EOX

As an alternative to ECX:
for locally advanced (inoperable) or metastatic oesophageal or gastric cancer, or metastatic small bowel cancer, including ampulla of Vater;
peri-operative use in oesophageal or gastric cancer;
adenocarcinoma of unknown primary

Drugs/Dosage:	Epirubicin*	50mg/m^2	IV	Day 1
	Oxaliplatin	130mg/m^2	IV	Day 1
	Capecitabine	625mg/m^2	PO	BD continuous throughout treatment

*For the Upper GI indications, epirubicin may be omitted, only if specified by Consultant, for patients with poor performance status or who do not wish to lose their hair[1], as well as those with poor cardiac function as specified below.

Administration: Capecitabine tablets (available as 500mg and 150mg) should be swallowed whole with water within 30 minutes after a meal.
Information is available via Pharmacy regarding dispersing the tablets for those patients with swallowing difficulties or with feeding tubes.
Epirubicin via fast running infusion of 0.9% sodium chloride
Oxaliplatin in 500ml glucose 5% over 2 hours

Frequency: 3 weekly cycle
Advanced / metastatic use: 6 - 8 cycles
All patients for full clinical review after 3 cycles - for locally advanced cases with no other assessable disease, a restaging OGD to assess mucosal response is required after Cycle 3.
Perioperative use: 3 cycles before surgery, plus a further 3 cycles post surgery

Main Toxicities: myelosuppression; alopecia; diarrhoea; mucositis; neurotoxicity (see Comments); palmar-plantar erythema (PPE); cardiomyopathy; cardiotoxicity due to capecitabine (see Comments); allergic reactions (see Comments); ovarian failure/infertility

Anti-emetics: Day 1: highly emetogenic Days 2 – 21: mildly emetogenic

Extravasation: Epirubicin is a vesicant

Regular Investigations:	FBC	Day 1
	LFTs & U&Es	Day 1
	Mg^{2+}	Day 1 (ideally, correct any low Mg^{2+} before oxaliplatin given)
	MUGA scan	see Comments
	Restaging	after Cycle 3 as indicated (see Frequency)

Comments: **Oxaliplatin and Neurotoxicity**

Acute Cold-related Dysaesthesia (CRD):
Many patients experience transient paraesthesia of hands & feet, and some experience laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion, and resolves within minutes to a few days. Symptoms are exacerbated by

cold, so patient should be well advised on precautions to be taken. Does not require treatment or dose reduction.
For laryngopharyngeal dysaesthesia, subsequent infusions should be given over 6 hours. Consideration to infusion of 10mmol of magnesium + 1gram of calcium gluconate in 0.9% sodium chloride 250ml over 1 hour, prior to starting the oxaliplatin, should also be made.
NB. The above management may also benefit patients who complain of pain/weakness in arm during oxaliplatin administration, but should **not** be used to try and alleviate CRD or cumulative neuropathy.

Cumulative dose related peripheral sensory neuropathy:
Usually occurs after a cumulative dose of 800mg/m^2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approx 3 – 5 months to recovery.

Allergic reactions to oxaliplatin during infusion: Immediate intervention is to stop the infusion and call for medical help. Treat with IV corticosteroid and antihistamine. After full recovery, the patient may continue with folinic acid and 5FU.
At Consultant discretion, the patient may be re-challenged with oxaliplatin, according to the grade of reaction, as detailed in the separate document "Oxaliplatin Hypersensitivity & desensitisation regimen".

Maximum cumulative dose Epirubicin = 950mg/m^2
A baseline MUGA scan should be performed where the patient is considered at risk of having significantly impaired cardiac contractility. If ejection fraction is less than 50%, epirubicin should be omitted from the regimen. MUGA scan should be repeated if there is suspicion of cardiac toxicity at any point during treatment.

Fluoropyrimidine therapy has been associated with cardiotoxicity (including myocardial infarction, angina, arrhythmias, cardiogenic shock, sudden death and ECG changes). Therefore exercise caution in patients with prior history of coronary heart disease, arrhythmias or angina pectoris.

Dose Modifications

Haematological Toxicity:	Neutrophils ≥ 1.0 x 10^9/l and Platelets ≥ 75 x 10^9/l	Proceed with treatment, if necessary adjusting epirubicin dose for any previous haematological toxicity as specified below:
	Neutrophils 0.5 – 0.9 x 10^9/l or Platelets 50 - 74 x 10^9/l	Stop capecitabine and delay treatment until recovery (e.g. 1 week later). Give oxaliplatin 100mg/m^2 and 75% dose epirubicin for subsequent cycles. Restart capecitabine at full dose.
	Neutrophils < 0.5 x 10^9/l or Platelets 25 - 49 x 10^9/l	Stop capecitabine and delay treatment until recovery (e.g. 1 week later). Give oxaliplatin 100mg/m^2 and 50% dose epirubicin for subsequent cycles. Restart capecitabine at full dose.
	Platelets < 25 x 10^9/l	Stop capecitabine and delay treatment until recovery. Omit epirubicin from subsequent cycles. Restart full dose capecitabine and oxaliplatin at 100mg/m^2.

If patient suffers an episode of Grade 3 febrile neutropenia at any time, continue after recovery with oxaliplatin 100mg/m^2 and 25% dose reduction for epirubicin. For any Grade 4 neutropenic

sepsis, discuss with Consultant before proceeding with oxaliplatin 100mg/m^2 and 50% dose reduction for epirubicin.

Renal Impairment:

CrCl (ml/min)	Capecitabine Dose	Oxaliplatin Dose
> 50	Give 100% dose	Give 100% dose
30 - 50	Give 75% dose	Give 100% dose
< 30	Omit	Limited information

Hepatic Impairment:

Bilirubin (µmol/l)	Epirubicin Dose
24 - 51	Give 50% dose
52 - 85	Give 25% dose
> 85	Omit

If bilirubin > 3 x ULN or ALT/AST > 2.5 ULN, omit capecitabine until liver function recovers.

Non-Haematological Toxicities:

Note that severe diarrhoea and/or severe mucositis early in the first treatment cycle can be the first presenting toxicity due to DPD enzyme deficiency, in which case potentially fatal neutropenia can quickly follow.

Capecitabine toxicities may be managed symptomatically, with modification of the dose (treatment interruption or dose reduction) according to the information below. Once the dose has been reduced, it should not be increased at a later time. Capecitabine doses omitted for toxicity are not replaced or restored.

Capecitabine Dose Adjustment Guidelines for Non-Haematological Toxicities

Common Toxicity Criteria	During Course of Therapy	Dose adjustment for next cycle (% of start dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2: 1st Appearance	Interrupt until resolved to Grade 0 – 1	Give 100% dose, except if PPE give 85% dose*
Grade 2: 2nd Appearance	Interrupt until resolved to Grade 0 – 1	Give 75% dose
Grade 2: 3rd Appearance	Interrupt until resolved to Grade 0 – 1	Give 50% dose
Grade 2: 4th Appearance	Discontinue treatment permanently	
Grade 3: 1st appearance	Interrupt until resolved to Grade 0 – 1	Give 75% dose, except if PPE give 70% dose*
Grade 3: 2nd appearance	Interrupt until resolved to Grade 0 – 1	Give 50% dose
Grade 3: 3rd appearance	Discontinue treatment permanently	
Grade 4: 1st appearance	Discontinue permanently **or, with Consultant approval,** interrupt until resolved to Grade 0 – 1	Give 50% dose

* If PPE Grade 2 - 3 occurs for the first time after 10 weeks, interrupt capecitabine. On resolution of toxicity to Grade 0 - 1, capecitabine may be re-introduced with NO dose reduction.

Neurological Toxicity:	Grade 1 of any duration or grade 2 paraesthesias lasting longer than 7 days but resolved before the next cycle is due, continue with oxaliplatin 130mg/m^2. Grade 2 paraesthesias persisting until next cycle; reduce oxaliplatin dose to 100mg/m^2. Grade 3 paraesthesias lasting longer than 7 days but resolved before next cycle is due; reduce oxaliplatin dose to 100mg/m^2. Grade 3 paraesthesias persisting until next cycle or Grade 4 of any duration, discontinue oxaliplatin permanently. Consider switching to ECarboX.
References:	Cunningham, D et al; NEJM 2008; 358: 36 – 46 (REAL-2) Cunningham, D et al; NEJM 2006; 355: 11-20 (peri-operative use of ECF) [1]Wagner, A et al; JCO 2006; 24 (18) : 2903 – 2909