		
Hepatic function (SPC/Real 2) Bilirubin Either AST or ALT ≤1.5 x ULN and ≤2.5 x ULN 1.5-3.0 x ULN and ≥2.5 x ULN >3.0 x ULN and >2.5 x ULN	 Full dose Full dose Discuss with consultant	 Full dose Full dose Stop capecitabine Discuss with consultant	 Full dose Do not give Do not give
Stomatitis (SPC) Grade 1 Grade ≥ 2	 Consider topical treatments eg. Difflam mouthwash or sucralfate, mouthwash 1g/5mls QDS As grade 1 plus, stop capecitabine until recovery, dose according to SPC table below.		
Diarrhoea (REAL 2/SPC) ≤Grade 1 ≥Grade 2	 Full dose all drugs Stop capecitabine, start loperamide 2-4mg QDS oral prn (max 16mg/24hrs) or codeine phosphate 30-60mg QDS. If diarrhoea resolves within 2 days restart all drugs full dose. If diarrhoea persists, wait until recovery then Capecitabine: dose reduction as per SPC table below		
Hand-Foot Syndrome (SPC) Grade 1 ≥Grade 2	 Stop capecitabine until recovery. Once recovered – restart full dose all drugs Stop capecitabine until recovery. Once recovered, dose according to SPC table below Phase III randomised controlled trials show no benefit from pyridoxine for prevention or treatment of 5FU induced hand/foot syndrome. Pyridoxine is not recommended		
DPD Deficiency (Focus)	1-3% of patients have markedly exaggerated capecitabine toxicity due to reduced capecitabine catabolism. Discuss with consultant		
Cardiotoxicity (Focus)	Uncommon. Capecitabine may provoke angina or MI in patients with ischaemic heart disease. Seek specialist opinion on upgraded anti-anginal medication and consider dose reduction or alternative non capecitabine treatment.		
Neurotoxicity (Focus)	Uncommon – Cerebellar Consider alternative non capecitabine treatment		

Capecitabine Non haematological toxicity (SPC)

NCIC Grade	During course of treatment	Dose adjustment for next cycle
Grade 1	Continue treatment	Capecitabine full dose
Grade 2 1st appearance 2nd appearance 3rd appearance 4th appearance	 Interrupt capecitabine until resolved to grade 0-1 Interrupt capecitabine until resolved to grade 0-1 Interrupt capecitabine until resolved to grade 0-1 Discontinue capecitabine permanently	 Capecitabine full dose Capecitabine 25% dose reduction. Capecitabine 50% dose reduction. Stop treatment
Grade 3 1st appearance 2nd appearance 3rd appearance	 Interrupt capecitabine until resolved to grade 0 to 1 Interrupt capecitabine until resolved to grade 0 to 1 Discontinue capecitabine treatment permanently	 Capecitabine 25% dose reduction Capecitabine 50% dose reduction Do not give
Grade 4 1st appearance	 Discontinue permanently. If consultant considers it is in best interest of patient to continue: interrupt capecitabine until resolved to grade 0 to 1	 Capecitabine 50% dose reduction

8. **CX: Cisplat-60/Cape1250** (CTIS: 1707)

Prehydrations			Day 1
Cisplatin	60mg/m^2	IV over 2hrs	Day 1
Post-hydrations			Day 1
Capecitabine	625mg/m^2 ie. total 1250mg/m^2/day	Oral twice a day after meals with food	Days 1 to 21

Interval between cycles: Repeat every 21 days

Number of cycles: HPB: 4-8 cycles

Tests before starting course of chemo: FBC, U&Es, Mg, LFTs, Crcl (calculated). Do EDTA if <60mls/min, tumour markers in table on page 3. Baseline ECG if history of ischaemic heart disease or cardiac risk factors.

Tests to OK/Confirm each cycle of chemo: FBC, U&Es, Mg. LFTs, Crcl (calculated). Do EDTA if rising serum creatinine

Supportive drugs with each cycle: Very high risk antiemetics as per NWLCN guidelines or as per local policy

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information:

Administration notes: See ECX page 19

Dose modifications:

Reference:

Gemcitabine Regimens

9. **Cisp60-Gem-1g** (CTIS: 563)

Pre-hydrations			Day 1
Cisplatin	60mg/m^2	IV over 2hrs	Day 1
Gemcitabine	1000mg/m^2	IV over 30mins	Days 1 and 8
Post-hydrations			Day 1

Interval between cycles: Repeat every 21 days

Number of cycles: Cholangiocarcinoma or Pancreas 1st line: 4-8 cycles

Tests before starting course of chemo: FBC, U&Es, LFTs, Crcl (calculated). Do EDTA if <60mls/min, tumour markers indicated in table on page 3,

Tests to OK/Confirm each cycle of chemo: FBC, U&Es, LFTs, Crcl (calculated). Do EDTA if rising serum creatinine

Supportive drugs with each cycle: Very high risk antiemetics as per NWLCN guidelines or as per local policy

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information:

Administration notes:

Gemcitabine can cause pain on administration. To avoid increasing haematological toxicity gemcitabine infusion time must not exceed 1 hour. If pain develops:

1. Keep gemcitabine infusion over 30 minutes and infuse 250mls sodium chloride simultaneously down the same line via a Y connector.
2. If above does not resolve pain, infusion time may be increased to 45 minutes after discussion with the consultant in charge.
3. If above does not resolve the pain, infusion time may be increased to 60minutes after discussion with consultant in charge.
   DO NOT INCREASE INFUSION BEYOND 60 MINUTES.

Dose modifications: Table Gem 1g-Cisp 60 below

Reference:

10. **Cisp25/Gem-1g Day 1 + 8** (CTIS: 1734) (Split dose – ABCO2)

Prehydration			Days 1 and 8
Cisplatin	25mg/m^2	IV over 1 hour	Days 1 and 8
Gemcitabine	1000mg/m^2	IV over 30 mins	Days 1 and 8
Post-hydrations			Days 1 and 8

Interval between cycles: Repeat every 21 days

Number of cycles: Cholangiocarcinoma or Pancreas 1st line: 4-8 cycles

Tests before starting course of chemo: FBC, U&Es, LFTs, Crcl (calculated). Do EDTA if <60mls/min. Tumour markers indicated in table on page 3,

Tests to OK/Confirm each cycle of chemo:	FBC, U&Es, LFTs, Crcl (calculated). Do EDTA if rising serum creatinine
Supportive drugs with each cycle:	High risk antiemetics as per NWLCN guidelines or as per local policy
Patient information:	Chemotherapy treatment booklet (local information/Macmillan) Your chemotherapy record (NWLCN red book) Chemotherapy alert card (NWLCN) Macmillan drug specific information sheets and information prescriptions as appropriate Neutropenia DVD (NWLCN)
Additional information:	See Gem-1g/Cisp60 page 22
Dose modifications:	Table Gem 1g-Cisp 60 below
Reference:	Table: Gem 1g-Cisp 60

Table: Gem 1g-Cisp60

Side-effect: Gem1g-Cisp60	**Dose Modification** (ABC02 trial)
Haematology Neutrophils x10^9/L and Platelets x10^9/L	
≥1.0 and ≥100	Full dose all drugs
0.5-0.9 or 50-99	Delay until recovery. (Discuss with consultant if >3 weeks) Then: Cisplatin: Full dose Gemcitabine: 25% dose reduction Day 1 + 8
<0.5 or <50	Delay until recovery. (Discuss with consultant if >3 weeks) Then: Cisplatin: 25% dose reduction Gemcitabine: 25% dose reduction
Renal function (NLCN) Cisplatin Standardised Mar09 based on ABC02 CrCl	If sudden increase in creatinine – investigate to rule out haemolytic uraemic syndrome NB. Under 60mls/min do EDTA or omit cisplatin.
≥60mls/min	Full dose all drugs
50-59mls/min	Cisplatin 25% dose reduction. Gemcitabine full dose
40-49mls/min	Cisplatin 50% dose reduction. Gemcitabine full dose
< 40mls/min	Do not give regimen
<u>Biliary tract obstruction</u> <u>No liver metastases</u> Bilirubin >1.5 x ULN ALT/AST/ALP >3.0 x ULN With liver metastases Bilirubin >1.5 x ULN ALT/AST/ALP >5.0 x ULN	Stop chemo until resolved (below these levels) Stop chemo until resolved (below these levels)
Lethargy Grade 3-4	Consider gemcitabine: 25% dose reduction If does not respond to dose reduction: stop treatment

Side-effect: Gem1g-Cisp60	**Dose Modification** (ABC02 trial)
Peripheral neuropathy Grade 1-2	Cisplatin: delay until recovery to baseline then continue at full dose. If no recovery do not give cisplatin Gemcitabine: full dose
Grade 3-4	Cisplatin: Do not give further cisplatin Gemcitabine: Continue with full dose
Oedema Grade 3-4	Dipstick urine test for protein. If positive do 24 hour urinary protein estimation. Delay until recovery to baseline (with appropriate diuretics) Then Gemcitabine: 25% dose reduction If does not respond to above measures – stop treatment.
Tinnitus If full recovery between cycles **If no recovery between cycles**	Full dose all drugs Cisplatin: Do not give Gemcitabine: Full dose

11. **Gemcitabine 1+8+15** (CTIS: 561)

Gemcitabine 1000mg/m^2 IVI over 30mins Days 1,8,15
Repeat every 28 days
N.B. Treatment may start with weekly chemotherapy for 7 weeks i.e. days 1,8,15,22,29,36 43, then one week off, then treatment follows day 1,8,15 repeat day 28.

Interval between cycles: 28 days
Number of cycles: Adjuvant or palliative
Pancreatic cancer: 6 cycles
Tests before starting course of chemo: FBC, U&Es, LFTs, Crcl (calculated), tumour markers indicated in table on HPB page 3
Tests to OK/Confirm each cycle of chemo: FBC, U&Es, LFTs, Crcl (calculated)
Supportive drugs with each cycle: Low risk antiemetics as per NWLCN guidelines or as per local policy
Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
Additional information: See Gem 1g/Cisp60 HPB page 22
Dose modifications: See Gemcitabine D1+8+15 table page 23
Reference: J. Clin Oncol 1997;6:2403-13. Burris et al

Table Gemcitabine D1+8+15

Side-effect: Gem D1+8+15			**Dose Modification** (ABC-02)
Haematology Neutrophils x 10^9/L		Platelets x 10^9/L	
≥1.0	and	≥100	Full dose all drugs
0.5-0.9	or	50-99	Delay until recovery. (Discuss with consultant if >3 weeks) Otherwise: Gemcitabine 25% dose reduction Days 1, 8 and15
<0.5	or	< 50	Delay until recovery. (Discuss with consultant if >3 weeks) Otherwise: Gemcitabine 25% dose reduction Days 1, 8 and 15
Renal function (NLCN 2009)			If sudden increase in creatinine – investigate to rule out haemolytic uraemic syndrome
		≥30mls/min	Gemcitabine full dose
		< 30mls/min	Do not give regimen
Biliary tract obstruction No liver metastases			
Bilirubin		>1.5 x ULN	Stop chemo until resolved (below these levels)
ALT/AST/ALP		>3.0 x ULN	Stop chemo until resolved (below these levels)
With liver metastases			
Bilirubin		>1.5 x ULN	Stop chemo until resolved (below these levels)
ALT/AST/ALP		>5.0 x ULN	Stop chemo until resolved (below these levels)
Side-effect: Gem D1+8+15			**Dose Modification** (ABC-02)
Lethargy			
		Grade 3-4	Consider gemcitabine: 25% dose reduction If does not respond to dose reduction: stop treatment
Oedema			
		Grade 3-4	Dipstick urine test for protein. If positive do 24 hour urinary protein estimation. Delay until recovery to baseline (with appropriate diuretics) Then Gemcitabine: 25% dose reduction If does not respond to above measures – stop treatment.

Targeted Therapies

12. **Imatinib** (CTIS: 1035)

Imatinib must be discussed and approved by the MDT

Imatinib 400mg Oral Once a day

NICE guidance does NOT permit dose escalation

Interval between cycles: Continuous treatment. Review every 28 days

Number of cycles: Kit (CD117) positive, metastatic inoperable GIST without evidence of progression. Continue until resistance develops

Tests before starting course of chemo: FBC, U&Es, LFTs, thyroid function, PET scan. Requires PCT approval for each patient

Tests to OK/Confirm each cycle of chemo: FBC, U&Es, LFTs, weight (check for fluid retention), thyroid function every 6 months.

Supportive drugs with each cycle: None

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information: Performing CT scans before 4-6 months of treatment is usually non-informative

Dose modifications:

Reference:

Table: Imatinib

Side effect: Imatinib	**Dose Modification** (SPC)
Hepatic function (SPC) Mainly hepatic excretion Only 13% excretion through kidney (SPC) Bilirubin >3xULN Or Transaminases >5xULN	Stop treatment until bilirubin <1.5xULN and transaminases <2.5xULN Treatment may be resumed at reduced dose If previous dose 400mg reduce to 300mg
Haematology (SPC) Neutrophils x10^9/L <1.0 and/or Platelets x10^9/L <50 1st occurrence 2nd occurrence	Stop treatment until neutrophils ≥1.5 and platelets ≥75 Resume treatment at original 400mg (adult) dose . In event of recurrence of neutrophils <1.0 x 10^9/L and/or platelets <50x10^9/L stop treatment until neutrophils ≥1.5 and platelets ≥75, then resume with reduced dose Eg. if previous dose 400mg – reduce to 300mg
Imatinib is a cytochrome P450 substrate – dose increases should be made (eg. 50% increase) when used concurrently with potent enzyme inducers (eg. rifampicin, phenytoin)	

13. **Sorafenib** (CTIS: 1735)

Apply to London Cancer Drugs Fund for funding

Sorafenib 400mg* Oral twice a day Continuous treatment
*Consider starting at 200mg BD and escalating dose if no grade 2 or 3 toxicity

Interval between cycles: Review/repeat tests every 28 days.

Number of cycles: **Apply to London Cancer Drugs fund for funding**
1st line advanced stage Hepatocellular carcinoma or Advanced hepatocellular carcinoma with underlying cirrhosis due to hepatitis C
Continue as long as clinical benefit or until unacceptable toxicity

Tests before starting course of chemo: FBC, U&Es, LFTs, BP, dipstick protein, 24 hour urine protein quantitative analysis, tumour markers in table on HPB page 3
Caution in patients with prior cardiac events, surgery, hypertension, intra abdominal tumours (risk of GI perforation) – see SPC

Tests to OK/confirm each cycle of chemo: FBC, U&Es, LFTs, BP, dipstick urine, 24 hour protein quantitative analysis every 4-5 weeks, thyroid function tests every 8 weeks.

Supportive drugs with each cycle: Chlorhexidine mouthwash 10mls QDS
Loperamide 2mg QDS PRN

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information:

Administration notes (SPC)

Sorafenib should be administered without food or with a low or moderate fat meal. If the patient intends to have a high fat meal, Sorafenib should be taken at least 1 hour before or 2 hours after the meal. Tablets should be swallowed with a glass of water.

Dose modifications:

Reference:

Table: Sorafenib Dose levels: Level 1: Sorafenib 400mg twice a day
Level 2: Sorafenib 400mg Once a day
Level 3: Sorafenib 400mg every two days

Side effect: Sorafenib			**Dose Modification** (Nexavar SPC/A6181170 trial)
Haematology Neutrophils $x10^9/L$		Platelets $x10^9/L$	
≥1.0	and	≥50	Treat on time with no change in dose.
0.5-0.9	or	25-49	Treat on time but reduce dose by one dose level.
<0.5	or	<25	Delay until neutrophils ≥1.0 and platelets ≥50 then restart but reduce dose by one level
Non Haematological Toxicity (except skin)			
		Grade 0-2	Treat on time with no change in dose
		Grade 3	Delay until toxicity ≤ grade 2 then restart but reduce one dose level
		Grade 4	Discontinue treatment
Renal function (SPC)			No dose adjustment is required in patients with mild, moderate or severe renal impairment. No data available in patients requiring dialysis. Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised.
Hepatic impairment (SPC)			No dose adjustment is required in patients with Child Pugh A and B (mild to moderate) hepatic impairment. No data available on patients with Child Pugh C (severe) hepatic impairment. Sorafenib is mainly eliminated via the hepatic route so exposure might be increased in patients with severe hepatic impairment. Discuss with consultant.

Side effect: Sorafenib	Dose Modification (Nexavar SPC/A6181170 trial)
Dermatological toxicities (SPC)	Hand foot skin reactions (Palmar-Plantar erythrodysaesthesia) and rash represent most common adverse drug reactions to Sorafenib. Rash and hand-foot skin reactions are usually CTC Grade 1 and 2 and generally appear during the first 6 weeks of treatment. Discuss with consultant Management may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification, and in severe or persistent cases permanent discontinuation of Sorafenib.
Arterial Hypertension (SPC)	Monitor BP and dipstick urine for protein before each cycle. Can be treated with standard antihypertensives and discuss with consultant. SPC: Hypertension is usually mild to moderate, occurs early in the course of treatment and is amenable to management with standard antihypertensive therapy. In cases of severe or persistent hypertension or hypertensive crisis despite institution of antihypertensive therapy, permanent discontinuation of sorafenib should be considered.
Haemorrhage (SPC)	An increased incidence of bleeding may occur following sorafenib administration. If any bleeding necessitates medical intervention it is recommended that permanent discontinuation of sorafenib should be considered. Do not administer sorafenib within 28 days before or after surgery.
Cardiac events (SPC)	Increased incidence of treatment-emergent cardiac ischaemic/infarction events with sorafenib compared to placebo. Temporary or permanent discontinuation of sorafenib should be considered in patients who develop cardiac ischaemia and/or infarction. NB. Patients with unstable coronary artery disease or recent MI were excluded from sorafenib studies.
GI Perforation (SPC)	GI perforation is an uncommon event, reported in less than 1% of patients taking sorafenib. In some cases this was not associated with apparent intra-abdominal tumour. If GI perforation, discontinue sorafenib
Drug Interactions (SPC)	Sorafenib is metabolised primarily in the liver – see SPC for detailed section on drug interactions.

14. **Sunitinib-50 (with break)** (CTIS: 1737)

Apply to London Cancer Drugs Fund for funding

Sunitinib	50mg*	Oral	Once a day	Days 1 to 28

Interval between cycles: Repeat every 42 days ie. 4 weeks treatment, followed by 2 week rest period.

Number of cycles: In line with NICE TA179 for
Unresectable and/or metastatic malignant GIST if:

- Imatininb treatment has failed because of resistance or intolerance and
- The drug cost of sunitinib (excluding any related costs) for the 1st cycle is met by the manufacturers.

Continue until disease progression.

Tests before starting course of chemo: FBC, U&Es, LFTs, BP, dipstick protein, 24 hour urine protein quantitative analysis, tumour markers in table on page 3

Tests to OK/confirm each cycle of chemo: FBC, U&Es, LFTs, BP, dipstick urine, 24 hour urine protein quantitative analysis every 4-5 weeks, thyroid function tests every 8 weeks.

Supportive drugs with each cycle: Chlorhexidine mouthwash 10mls QDS
Loperamide 2mg QDS PRN

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information:

Administration notes (SPC)

Sunitinib may be taken with our without food.

If a dose is missed the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

Dose modifications: Sunitinib dose reductions may be made in 12.5mg decrements depending on the type and severity of toxicity as outlined below.

Table: Sunitinib

Side effect: Sunitinib	**Dose Modification** (Sunitinib vs Sorafenib trial in advanced HCC)
Non Haematological Toxicities eg. diarrhoea, hand/foot, fatigue, mucositis	
Grade 1	Continue at the same dose level
Grade 2	Continue at the same dose level
Grade 3 1st appearance	Withhold dose until toxicity is ≤ grade 1 or has returned to baseline. Then resume treatment at the same dose level Grade 3 hypophosphatemia without clinical symptoms – Discuss with consultant.
Recurrent	If toxicity recurs with grade 3 severity, withhold dose until toxicity is ≤ grade 1 or returned to baseline. Discuss with consultant and reduce the dose by 1 dose level ie. reduce dose by 12.5mg and resume treatment
Grade 4	Withhold dose until toxicity is ≤ grade 1 or has returned to baseline. Discuss with consultant and either reduce the dose by 1 dose level ie. reduce dose by 12.5mg or discontinue. Grade 4 hyperuricaemia without clinical symptoms – discuss with consultant
Haematological side effects other than lymphopenia	
Grade 1	Continue at same dose level
Grade 2	Continue at same dose level
Grade 3 1st appearance	Withhold dose until toxicity is ≤ grade 2 or has returned to

Side effect: Sunitinib	**Dose Modification** (Sunitinib vs Sorafenib trial in advanced HCC)
	baseline, then resume treatment at the same dose level.
Recurrence	If the toxicity recurs with grade 3 severity withhold dose until toxicity is ≤ grade 2 or baseline. Discuss with consultant and reduce the dose by 1 dose level ie. reduce dose by 12.5mg and resume treatment.
Grade 4	Withhold dose until toxicity is ≤ grade 2 or has returned to baseline, then reduce the dose by 1 dose level ie. reduce dose by 12.5mg and resume treatment
Lymphopenia Grade 3 or Grade 4	Patients who develop grade 3 or 4 lymphopenia may continue treatment without interruption.
Drug Interactions (SPC)	<u>CYP3A4 Inducers eg. rifampicin</u> Co-administration of potent CYP3A4 inducers may DECREASE sunitinib plasma concentrations. Combination with inducers should therefore be avoided. If this is not possible the dose of sunitinib may need to be increased. See SPC <u>CYP3A4 Inhibitors eg. ketoconazole</u> Co-administration of potent CYP3A4 inhibitors may INCREASE sunitinib plasma concentrations. Selection of an alternative concomitant medication with no minimal or minimal enzyme inhibition potential is recommended. If this is not possible, the dosage of sunitinib may been to be reduced. See SPC
Skin discolouration (SPC)	Yellow skin discolouration occurs in approximately 30% of patients. Depigmentation of hair or skin may also occur. Also dryness, thickness or cracking of skin, blister or rash on palms/soles. These events not cumulative, were typically reversible and generally did not result in treatment discontinuation.
Haemorrhage (SPC)	An increased incidence of bleeding may occur following sunitinib administration. These events may occur suddenly. If any bleeding necessitated medical intervention, then permanent discontinuation of sunitinib should be considered.
Hypertension (SPC)	Monitor BP and dipstick urine for protein before each cycle. Can be treated with standard antihypertensives <u>and</u> discuss with consultant. Temporary suspension is recommended in patients with severe hypertension not controlled with medical management. Sunitinib treatment may be resumed once hypertension is appropriately controlled.
Renal function (SPC)	No clinical studies have been performed in patients with impaired renal function
Hepatic function (SPC)	No dose adjustment is recommended when administering sunitinib to patients with mild/moderate (Child Pugh Class A or B) hepatic impairment. Sunitinib has not been studied in patients with Child Pugh Class C hepatic impairment.

15. **Sunitinib-37.5 Continuous** (CTIS: 1736)
Apply to London Cancer Drugs Fund for funding

Sunitinib	37.5mg	Oral	Once a day	Days 1 to 28

Interval between cycles: Repeat every 28 days ie. no rest period.

Number of cycles: **Apply to London Cancer Drugs fund** for unresectable or metastatic pancreatic neuroendocrine tumours (excluding poorly differentiated tumours) with disease progression.

Continue until progressive disease

In line with NICE TA179 for
Unresectable and/or metastatic malignant GIST if:

- Imatininb treatment has failed because of resistance or intolerance and
- The drug cost of sunitinib (excluding any related costs) for the 1st cycle is met by the manufacturers.

Continue until disease progression.

Tests before starting course of chemo: FBC, U&Es, LFTs, BP, dipstick protein, 24 hour urine protein quantitative analysis, tumour markers in table on page 3

Tests to OK/confirm each cycle of chemo: FBC, U&Es, LFTs, BP, dipstick urine, 24 hour urine protein quantitative analysis every 4-5 weeks, thyroid function tests every 8 weeks.

Supportive drugs with each cycle: Chlorhexidine mouthwash 10mls QDS
Loperamide 2mg QDS PRN

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information:

Administration notes (SPC)
Sunitinib may be taken with our without food. Avoid grapefruit juice (CYP3AL inhibitor).

Nursing notes:
If a dose is missed the patient should not take an additional dose. The patient should take the usual prescribed dose the next day.

Interactions: See page 30 and SPC

Dose modifications: See page 30

16. **Everolimus-10** (CTIS: 1738)
Apply to London Cancer Drugs Fund

Everolimus	10mg	Oral once a day Swallow whole with glass of water	Days 1 to 28

Interval between cycles: Continuous treatment until progression
Repeat tests every 28 days

Number of cycles: **Apply to Cancer Drugs Fund for**
Unresectable or metastatic well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Tests before starting course of chemo: FBC, U&Es, LFTs, fasting blood glucose, chest X-Ray, serum cholesterol and triglycerides. Tumour markers page 3. Treat existing infections before commencing treatment.

Tests to OK/confirm each cycle of chemo: FBC, U&Es, LFTs
Fasting blood glucose every 4 weeks
Serum cholesterol and triglycerides every 4 weeks
Chest X-Ray 4 weeks

Supportive drugs with each cycle: No routine supportive drugs

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
NWLCN Chemotherapy alert card
Macmillan drug specific information sheets,
NWLCN Neutropenia DVD

Additional information:

Swallow whole with a glass of water, with our without food, at the same time each day. Do not crush or chew. If a dose is missed, do not take and additional dose but take the usual prescribed next dose.

Patient should be advised to report promptly any new/worsening respiratory symptoms.

Avoid live vaccines during treatment.

Dose modifications:

Table: Everolimus

Side Effect (Everolimus)	**Dose Modification**
<u>Haematology</u> Neutrophils $x10^9$/L / Platelets $x10^9$/L / Hb g/dL	
≥1.0 and ≥50 and ≥9	Full dose.
<1.0 and/or <50 and/or <9	Do not give until recovered to above levels.
<u>Renal Function</u> CrCl ≥25mls/min	SPC states no dose adjustment required
<u>Hepatic Function</u> Child-Pugh Class B (Moderate hepatic impairment)	Reduce dose to Everolimus 5mg once a day
Child-Pugh Class C (Severe hepatic impairment)	Not recommended
<u>Non Infectious Pneumonitis</u> See SPC for diagnosis	
Radiological changes suggestive of non-infection pneumonitis with few or no symptoms	Continue without dose adjustment
Radiological changes suggestive of non-infectious pneumonitis with moderate symptoms	Discuss with consultant. Consider interrupting treatment until symptoms improve. Corticosteroids may be indicated. If restarted give everolimus 5mg once a day.
Severe symptoms of non-infections pneumonitis	Stop everolimus. Corticosteroids may be indicated until clinical symptoms resolve.

Side Effect (Everolimus)	Dose Modification
	Discuss with consultant and if therapy to restart give everolimus 5mg once a day
Opportunistic Infections Localised and/or systemic infections Pre-existing infections Invasive systemic fungal infection	 Treat promptly Treat appropriately BEFORE starting treatment. Stop everolimus promptly and discontinue permanently. Treat infection appropriately
Oral Ulceration; Mouth ulcers, stomatitis and oral mucositis	Treat topically. Avoid alcohol and peroxide containing mouthwashes Only use antifungal agents if fungal infection diagnosed.
Blood Glucose and Lipids Hyperglycaemia Hyperlipidaemia Hypertriglyceridaemia	Monitor and institute therapy to correct abnormalities. Hyperglycaemia prior to treatment commencing should be corrected if possible before starting everolimus.
Interactions Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided	 See SPC for guidance
Wound Healing	Everolimus is associated with impaired wound healing. Care should be exercised in pre surgical patients or patients with other wounds

Streptozocin Regimens

There is a world wide shortage of streptozocin (2009). Contact pharmacy to secure supplies. DO NOT consent new patients until pharmacy has confirmed supplies have been secured for the whole course for the new patient. Decision to prescribe streptozocin must be discussed at MDT

17. **STZ / 5FU** (Cycle 1, Day1+2 loading CTIS: 1228, maintenance CTIS: 1225)

Cycle 1:

Streptozocin	1000mg/m^2	IV over 4 hours	Day 1,2,8,15,22,29
5Fluorouracil	1000mg/m^2	IV over 1 hour	Day 1,2,8,15,22,29

Subsequent cycles (3-4 week interval):

Streptozocin	1000mg/m^2	IV over 4 hours	Day 1,8,15,22,29
5Fluorouracil	1000mg/m^2	IV over 1 hour	Day 1,8,15,22,29

Interval between cycles: Cycle 1: Loading dose days 1 and 2 then repeat weekly for 4 further weeks
Then 3-4 weeks no treatment, restart week 9/10). Do not reload after cycle 1. Subsequent cycles (no loading) weekly chemo for 5 weeks, 3-4 weeks no treatment, restart week 9/10

Number of cycles: Neuroendocrine tumours:
1st line/relapse 4 cycles then reassess. Can be repeated.

Tests before starting course of chemo: FBC, U&Es, LFTs, Crcl with 24 hour urine protein quantitative analysis, tumour markers as indicated in table on page 3

Test to OK/Confirm each cycle of chemo: FBC, U&Es, LFTs, Crcl with 24 hour urine protein quantitative analysis with every 5

week cycle, Dipstick for proteinuria with every weekly cycle. Review treatment if proteinuria

Supportive drugs with each cycle: High risk antiemetics as per NWLCN guidelines or as per local policy

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
If borderline proteinuria, patient may need to do dipstick for urine analysis at home.

Additional information: Streptozocin painful if given too quickly.

Dose modifications: See table Strep/5FU below

Reference:

Table Strep/5FU

Side-effect: Strep/5FU			**Dose Modification** (Dr Wasan)
Haematology Neutrophils $X10^9/L$		Platelets $x10^9/L$	
≥1.5	and	≥100	Full dose
<1.5	or	<100	Do not give. Discuss with consultant
Diarrhoea		≥Grade 2	5FU : 25% dose reduction
Proteinuria			Streptozocin : Consider dose reduction or stopping streptozocin
Renal impairment (DI Oncol Handbook 2004)			
		≥50ml/min	Full dose
		10-49mls/min	Streptozocin: 25% dose reduction
		< 10ml/min	Discuss with consultant. Streptozocin: 50% dose reduction

18. **Strep 5FU 5 day** (CTIS: 1222)

Strepozocin	500mg/m^2	IV over 4 hours	Days 1 to 5
5-Fluorouracil	400mg/m^2	IV over 1hour	Days 1 to 5

Interval between cycles: Repeat every 4-5 weeks

Number of cycles: Neuroendocrine tumours: 4 cycles and reassess

Tests before starting course of chemo: FBC, U&Es, LFTs, Crcl with 24 hour urine protein quantitative analysis, tumour markers as indicated in table on page 3

Test to OK/Confirm each cycle of chemo: FBC, U&Es, LFTs, Crcl with 24 hour urine protein quantitative analysis with every 5 week cycle, Dipstick for proteinuria with every cycle.

Supportive drugs with each cycle: High risk antiemetics as per NWLCN guidelines or as per local policy

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)

	Macmillan drug specific information sheets and information prescriptions as appropriate Neutropenia DVD (NWLCN) If borderline proteinuria, patient may need to do dipstick urine analysis at home
Additional information:	Streptozocin painful if given too quickly.
Dose modifications:	See table Strep/5FU on page 34
Reference:	

19. **Strep 5FU 3 day** (CTIS: 1741)

Streptozocin	500mg/m^2	IV over 4 hours	Days 1 to 3
5-Fluorouracil	400mg/m^2	IV over 1hour	Days 1 to 3

Interval between cycles:	Repeat every 3-4 weeks
Number of cycles:	Neuroendocrine tumours: 4 cycles and reassess
Tests before starting course of chemo:	FBC, U&Es, LFTs, Crcl with 24 hour urine protein quantitative analysis, tumour markers as indicated in table on page 3
Test to OK/Confirm each cycle of chemo:	FBC, U&Es, LFTs, Crcl with 24 hour urine protein quantitative analysis with every 5 week cycle, Dipstick for proteinuria with every cycle.
Supportive drugs with each cycle:	High risk antiemetics as per NWLCN guidelines or as per local policy
Patient information:	Chemotherapy treatment booklet (local information/Macmillan) Your chemotherapy record (NWLCN red book) Chemotherapy alert card (NWLCN) Macmillan drug specific information sheets and information prescriptions as appropriate Neutropenia DVD (NWLCN) If borderline proteinuria, patient may need to do dipstick urine analysis at home
Additional information:	Streptozocin painful if given too quickly.
Dose modifications:	See table Strep/5FU on page 34
Reference:	

20. **Streptozocin/Modified DeGramont** (Strep/MdG CTIS: 1739)

Streptozocin	1000mg/m^2	IV over 4 hours	Day 1 and 2
Folinic acid	350mg	IV over 2 hours	Day 1
5Fluorouracil	400mg/m^2	IV bolus	Day 1
5Fluorouracil	2400mg/m^2	IV over 46 hours	Day 1

Interval between cycles:	Repeat every 14-21 days
Number of cycles:	Neuroendocrine tumours where intolerant of 5FU bolus or frequent attendance problematic 6 cycles
Tests before starting course of chemo:	FBC, U&Es, LFTs, Crcl with 24 hour urine protein quantitative analysis, tumour markers as indicated in table on page 3
Test to OK/Confirm each cycle of chemo:	FBC, U&Es, LFTs, Crcl with 24 hour urine protein quantitative analysis with every other cycle, Dipstick for proteinuria with every cycle. Review treatment if proteinuria
Supportive drugs with each cycle:	High risk antiemetics as per NWLCN guidelines or as per local policy

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
If borderline proteinuria, patient may need to do dipstick urine analysis at home

Additional information: Streptozocin painful if given too quickly.

Dose modifications: See table Strep/MdG on below

Reference:

Table: Streptozocin/MdG

Side-effect: Strep/MdG	**Dose Modification** (Source: Focus (CR08) Trial/2000)
Haematology (CR08) Neutrophils x10^9/L and Platelets x10^9/L	
≥1.5 and ≥100	Full dose
<1.5 or <100	Do not give. Discuss with consultant
Renal function (DI Oncol Handbook 2004)	
≥50mls/min	Full dose
10-49mls/min	Streptozocin 25% dose reduction
<10mls/min	Discuss with consultant. Consider streptozocin 50% dose reduction. 5FU guidance unclear
Hepatic function	Unclear guidance. Discuss with consultant
Stomatitis (Focus)	If mouth ulcers occur despite routine chlorhexidine mouthwash: 5FU: 20% dose reduction (bolus and infusion). Continue with this reduced dose unless further toxicity occurs.
Diarrhoea (Focus)	Between cycles – treat symptomatically Loperamide 2-4mg QDS PRN and/or codeine phosphate 30-60mg QDS PRN Not resolved by next cycle: Delay 1 week/until recovered If diarrhoea still a problem • Despite symptomatic treatment • Or more than one delay is required Then dose reduce 5FU: 20% dose reduction (bolus and infusion). Continue with this reduced dose unless further toxicity occurs.
Hand-Foot Syndrome ≥Grade 2	Stop 5FU until recovery then restart with 5FU 20% dose reduction (bolus and infusion) for subsequent cycles Phase III randomised controlled trials show no benefit from pyridoxine for prevention or treatment of 5FU induced hand/foot syndrome. Pyridoxine is not recommended
Proteinuria	Streptozocin – consider dose reduction or stopping streptozocin

21. **<u>Streptozocin-5FU-Cisplatin</u>** (CTIS: 1740)

Streptozocin	1000mg/m^2	IV over 4 hours	Day 1
5Fluorouracil	500mg/m^2	IV over 1 hour	Day 1
Cisplatin	60mg/m^2	IV over 2 hours	Day 1
Post hydrations			

Interval between cycles: Repeat every 21 days

Number of cycles: Neuroendocrine tumours where frequent/ weekly appointments problematic
4 cycles then reassess. Can be repeated

Tests before starting course of chemo: FBC, U&Es, LFTs, Crcl with 24 hour urine protein quantitative analysis, tumour markers as indicated in table on page 3

Test to OK/Confirm each cycle of chemo: FBC, U&Es, LFTs, Crcl with 24 hour urine protein quantitative analysis with every other cycle, Dipstick for proteinuria with every cycle. Review treatment if proteinuria

Supportive drugs with each cycle: High risk antiemetics as per NWLCN guidelines or as per local policy

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
If borderline proteinuria, patient may need to do dipstick urine analysis at home

Additional information: Streptozocin painful if given too quickly.

Dose modifications: See table below

Reference:

Table: Strep/5FU/Cisp

Side-effect: Strep/5FU/Cisp	Dose Modification

Haematology Neutrophils $x10^9$/L	and	Platelets $x10^9$/L	
≥1.5	and	≥100	Full dose
<1.5	or	<100	Do not give. Discuss with consultant
Diarrhoea ≥ Grade 2			5FU: 25% dose reduction
Renal function (DI Oncol Handbook 2004) Cisplatin standardised in Mar09 based on ABC02 Crcl ≥60mls/min 50-59mls/min 40-49mls/min <40mls/min			Full dose Cisplatin: 25% dose reduction 5FU and streptozocin: full dose Cisplatin: 50% dose reduction Streptozocin: 25% dose reduction 5FU: Full dose Do not give cisplatin Discuss with consultant
Proteinuria			Streptozocin: Consider dose reduction or stopping streptozocin

22. **Strep/Dox** (CTIS: 89)

Doxorubicin	50mg/m^2	IV bolus	Day 1 and 22
Streptozocin	500mg/m^2	IV over 4 hours	Days 1 to 5

Interval between cycles: Repeat every 6 weeks

Number of cycles: Neuroendocrine tumours resistant disease: 4 cycles and reassess

Tests before starting course of chemo: FBC, U&Es, LFTs, Crcl with 24 hour urine protein quantitative analysis, tumour markers indicated in table on page 3

Test to OK/Confirm each cycle of chemo: FBC, U&Es, LFTs, Crcl with 24 hour urine protein quantitative analysis every other cycle (every 6 weeks). Dipstick for proteinuria with every cycle. Review treatment if proteinuria

Supportive drugs with each cycle: High risk antiemetics as per NWLCN guidelines or as per local policy

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
If borderline proteinuria, patient may need to do dipstick test for urine analysis at home.

Additional information: Streptozocin painful if given too quickly.

Dose modifications: See table below

Reference:

Table: Strep/Dox

Side-effect: Strep/Dox	Dose Modification

Side-effect: Strep/Dox			Dose Modification
Haematology Neutrophils $x10^9$/L		Platelets $x10^9$/L	
≥1.5	and	≥100	Full dose
<1.5	or	<100	Do not give. Discuss with consultant
Proteinuria			Streptozocin : Consider dose reduction or stopping stretozocin
Renal impairment (DI Oncol Handbook 2004)			
		≥50ml/min	Full dose
		10-49mls/min	Streptozocin: 25% dose reduction
		< 10ml/min	Discuss with consultant. Consider streptozocin: 50% dose reduction
Hepatic function			
Bilirubin		<19micromol/L	Full dose
		20-51micromol/L	Doxorubicin/Epirubicin 50% dose reduction
		52-84micromol/L	Doxorubicin/Epirubicin 75% dose reduction
		>85micromol/L	Do not give
		If AST 2-3xULN	Doxorubicin 25% dose reduction

Anthracycline Regimens

23. **Doxorubicin 75 Systemic** (CTIS: 1742)

Doxorubicin 75mg/m^2 IV bolus Day 1

Interval between cycles: Repeat every 21 days
Number of cycles: Hepatocellular carcinoma with Childs Pugh A or possibly good B: 4-6 cycles
Tests before starting course of chemo: FBC, U&Es, LFTs, INR, tumour markers indicated in table on page 3, Childs Pugh score, cardiac assessment. Check lifetime cumulative doxorubicin dose does not exceed 450mg/m^2/lifetime
Test to OK/Confirm each cycle of chemo: FBC, U&Es, LFTs, INR, Childs Pugh score
Supportive drugs with each cycle: High risk antiemetics as per NWLCN guidelines or as per local policy
Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
Additional information: Consider cold cap

Administration notes:
Doxorubicin is a vesicant and must be administered according to WLCN administration policy.

Dose modifications: See table page 40
Reference:

Table: Doxorubicin/Epirubicin

Side-effect: Dox/Epi			Dose Modification (HEP-1)
Haematology (HEP-1)			
Neutrophils $x10^9/L$		Platelets $x10^9/L$	
≥1.5	and	≥100	Full dose
<1.5	or	<100	Do not give. Discuss with consultant
Hepatic Function (HEP-1)			
Bilirubin			
		< 18 micromol/L	Full dose
		18-50 micromol/L	Doxorubicin/epirubicin: 50% dose reduction
		> 50 micromol/L	Do not give

24. **Epirubicin 50 Systemic** (CTIS: 1743)

Epirubicin	50mg/m^2	IV bolus	Day 1

Interval between cycles: Repeat every 21 days
Number of cycles: Hepatocellular carcinoma with
Childs Pugh A or possibly good B: 4-6 cycles
Tests before starting course of chemo: FBC, U&Es, LFTs, tumour markers indicated in table on page 1, INR, Childs Pugh score, cardiac assessment. Check lifetime cumulative epirubicin dose does not exceed 900mg/m^2/lifetime.
Tests to OK/Confirm chemo: FBC, U&Es. LFTs, Childs Pugh score
Supportive drugs with each cycle: High risk antiemetics as per NWLCN guidelines or as per local policy
Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
Additional nursing information: Consider cold cap. See Doxorubin page 39
Dose modifications: see Doxorubicin/epirubicin table above
Reference:

Chemo Embolisation

25. **Cisplatin-Chemoembolisation** (CTIS: 1744)
This is only indicated if approved by the Liver MDT and there is no evidence of portal venous involvement.

'Fluids only' for 3 hours before procedure			Day 1
Prophylactic antibiotics 1 hour before procedure			Day 1
Selective cannulation of hepatic artery (arteries) supplying the tumour			Day 1
Then			
Cisplatin	50mg (flat dose)	} mixed by radiologist and given Intra arterially	Day 1
Lipiodol	4-10mls	}	
Followed by			
Embolisation with PVA particles >300microns		Intra arterially	Day 1

(any component may be omitted if clinically indicated)
Antibiotics post procedure

Interval between cycles: 6-10 weeks if patient shows no persistent ill effects
Number of cycles: Only for loco-regional treatment of HCC confined to the liver

Hepatocellular carcinoma with
Childs Pugh A or possibly good B: Aim for 2 cycles. If tolerated may be repeated beyond 2 cycles in selective good responders

Tests before starting course of chemo: Preliminary hepatic artery angiography (under local anaesthetic, sedation, analgesia) to map out anatomy of hepatic arteries and confirm patency of portal vein.
FBC, U&Es, LFTs, INR. Crcl calculated (do EDTA if <60mls/min), tumour site markers in table on page 3. Childs Pugh score, cardiac assessment

Tests before each cycle: FBC, U&Es, LFTs, INR, Childs Pugh score

Supportive drugs with each cycle: Fluids only 3 hours before procedure.
Prophylactic antibiotics 1 hour pre procedure
Lipiodol as above
Emboli (PVA) as above
Prophylactic antibiotics post procedure
High risk antiemetics as per NWLCN guidelines or as per local policy

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information:

Dose modification: Discuss with consultant

Reference:

26. **<u>Doxorubicin Chemoembolisation</u>** <u>(CTIS: 1266)</u>

This is only indicated if approved by Liver MDT and no evidence of portal venous involvement.

'Fluids only' for 3 hours before procedure			Day 1
Prophylactic antibiotics 1 hour before procedure			Day 1
Selective cannulation of hepatic artery (arteries) supplying the tumour			Day 1
Then			
Doxorubicin	60mg (flat dose)	} mixed by radiologists and given intra arterially	Day 1
Lipiodol	4-10mls	}	
Followed by			
Embolisation with PVA particles >300microns		Intra arterially	Day 1

(any component may be omitted if clinically indicated)

Antibiotics post procedure

Interval between cycles: 6-10 weeks if patient shows no persistent ill effects

Number of cycles: Only for loco-regional treatment of HCC confined to liver
Hepatocellular carcinoma with Child's Pugh A
or possible good B: Aim for 2 cycles if tolerated. May be repeated beyond 2 cycles in selective good responses

Tests before starting course of chemo: Preliminary hepatic artery angiography (under local anaesthetic, sedation, analgesia) to map out

anatomy of hepatic arteries and confirm patency of portal vein.
FBC, U&Es, LFTs, INR, tumour markers in table on page 3. Childs Pugh score, cardiac assessment. Check lifetime cumulative doxorubicin dose does not exceed 450mg/m^2/lifetime

Tests before each cycle: FBC, U&Es, LFTs, INR, Childs Pugh score

Supportive drugs with each cycle: Fluids only 3 hours before procedure.
Prophylactic antibiotics 1 hour pre procedure
Lipiodol as above
Embolisation particles (PVA) as above
Prophylactic antibiotics post procedure
Low risk antiemetics as per NWLCN guidelines or as per local policy

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information: Alopecia can occur with only 1 cycle

Dose modification: See Doxorubicin/Epirubicin table page 40

Reference:

Additional Private Care Regimens

27. **EOX** (CTIS: 1704)

Epirubicin	50mg/m^2	IV bolus	Day 1
Oxaliplatin	130mg/m^2	IV over 2 hours	Day 1
Capecitabine	625mg/m^2 ie. total 1250mg/m^2/day See dose table page 17	Orally twice a day with water after a meal	Days 1 to 21

Interval between cycles: Repeat every 21 days

Number of cycles: Subject to local approval/funding: 6 cycles

Tests before starting course of chemo: FBC, U&Es, LFTs, Crcl (calculated), tumour markers indicated in table on page 3.
Cardiac assessment: patients with a history of ischaemic heart disease and abnormal ECG should have pre-treatment evaluation of cardiac function with MUGA scan or equivalent. If left ventricular ejection fraction is less than 50% prior to treatment then omit epirubicin.

Tests to OK/Confirm each cycle of chemo: FBC, U&Es, LFTs. Crcl (calculated).

Supportive drugs with each cycle: High antiemetics as per NWLCN guidelines or as per local policy
Chlorhexidine mouthwash 10mls QDS.

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information:

Administration notes:

Capecitabine:

Patients must attend a nurse capecitabine clinic prior to cycles 1 and 2 or specialist chemotherapy nurse review as per local policy. Capecitabine tablets should be taken with water 30 minutes after food and approximately 12 hours apart. Patients must be given written and verbal information on capecitabine including how to take the tablets, when to stop (ie. In the event of toxicity and after 14 days), and whom to contact when side effects occur. Written information should be sent to the patient's GP. Capecitabine interacts with warfarin and phenytoin and therefore patients on these drugs must have their blood levels monitored more regularly. Capecitabine is contraindicated with allopurinol.

Epirubicin: Vesicant follow WLCN administration policy

Oxaliplatin:

Oxaliplatin is incompatible with normal saline, therefore, the venous access device and administration sets should be flushed with 5% glucose. Patients should be advised to keep warm as exposure to cold post oxaliplatin infusion may aggravate symptoms of peripheral neuropathy and laryngopharyngeal dysthesia. In the event of laryngopharyngeal symptoms during an oxaliplatin infusion, reassure the patient that the symptoms are likely to resolve. This must not be confused with an allergic response which requires emergency intervention. The patient who suffers from laryngopharyngeal spasm may be re-challenged with oxaliplatin at a slower infusion rate of up to 6 hours. On occasions pain may be experienced in the infusion arm, if so, slow infusion rate to a maximum 6 hours. Consider CVAD if problematic.

Dose modifications: Table EOX below

Reference: ASCO Abstract REAL 2

Table: EOX

Side-effects: EOX			**Dose Modifications** (Source REAL 2)		
Haematology (REAL 2)			**Oxaliplatin**	**Capecitabine**	**Epirubicin**
Neutrophils x 10^9/L		Platelets x 10^9/L			
≥1.0	and	≥ 75	Full dose	Full dose	Full dose
0.5-0.9	or	50-74	Delay oxaliplatin until recovery then restart with oxaliplatin 100mg/m^2	Stop capecitabine until recovery then full dose	Delay until recovery then give epirubicin 25% dose reduction
< 0.5	or	25-49	Delay oxaliplatin until recovery then restart with oxaliplatin 100mg/m^2	Stop capecitabine until recovery then full dose	Delay until recovery then give epirubicin 50% dose reduction
			Oxaliplatin	**Capecitabine**	**Epirubicin**
Any	and	<25	Delay oxaliplatin until recovery then restart with oxaliplatin 100mg/m^2	Stop capecitabine until recovery then full dose	Do not give

Side-effects: EOX	**Dose Modifications** (Source REAL 2)		
Neutropenic fever OR Grade 3 infection/fever with neutropenia (ANC <1) at any time	Reduce to oxaliplatin 100mg/m^2 on subsequent cycles	Full dose on subsequent cycles	Epirubicin: 25% dose reduction on subsequent cycles
Grade 4 infection/fever with neutropenia (ANC <1) at any time	Reduce to oxaliplatin 100mg/m^2 on subsequent cycles	Full dose on subsequent cycles	Epirubicin: 50% dose reduction on subsequent cycles
Hepatic function (SPC/Real 2) Bilirubin Either AST or ALT			
≤1.5 x ULN and ≤2.5 x ULN	Full dose	Full dose	Full dose
1.5-3.0 x ULN and ≥2.5 x ULN	Discuss with consultant	Full dose	Do not give
>3.0 x ULN and >2.5 x ULN	Discuss with consultant	Stop capecitabine Discuss with consultant	Do not give
Renal function (Focus 2/SPC) ≥50mls/min	Full dose	Full dose	Full dose
40-49mls/min	Full dose	Capecitabine SPC recommends no dose adjustment of starting dose for 1250mg/m^2/day, but recommends careful monitoring and prompt treatment interruption if patient develops a grade 2, 3 or 4 adverse event and dose adjustments as per SPC table on page 21 25% dose reduction	Full dose
30-39mls/min	Full dose	Discuss with consultant	Full dose
< 30mls/min	Do not give EOX	Do not give EOX	Do not give EOX
Cardiotoxicity (REAL 2) Unexplained cardiac failure	Any patient who develops unexplained cardiac failure while on treatment should undergo evaluation of cardiac function with a MUGA scan or echocardiogram. If left ventricular function is less than the lower limit of normal range then epirubicin should be omitted.		
Stomatitis (SPC/REAL 2) Grade 1	Consider topical treatments eg. Difflam mouthwash or sucralfate, mouthwash 1g/5mls QDS		
≥Grade 2	As Grade 1 plus stop capecitabine until recovery, then restart with dose according to SPC table page 20		
Recurrent Grade 3	As Grade 2 but if Grade 3 / 4 stomatitis recurs despite		

Side-effects: EOX	**Dose Modifications** (Source REAL 2)
	appropriate capecitabine dose reduction then reduce oxaliplatin doses to 100mg/m^2 in subsequent cycles
Diarrhoea (REAL 2/SPC) ≤Grade 1 ≥Grade 2 Recurrent ≥Grade 3	 Full dose all drugs Stop capecitabine, start loperamide 2-4mg QDS prn oral (max 16mg/24hrs) or codeine phosphate 30-60mg oral QDS. If diarrhoea resolves within 2 days restart all drugs full dose. If diarrhoea persists, wait until recovery then restart Capecitabine: dose reduction as per SPC table page 20 As for Grade 2 but if grade 3 / 4 diarrhoea recurs despite appropriate capecitabine dose reduction then reduce oxaliplatin dose to 100mg/m^2 in subsequent cycles
Hand-Foot Syndrome (SPC) Grade 1 ≥Grade 2	 Stop capecitabine until recovery. Once recovered – restart full dose all drugs Stop capecitabine until recovery. Once recovered, restart chemo with dose according to SPC table page 20 Phase III randomised controlled trials show no benefit from pyridoxine for prevention or treatment of 5FU induced hand/foot syndrome. Pyridoxine is not recommended
Neurotoxicity (REAL 2) Cold related dysaethesia Lasting 1-7 days Lasting >7 days Persistent between cycles	 Full dose Full dose Oxaliplatin: withhold until recovery then restart oxaliplatin at 100mg/m^2 If recurs despite dose reduction, omit oxaliplatin in subsequent cycles. Discuss carboplatin substitution with consultant.
Parasthesia without pain Lasting 1-7 days Lasting >7 days Persistent between cycles	 Full dose Full dose Oxaliplatin: withhold until recovery then restart oxaliplatin at 100mg/m^2 If recurs despite dose reduction, omit oxaliplatin in subsequent cycles. Discuss carboplatin substitution with consultant
Parasthesia with pain Lasting 1-7 days Lasting >7 days Persistent between cycles	. Full dose Oxaliplatin: reduce dose to 100mg/m^2 on subsequent cycles If recurs despite dose reduction omit oxaliplatin on subsequent cycles Stop oxaliplatin. Discuss carboplatin substitution with consultant
Paraesthesia with functional impairment Lasting 1-7 days Lasting >7 days Persistent between cycles	 Full dose Oxaliplatin: reduce dose to 100mg/m^2 on subsequent cycles. If recurs despite dose reduction omit oxaliplatin on subsequent cycles. Stop oxaliplatin. Discuss carboplatin substitution with consultant

28. **Radio Embolisation: Recruit to trials whenever possible**

Radioembolisation (RE) is a technique that has been developed to target multiple sites of disease within the liver as a form of bracytherapy. SIR-Spheres (Sirtex Medical Ltd, Sydney, Australia) contain the pure β-emitter, yttrium-90, labelled to resin microspheres with a mean diameter of approximately 32 μm. The physical half-life of yttrium-90 is 64.1 hours.

In a single out-patient procedure involving trans-femoral catheterisation and fluoroscopic guidance, approximately 40 to 80 million microspheres are injected into the arterial supply of the liver. Hepatic metastases can derive approximately 90% of their blood flow from the arterial vasculature rather than the portal venous system, and this characteristic ensures that the microspheres become lodged in the malignant microvasculature.

Since RE delivers high doses of ionising radiation to the tumour compartment whilst maintaining radiation exposure of the normal liver to a tolerable level, it can be regarded as a form of brachytherapy. It has also been termed selective internal radiotherapy (SIRT).

Yttrium 90 SIR – Spheres microspheres plus OxMdG
For Additional Private Care

Summary:

Cycle 1	Full dose OxMdG (CTIS: 327)
Cycle 2	Radio embolisation plus reduced dose OxMdG (CTIS: 1746)
Cycle 3	Reduced dose OxMdG (CTIS: 1746)
Cycle 4	Reduced dose OxMdG (CTIS: 1746)
Cycle 5 to 12	Full dose OxMdG (CTIS: 327)

Cycle 1 (Full dose OxMdG) (CTIS: 327)

Folinic acid	350mg	IV over 2 hours	Day 1
Oxaliplatin	85mg/m^2	IV over 2 hours	Day 1
5Fluorouracil	400mg/m^2	IV bolus dose	Day 1
5Fluorouracil	2400mg/m^2	IV over 46hours	Day 1

Cycle 2 only (Radio embolism plus reduced dose OxMdG) (CTIS: 1746)

Folinic acid	350mg	IV over 2 hours	Day 1
Oxaliplatin	**60**mg/m^2	IV over 2 hours	Day 1
5Fluorouracil	400mg/m^2	IV bolus dose	Day 1
5Fluorouracil	2400mg/m^2	IV over 46hours	Day 1
Radio-embolism using SIR-spheres microspheres (yttrium-90)	Consult manufacturers users manual for dose Dose calculated based on BSA, % tumour involvement and "percentage lung shunting"		Day 3

Cycles 3 and 4 (Reduced dose OxMdG) (CTIS: 1746)

Folinic acid	350mg	IV over 2 hours	Day 1
Oxaliplatin	**60**mg/m^2	IV over 2 hours	Day 1
5Fluorouracil	400mg/m^2	IV bolus dose	Day 1
5Fluorouracil	2400mg/m^2	IV over 46hours	Day 1

Cycle 5 to 12
As cycle 1

Interval between cycles: Repeat every 14 days as detailed above

Number of cycles: **For additional private care only**
Only for loco-regional treatment of HCC confined to liver.
Hepatocellular carcinoma with
Childs Pugh A or possible good B 12 cycles
(ie. one radioembolisation)

Tests before starting course of chemo:

- Preliminary arteriogram of liver (within 32 days of RE) to determine

vascular anatomy of the liver (to provide "road map" of arterial supply of liver to plan delivery of SIR-spheres – see User manual

- "Break through" macro-aggregated albumin (MAA) nuclear scan within 32 days of RE (to calculate percentage of SIR-spheres that will pass through the liver and lodge in lungs due to arteriovenous shunts. Dose must be adjusted to limit y^{99} damage to lung – see SIR-spheres User manual.
- Contrast enhanced helical CT scan to calculate % tumour involvement (needed to calculate SIR-sphere dose see SIR-sphere users manual)

FBC, U&Es, LFTs, Crcl (calculated). Do EDTA if ≤60mls/min, INR, tumour markers in table on page 3, Childs Pugh score

Tests to OK/confirm each cycle of chemo: FBC, U&Es, LFTs, INR, Childs Pugh score

Supportive drugs with each cycle:
High risk antiemetics as per NWLCN guidelines or as per local policy
NB. In cycle 2 continue $5HT_3$ antiemetics to cover day of RE as a minimum
Chlorhexidine mouthwash 10mls QDS
Loperamide 2-4mg QDS PRN (max 16mg/day)
Proton pump inhibitor from day of diagnostic hepatic arteriogram for minimum 8 weeks.
Fluids only 3 hours before RE
Prophylactic antibiotics 1 hour before procedure according to local policy
Prophylactic narcotic analgesia for RE procedure.
Minor opioids (dihydrocodeine) usually sufficient but major opioids (eg pethidine) may be required within first 24 hours of RE.
Prophylactic antibiotics post procedure according to local policy.

Patient Information:
Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
SIR-Sphere patient information

Additional information:

Dose modification:

Table: SIR-Spheres

Side-effect	**Dose Modification** (FOXFIRE TRIAL)
Fever	Most patients (up to 80%) develop a mild fever that lasts several days following RE administration but which does not require treatment
Abdominal Pain	RE is followed by abdominal pain in approximately 50% of patients. This can vary from minor discomfort (grade 1) through to grade 3. In almost all cases it is self limiting (dissipating within 24 hours) but it may require narcotic analgesia (in about one third of patients). It is routinely managed by prophylactic pre-medication.
Lethargy	Post RE treatment lethargy (approximately 40% of cases) may occur anywhere between 1 week and 8 weeks post treatment and can last up to 10 days.
Nausea	Post RE treatment mild nausea (40-50% of cases) is most common in patients who have received multiple courses of chemo. Symptoms rarely last more than 24 hours and can be managed by prophylactic antiemetics medication
Gastritis/Duodenitis/Ulceration	Discuss with consultant. One of the most common potentially serious complications. Incidence rate of gastritis/duodenitis can be reduced by experience and meticulous attention to the administration procedure so as to ensure that there is minimal chance of SIR-spheres entering small arteries supplying the gut
Radiation Hepatitis	Discuss with consultant. The other most common potentially serious complication. Radiation hepatitis is largely, but not totally, preventable by using correct SIR-sphere dose and making allowances for dose reduction where there is increased risk of causing radiation damage, such as in poor liver reserve or small volume tumour mass in liver – see SIR-Sphere user manual
Pancreatitis	Discuss with consultant Rare complication is acute pancreatitis resulting from SIR-sphere refluxing back down hepatic artery and lodging in the pancreas and liver abscess from infection of necrotic tumour.
Haematological	Discuss with consultant There is some evidence that there is a decrease in leukocyte (lymphocyte and neutrophils) levels following RE with a nadir 6-8 weeks after the RE procedure. The mechanism of leucopenia is unknown, although current clinical data (2009) suggest this adverse effect may have clinical sequelae when RE is used in combination with systemic radiosensitisers eg 5FU/Oxaliplatin.

Table: OxMdG

Side-effect: OxMdG	**Dose Modification** (Source: Focus Trial/SPC/Coin Trial)
Haematology (Coin) Neutrophils x10^9/L and Platelets x10^9/L	Myelotoxicity more frequent (30%) with OxMdG than with MdG.
≥1.5 and ≥75	Full dose all drugs
<1.5 or <75	Delay 1 week then recheck FBC. Only give if neutrophils and platelets above these limits. Lower limit for platelets is due to possible mild thrombocytopenia after a number of cycles of OxMdG.
If more than 1 delay or 1 delay ≥2 weeks:	Wait for full recovery then: Oxaliplatin: Full dose 5FU: Omit bolus dose but give full dose infusion. Continue without bolus dose on subsequent cycles. If further delays for myelotoxicity occur despite 20% dose reduction discuss with consultant.
Neutrophils <1.0x10^9/L at any time (SPC)	Oxaliplatin: 25% dose reduction in addition to any 5FU reduction above
Renal Function (Coin) Crcl	Oxaliplatin – Not nephrotoxic but is renally cleared. If Crcl calculated is <60mls/min, do EDTA
≥30mls/min	Full dose all drugs
<30mls/min	Oxaliplatin: Omit 5-FU: 25% dose reduction (bolus and infusion)
Hepatic Function (Coin)	NB. Significantly impaired hepatic function may be a sign of disease progression ie. review treatment. Oxaliplatin not principally cleared by liver but is evidence of delayed clearance in patients with marked hepatic dysfunction.
AST/ALT >5 x ULN Bilirubin > 3 x ULN (>51micromol/l)	Withhold 5FU until recovery Oxaliplatin: 50% dose reduction 5-Fluorouracil: 50% dose reduction (bolus and infusion)
Neurotoxicity	Oxaliplatin : peripheral sensory symptoms 5FU : uncommon and cerebellar. Consider other chemo regimen
Paraesthesia of hands and feet Dysaesthesia in throat (often precipitated by cold)	These symptoms are precipitated by cold. If symptoms lasts few hours to a few days after oxaliplatin administration, no treatment or dose reduction required. Acute laryngopharyngeal dysaesthesia during or within the hours following the oxaliplatin 2 hour infusion – administer next oxaliplatin over 6 hours (SPC). If symptoms last longer than 7 days and are troublesome reduce oxaliplatin dose from 85mg/m^2 to 65mg/m^2 (metastatic setting) or 75mg/m^2 (adjuvant) (SPC). If parasthesia without functional impairment persists until the next cycle reduce oxaliplatin from 85mg/m^2 to 65mg/m^2 (metastatic setting) or 75mg/m^2 (adjuvant) (SPC) If parasthesia persist until next cycle omit oxaliplatin, give

Side-effect: OxMdG	**Dose Modification** (Source: Focus Trial/SPC/Coin Trial)
	DeGramont alone until fully resolved. Resumption of oxaliplatin may be considered once fully resolved. Check dose with consultant (SPC).
Stomatitis (Coin)	If mouth ulcers occur despite chlorhexidine mouthcare delay until recovery to grade 1 or less then 5FU: 20% dose reduction (bolus and infusion). If further toxicity occurs despite above reductions then: 5FU: 40% dose reduction (bolus and infusion) Oxaliplatin: 20% dose reduction
Diarrhoea Between cycles (Coin) Not resolved by next cycle Unresolved If Grade 4 diarrhoea, neutrophils <1.0 and platelets <50 (SPC)	Between cycles - treat symptomatically loperamide 2-4mg QDS (max 16mg/24hrs) and/or codeine phosphate 30-60mg QDS as required Not resolved by next cycle: Delay 1 week/until resolved If problematic despite symptomatic treatment or more than 1 delay give 5FU: 20% dose reduction (bolus and infusion) Oxaliplatin : 20% dose reduction If further toxicity occurs despite above dose reduction then 5FU: 20% dose reduction (bolus and infusion) Oxaliplatin: further 20% dose reduction Delay until recovered then reduce oxaliplatin from 85mg/m^2 to 65mg/m^2 (metastatic) or to 75mg/m^2 (adjuvant) plus 5FU: 20% dose reduction bolus and infusion
Hand-Foot Syndrome ≥Grade 2	5FU: 20% dose reduction (bolus and infusion) Phase III randomised controlled trials show no benefit from pyridoxine for prevention or treatment of 5FU induced hand/foot syndrome. Pyridoxine is not recommended
DPD Deficiency (FOCUS)	1-3% of patients have markedly exaggerated 5FU toxicity due to reduced 5FU Catabolism. Discuss with consultant
Cardiotoxicity (FOCUS)	Uncommon. 5FU may provoke angina attack or MI in ischaemic heart disease. Seek specialist opinion on upgraded anti-anginal medication and consider dose reduction or alternative non 5FU treatment.

Side-effect: OxMdG	Dose Modification (Source: Focus Trial/SPC/Coin Trial)
Allergic reactions to oxaliplatin Approximately 9.1% (SPC) incidence of acute hypersensitivity to oxaliplatin usually after more than 6 cycles have been administered. During administration patient may develop rash, fever, swollen mouth/tongue hyper or hypotension etc. This rarely develops to full blown anaphylaxis even with repeated treatment	**Grade 1 and 2** If acute hypersensitivity occurs: • Discontinue infusion • Treat with IV corticosteroids and antihistamine • After full recovery continue with 5FU/FA alone • Rechallenge at consultant's discretion with: (COIN) Dexamethasone 4mg orally every 6 hours starting 24 hours pre chemo Dexamethasone 8mg IV 30 minutes pre chemo Chlorphenamine 10mg IV bolus dose 30 mins pre chemo Ranitidine 50mg IV bolus dose 30mins pre chemo Continue dexamethasone, chlorphenamine and ranitidine for 24-48 hours after oxaliplatin **Grade 3 and 4** Treat for full anaphylaxis. DO NOT GIVE further oxaliplatin

29. **Yttrium 90 SIR – Spheres microspheres plus Ir-MdG**
For additional Private Care only
Summary:
This regimen is used where radioembolisation is added to the treatment of a patient already receiving IrMdG. Prior to radioembolisatoin full dose IrMdG is used (colorectal page 13, CTIS: 751).

For the radiembolisation cycle, reduced dose IrMdG must be used (see below CTIS: 1745)

Post radioembolisation, reduced dose IrMdG may be still used for up to 2 cycles post radioembolisation. Regimen must be confirmed by consultant.

Radio Embolisation Cycle (Reduced dose IrMdG, CTIS 1745)

Atropine	250mcg	SC bolus dose	Day 1
Irinotecan	100mg/m^2	IV over 30 mins	Day 1
Folinic acid	350mg	IV over 2 hours	Day 1
5Fluorouracil	400mg/m^2	IV bolus dose	Day 1
5Fluorouracil	2400mg/m^2	IV over 46hours	Day 1
Radio-embolism using SIR-spheres microspheres (yttrium-90)	Consult manufacturers users manual for dose Dose calculated based on BSA, % tumour involvement and "percentage lung shunting"		Day 3

Post Radio Embolisation – reduced dose IrMdG (CTIS 1745) may be used for up to 2 cycles. Check with consultant.

Atropine	250mcg	SC bolus dose	Day 1
Irinotecan	100mg/m^2	IV over 30 mins	Day 1
Folinic acid	350mg	IV over 2 hours	Day 1
5Fluorouracil	400mg/m^2	IV bolus dose	Day 1
5Fluorouracil	2400mg/m^2	IV over 46hours	Day 1

Interval between cycles: Repeat every 14 days as detailed above
Number of cycles: **For additional private care only pending review by London**

Cancer Drugs Fund

Only for loco-regional treatment of HCC confined to liver.

Hepatocellular carcinoma with

Childs Pugh A or possible good B 1 cycle of radioembolisation

Tests before starting course of chemo:

- Preliminary arteriogram of liver (within 32 days of RE) to determine vascular anatomy of the liver (to provide "road map" of arterial supply of liver to plan delivery of SIR-spheres – see User manual
- "Break through" macro-aggregated albumin (MAA) nuclear scan within 32 days of RE (to calculate percentage of SIR-spheres that will pass through the liver and lodge in lungs due to arteriovenous shunts. Dose must be adjusted to limit y^{99} damage to lung – see SIR-spheres User manual.
- Contrast enhanced helical CT scan to calculate % tumour involvement (needed to calculate SIR-sphere dose see SIR-sphere users manual)

FBC, U&Es, LFTs, Crcl (calculated). Do EDTA if ≤60mls/min, INR tumour markers in table on page 3, Childs Pugh score

Tests to OK/confirm each cycle of chemo: FBC, U&Es, LFTs, INR, Childs Pugh score

Supportive drugs with each cycle:
High risk antiemetics as per NWLCN guidelines or as per local policy
NB. In cycle 2 continue $5HT_3$ antiemetics to cover day of RE as a minimum
Chlorhexidine mouthwash 10mls QDS
Loperamide 2-4mg QDS PRN (max 16mg/day)
Proton pump inhibitor from day of diagnostic hepatic arteriogram for minimum 8 weeks.
Fluids only 3 hours before RE
Prophylactic antibiotics 1 hour before procedure according to local policy
Prophylactic narcotic analgesia for RE procedure.
Minor opioids (dihydrocodeine) usually sufficient but major opioids (eg pethidine) may be required within first 24 hours of RE.
Prophylactic antibiotics post procedure according to local policy.

Patient Information:
Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
SIR-Sphere patient information

Additional information:

Dose modification: Discuss with consultant. SIR Spheres see page 48

Table: Irinotecan-MdG

Side-Effect: IrMdG	**Dose Modification** (Source: Focus Trial/SPC)
Haematological Neutrophils x10^9/L and Platelets x10^9/L	Myelotoxicity more common than with Degramont alone
≥1.5 and ≥100	Full dose
<1.5 or <100	Delay 1 week and recheck FBC. Only give when neutrophils and platelets are above these limits.
If neutropenia grade 4, or febrile neutropenia, or thrombocytopenia grade 4 or leucopenia grade 4 occurs (SPC July 02) or if more than 1 delay or 1 delay greater than 2 weeks	} Irinotecan: 20% dose reduction } 5FU (bolus and infusion): 20% dose reduction } } If further delays occur for myelotoxicity despite 20% } reduction, discuss with consultant }
Renal function Crcl ≤50mls/min	Unclear guidance. Discuss with consultant
Hepatic Function (SPC) Bilirubin and ALP	Irinotecan and metabolites cleared by biliary excretion. Delayed clearance in cholestasis.
<1.5 x ULN and ≤5.0 x ULN	Full dose all drugs
1.5-3.0 x ULN or >5.0 x ULN	Irinotecan: 50% dose reduction 5-Fluorouracil: Full dose
>3 x ULN and Any	Irinotecan: Do not give 5-Fluorouracil: 50% dose reduction
Stomatitis (Focus)	Routine mouth care with chlorhexidine mouthwash. If mouth ulcers occur despite this, dose reduce 5FU: 20% dose reduction (bolus and infusion) for all subsequent cycles
Diarrhoea Immediate diarrhoea (within first 24 hours)	Incidence of immediate diarrhoea is low due to use of atropine premed. If acute diarrhoea/cholinergic syndrome occurs administer another dose of atropine 250mcg SC stat.
Delayed diarrhoea occurring more than 24 hours after irinotecan and at any time before next cycle: Initial treatment	Irinotecan induced delayed diarrhoea should be treated early with high dose loperamide, 4mg after first loose stool then 2mg every 2 hours until 12 hours after last loose stool (up to 24mg/day for a maximum of 48 hours because or risk of paralytic ileus).
Lasts >24 hours	If diarrhoea lasts > 24 hours add Ciprofloxacin PO 500mg BD.
Lasts >48 hours	If diarrhoea lasts > 48 hours or patient reports symptoms of dehydration, admit acutely for rehydration

Side-Effect: IrMdG	**Dose Modification** (Source: Focus Trial/SPC)
	and further management.
Grade 3-4	After an episode of severe diarrhoea (grade 3/4), delay until full recovery then resume at Irinotecan: 20% dose reduction 5FU (bolus & infusion) : 20% dose reduction.
Unresolved by next cycle	If diarrhoea from previous cycle (even if not severe) not resolved by next cycle due - delay 1 week.
Hand-Foot Syndrome ≥ Grade 2	5FU: 20% dose reduction (bolus and infusion) Irinotecan: full dose. Phase III randomised controlled trials show no benefit from pyridoxine for prevention or treatment of 5FU induced hand foot syndrome. Pyridoxine is not recommended.
DPD Deficiency (Focus)	1-3% of patients have markedly exaggerated 5FU toxicity due to reduced 5FU catabolism. Discuss with consultant
Cardiotoxicity (Focus)	Uncommon. 5FU may provoke angina attack or MI in patients with ischaemic heart disease. Seek specialist opinion on upgraded anti-anginal medication and consider dose reduction or alternative non 5FU treatment.
Neurotoxicity (Focus)	Uncommon – Cerebellar Consider alternative Non 5FU treatment

Chemo-Radiation Regimens

30. **5FU320/FA20 5 days plus Radiotherapy (CTIS: 204)**

Folinic Acid	20mg/m^2	IV bolus	Days 1 to 5 and	Days 15-19
5-Fluorouracil	320mg/m^2	IV bolus	Days 1 to 5 and	Days 15-19

Interval between cycles: Single course – no repeats. Chemotherapy administered weeks 1 and 3 of a four week course of radiotherapy.

Number of cycles: Pancreatic cancer: Single course (based on ESPACII data; selected patients only).

Tests before starting course of chemo: FBC, U&Es, LFTs, Crcl (calculated), tumour markers indicated in table on HPB page 3

Tests to OK/confirm each cycle of chemo: FBC, U&Es, LFTs

Supportive drugs with each cycle: Low risk antiemetics

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information:

Dose modifications: See MAYO page 8-9

Reference:

31. **Gemcitabine-300 + RT (CTIS: 1260)**

Gemcitabine	300mg/m^2	IV over 30 minutes 2 hours before radiotherapy fraction	Day 1

Interval between cycles: Repeat day 7 ie. Given weekly during course of radiotherapy

Number of cycles: Pancreatic cancer: 1st line in accordance with NICE guidance but at a reduced dose during course of radiotherapy usually weekly for 5 weeks

Tests before starting course of chemo: FBC, U&Es, LFTs, tumour markers indicated in table on page 3

Tests to OK/confirm each cycle of chemo: FBC, U&Es, LFTs

Supportive drugs with each cycle: Low risk antiemetics as per NWLCN guidelines or as per local policy

Patient information: Chemotherapy treatment booklet (local information/Macmillan)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)

Additional information: See Gemcitabine administration notes page 22

Dose modifications: See table page 25

Reference:

32. **Capecitabine 1650 + RT (CTIS: 1028)**

Capecitabine 825mg/m^2 Oral twice a day Days 1 to 5
(ie. total 1650mg/m^2/day)
See dose table below

Body Surface Area (m^2)	Dose 825mg/m^2 Twice a day		
	Dose per Administration (mg)	Number of 150mg and/or 500mg tablets per administration. (Each administration to be given morning and evening)	
		150mg	500mg
≤1.26	1000	-	2
1.27-1.29	1000	-	2
1.30-1.49	1150	1	2
1.50-1.66	1300	2	2
1.67-1.78	1450	3	2
1.79-1.92	1500	-	3
1.93-2.06	1650	1	3
2.07-2.18	1800	2	3
≥2.19	1800	2	3

Interval between cycles: Administer Monday to Friday only each week during the 5 weeks of radiotherapy. Repeat tests every 2-3 weeks. Ideally RT should be delivered within 2 hours of capecitabine dose.

Number of cycles: Monday to Friday during 5 weeks of radiotherapy.

Tests before starting course of chemo: FBC, U&Es, LFTs, Crcl calculated. Do EDTA if <60mls/min. Tumour markers in table on page 3. Baseline ECG if history of ischaemic heart disease or cardiac risk factors

Test to OK/Confirm each cycle of chemo: FBC and U&Es (weekly), LFTs (every 2-3 weeks). Do EDTA if rising serum creatinine

Supportive drugs with each cycle: Low risk antiemetics as per NWLCN guidelines or as per local policy
Chlorhexidine mouthwash 10mls QDS

Patient information: Chemotherapy treatment booklet (local information/Macmillian)
Your chemotherapy record (NWLCN red book)
Chemotherapy alert card (NWLCN)
Macmillan drug specific information sheets and information prescriptions as appropriate
Neutropenia DVD (NWLCN)
Patient must attend capecitabine radiotherapy nurse counselling for cycle 1 and 2

Additional information: See page 18

Dose modifications: For chemotherapy dose modifications see table Capecitabine + RT below.

Reference: IJROBP 2005. Kim JC et al

Table: Capecitabine + RT

NB. Palliative patients or radical chemo-radiation patients will require greater dose reductions than above based on individual patient parameters. Discuss with consultant.

Side-effects: Capecitabine +RT	**Dose Modifications** (Scope/SPC)
Haematology Neutrophils x 10^9/L and Platelets x 10^9/L	
≥1.5 and ≥100	Full dose.
<1.5 or <100	Delay 1 week or until recovery. If >1 delay or 1 delay ≥2 weeks dose reduce Capecitabine: 20% dose reduction. Continue at this lower dose for subsequent cycles unless further toxicity occurs. If further delay(s) for myelotoxicity occur despite 20% dose reduction, discuss with consultant
Renal function (Scope) Crcl ≥50mls/min 40-49mls/min 30-39mls/min <30mls/min	 Full dose Capecitabine 25% dose reduction. Capecitabine 50% dose reduction Do not give
Hepatic function Bilirubin and Either AST or ALT	
≤3 x ULN and ≤2.5 x ULN	Full dose
>3 x ULN or >2.5 x ULN	Capecitabine withhold until recovery then discuss with consultant
Diarrhoea Grade 1 ≥Grade 2	Loperamide 2-4mg oral QDS PRN max 16mg/24hours As grade 1 plus stop capecitabine until recovery then reduce dose according to SPC table page 58
Stomatitis (SPC) Grade 1 ≥ Grade 2	Consider topical treatments eg Difflam mouthwash or sucralfate 1g/5ml mouthwash Stop capecitabine until recovery Consider topical treatments as grade 1 and reduce dose according to SPC table page 58
Hand-Foot Syndrome Grade 1 ≥Grade 2	Stop capecitabine until recovery. Once recovered restart with full dose. Stop capecitabine until recovery. Once recovered, reduce dose according to SPC table page 58 Phase III randomised controlled trials show no benefit from pyridoxine for prevention or treatment of 5FU induced hand foot syndrome. Pyridoxine is not recommended.
DPD Deficiency	1-3% of patients have markedly exaggerated capecitabine toxicity due to reduced capecitabine catabolism. Discuss with consultant.
Cardiotoxicity	Uncommon. Capecitabine may provoke angina or MI in patients with ischaemic heart disease. Seek specialist opinion on upgraded anti-anginal medication and consider dose reduction or alternative non-capecitabine treatment.
Neurotoxicity	Uncommon – Cerebellar Consider alternative non-capecitabine treatment

Capecitabine Non haematological toxicity (SPC)

NCIC Grade	**During course of treatment**	**Dose adjustment for next cycle**
Grade 1	Continue treatment	Capecitabine full dose
Grade 2 1st appearance 2nd appearance 3rd appearance 4th appearance	 Interrupt capecitabine until resolved to grade 0-1 Interrupt capecitabine until resolved to grade 0-1 Interrupt capecitabine until resolved to grade 0-1 Discontinue capecitabine permanently	 Capecitabine full dose Capecitabine 25% dose reduction. Capecitabine 50% dose reduction. Stop treatment
Grade 3 1st appearance 2nd appearance 3rd appearance	 Interrupt capecitabine until resolved to grade 0 to 1 Interrupt capecitabine until resolved to grade 0 to 1 Discontinue capecitabine treatment permanently	 Capecitabine 25% dose reduction Capecitabine 50% dose reduction Do not give
Grade 4 1st appearance	 Discontinue permanently. If consultant considers it is in best interest of patient to continue: interrupt capecitabine until resolved to grade 0 to 1	 Discontinue permanently. If consultant considers it is in best interest of patient to continue then:- Capecitabine 50% dose reduction