GEMCITABINE and CAPECITABINE

For adjuvant use after surgical removal of pancreatic cancer
An option for **first line use** in locally advanced or metastatic pancreatic cancer

Drug/Dose:	Gemcitabine	1000mg/m^2	IV	Day 1, Day 8 and Day 15
	Capecitabine	830mg/m^2	PO	BD daily for 21 days, then 7 days rest

Administration: Gemcitabine in 250ml 0.9% sodium chloride over 30 minutes
Capecitabine tablets (available as 500mg and 150mg) should be swallowed whole with water within 30 minutes after a meal.
Information, provided by Roche, is available via Pharmacy regarding dispersing the tablets for those patients with swallowing difficulties or with feeding tubes.

Frequency: 4 week cycle: up to 6 cycles in advanced setting
6 cycles in adjuvant setting

Main Toxicities: myelosuppression; erythematous rash; flu-like syndrome; peripheral oedema (mild –moderate & reversible); diarrhoea; mucositis; palmar-plantar erythema (PPE); cardiotoxicity due to capecitabine (uncommon); ovarian failure/infertility

Anti-emetics: mildly emetogenic

Extravasation: gemcitabine is a non-vesicant

Regular Investigations:	FBC	Day 1, Day 8 and Day 15
	U&Es and LFTs	Day 1
	CA 19-9	Day 1

Dose Modifications

Haematological Toxicity:

Day of Cycle	Blood Counts	Gemcitabine	Capecitabine
Day 1	Neutrophils > 1.0 and platelets > 100	Full dose, or modified as notes below*	Full dose, or modified as notes below*
	Neutrophils ≤ 1.0 or platelets ≤ 100	Delay cycle for 1 week	
Day 8 and Day 15**	Neutrophils > 1.0 and platelets > 100	100% of Day 1 dose	100% of Day 1 dose
	Neutrophils 0.5 – 1.0 or platelets 50 - 100	75% of Day 1 dose	100% of Day 1 dose
	Neutrophils < 0.5 or platelets < 50	Omit (do not delay; if Day 15 start next cycle in 2 weeks)	Omit (do not delay; if Day 15 start next cycle in 2 weeks)

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*If ≥ 2 weeks delay in starting Day 1 of a cycle due to haem toxicity, start gemcitabine at 75% dose for all subsequent cycles. Continue capecitabine at 100%.

*If ≥ 2 weeks delay in starting Day 1 for 2 consecutive cycles due to haem toxicity, start both gemcitabine and capecitabine at 75% dose for subsequent cycles.

*If both Day 8 and Day 15 gemcitabine doses of the previous cycle have been reduced or omitted, start the next cycle with 75% dose gemcitabine and 100% dose capecitabine. Do not re-escalate the dose.

*Following any episode of neutropenic sepsis, once recovered, recommence both gemcitabine and capecitabine at 75% dose, with no future dose re-escalation.

**On Day 8 and Day 15, dose according to the neutrophil and platelet counts on that day.

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.
Toxicity due to capecitabine may be managed symptomatically and/or modification of the dose (treatment interruption or dose reduction). Use the table below for dose adjustment guidelines. Once the dose has been reduced, it should not be increased at a later time. Doses of capecitabine omitted for toxicity are not replaced or restored. Instead the patient should resume the planned treatment cycle.

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 Grade 0 – 1	Give 100% dose
2nd Appearance	Interrupt until Grade 0 – 1	Give 75% dose
3rd Appearance	Discontinue permanently	
Grade 3: 1st appearance	Interrupt until Grade 0 – 1	Give 75% dose
2nd appearance	Interrupt until Grade 0 – 1	Give 50% dose
3rd appearance	Discontinue permanently	
Grade 4: 1st appearance	Discontinue permanently	

Renal Impairment:

CrCl (ml/min)	Capecitabine Dose
> 50	Give 100% dose
30 – 50	Give 75% dose
< 30	Omit

If CrCl < 30ml/min, consider dose reduction of gemcitabine – clinical decision

Hepatic Impairment: If bilirubin > 27 µmol/L, initiate treatment with gemcitabine 800mg/m^2
If bilirubin > 3 x ULN or ALT/AST > 2.5 ULN, omit capecitabine until liver function recovers.

References:
Cunningham, D et al ; JCO 2009 ; 27 (33) : 5513 – 5518 (advanced)
Hermann, R et al ; JCO 2007 ; 25 (16) : 2212 – 2217 (advanced)
Abstract LBA4006 at ASCO 2016 (adjuvant)