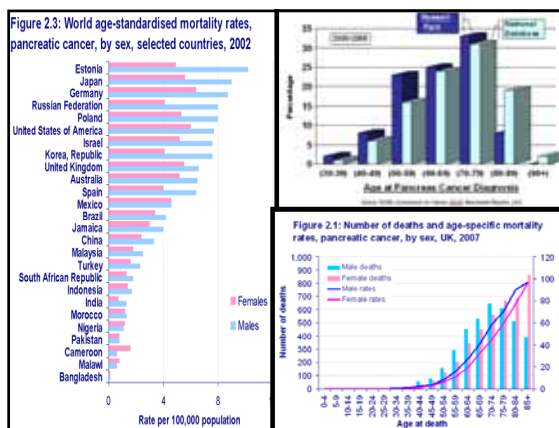

Management of Metastatic Pancreatic Cancer
 Malcolm J. Moore MD
 Princess Margaret Hospital
 University of Toronto

Metastatic Pancreatic Cancer

- Disease overview.
- Review of clinical research over last 10 years
 - Combination chemotherapy
 - Targeted therapy
- Focus on new data from ASCO 2009
- Lessons learned



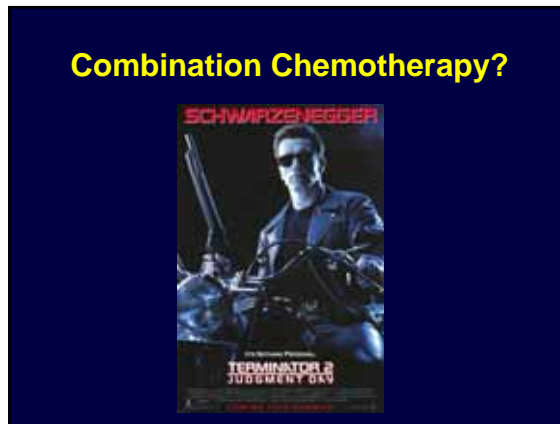
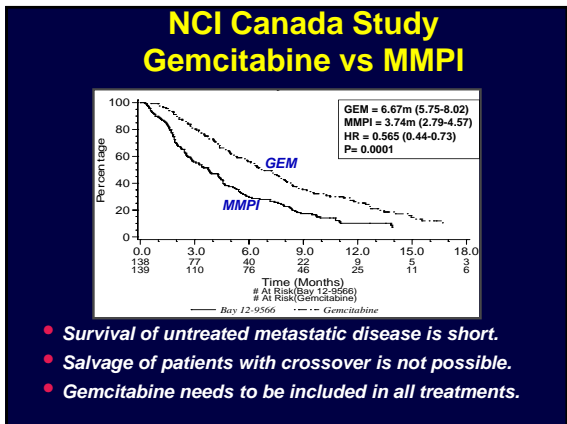
Pancreatic Cancer

- Screening, early detection not available
- Most patients are diagnosed with advanced disease.
- Median survivals
 - Metastatic disease (50-60%) 3-6 months
 - Locally advanced (25-35%) 9-12 months
 - Resected disease (10-20%) 14-21 months

Gemcitabine Registration Study in Pancreatic Cancer

	Gemcitabine N = 63	5-FU N = 63	p-value
Clinical benefit response†	24%	5%	0.002
Survival	—	—	0.002
Median survival, months	5.7	4.4	—
1-year survival	18%	2%	—
Partial response	5.4%	0	—
Stable disease	39%	19%	—
Time to progression, months	2.3	0.9	0.0002

† Composite of measurements of pain (analgesic consumption and pain intensity), KPS and weight
 Burris HA, Moore MJ, Andersen J, et al. *J Clin Oncol*. 1997;15:2403-2413



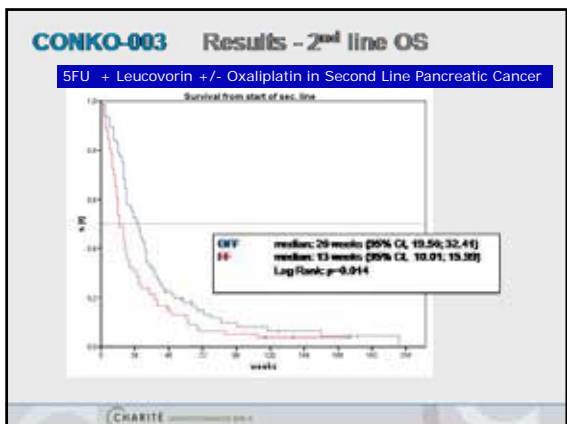
Randomised phase III trials in pancreatic cancer (median overall survival in months)

	Gem	Gem + X	p value
Gem ± marimastat (Bramhall, BJC 2002)	5.5	5.5	NS
Gem ± tipifarnib (Van Cutsem, JCO 2004)	6.0	6.4	NS
Gem ± oxatecan (Abou-Alfa, JCO 2006)	6.2	6.7	NS
Gem ± CPT-11 (Rocha-Lima, JCO 2006)	6.6	6.3	NS
Gem ± pemetrexed (Oettle, Ann Oncol 2006)	6.3	6.2	NS
Gem ± 5-FU bolus (Berlin, JCO 2002)	5.4	6.7	NS
Gem ± capecitabine (Herrmann, JCO 2007)	7.3	8.4	NS
Gem ± 5-FU/LV (Riess, JCO 2005)	6.2	5.9	NS
Gem ± capecitabine** (Cunningham, ECCO 2005)	6.0	7.4	0.026 (?)
Gem ± cisplatin (Heinemann, JCO 2006)	6.0	7.5	NS
Gem ± oxaliplatin (Louvet, JCO 2005)	7.1	9.0	NS
Gem ± oxaliplatin (Poplin, ASCO 2006)	4.9	5.9	NS
Gem ± cisplatin (Colucci, ASCO 2009)	8.3	7.2	NS
Gem ± erlotinib (Moore, JCO 2007)	5.9	6.4	0.011
Gem ± bevacizumab (Kindler, ASCO 2007)	6.1	5.8	NS
Gem ± cetuximab (Phillip, ASCO 2007)	5.9	6.4	NS

Gemcitabine + Cytotoxic vs Gemcitabine- Meta-analysis.

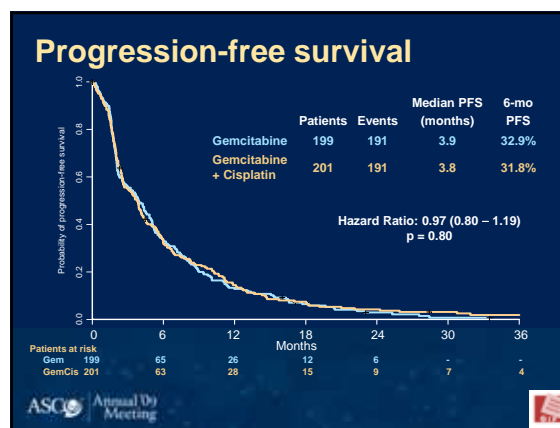
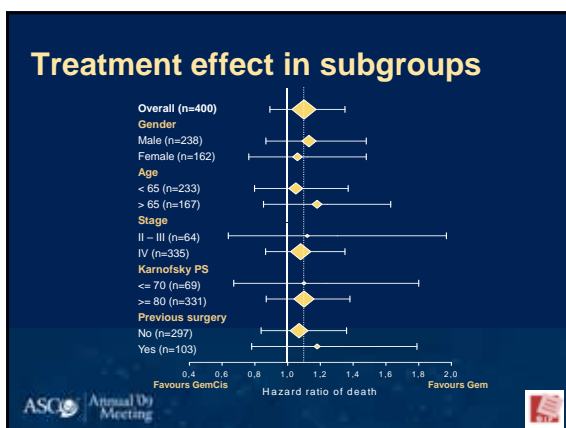
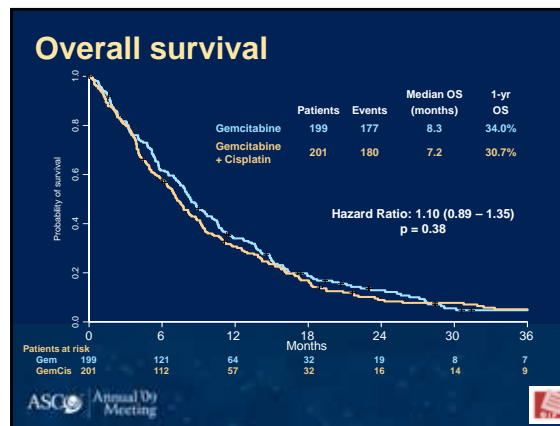
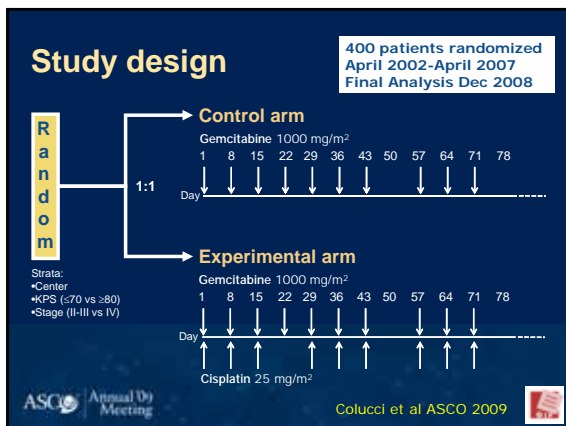
	HR Survival	P-Value	Number of Trials
Gem + platinum	0.85	0.01	5
Gem + 5-FU	0.90	0.03	6
Good PS 90%+	0.76	<0.0001	5
Poor PS 60- 80%	1.08	0.40	

Heinemann et al, BMC Cancer 2008



Gemcitabine + 'Encapsulated Paclitaxel'

	Median Survival (months)	PFS (months)	Response Rate	# of Patients
Gem + ENDO TAG	8.4-9.4	4.1-4.6	PR+SD 54%	150 3 arms
Gem + Albumin-bound Paclitaxel	9.0	5.4	RR 26% SD 41%	63



Clinical Benefit and Quality of life

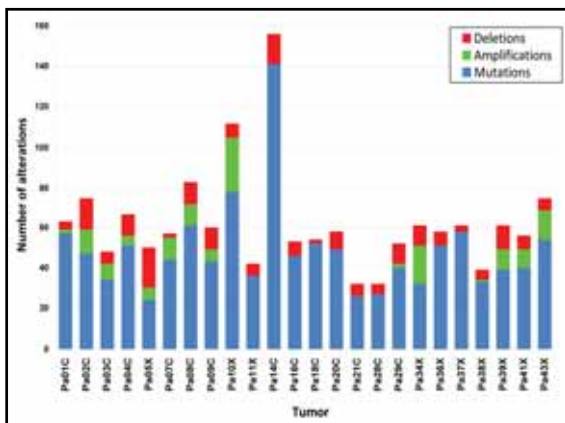
- Clinical Benefit 23% with gem and 15% with gem + cisplatin
- Changes from baseline after 4 weeks are described here
- Global QoL: trend favouring single-agent gemcitabine (p=0.07)
- Statistically significant differences:
 - Social functioning (worse with GemCis, p=0.01)
 - Hepatic symptoms (better with GemCis, p=0.01)

ASCO Annual Meeting

Targeted therapy and the genetics of pancreatic cancer.

- Sequencing of over 20,000 protein coding genes in 24 pancreatic cancers.
- Average number of genetic mutations was 63.
- Clustered into abnormalities in 12 core signaling pathways that were found in 67-100% of cases.
- However, marked heterogeneity in individual tumors both in which pathways affected and what the mutations in those pathways were.

Jones et al, Science 2008



Angiogenesis: CALGB 80303 Gemcitabine +/- Bevacizumab

	GEM + BEVACIZUMAB (n=302)	GEM ALONE (n=300)	HR	p
Median survival (mos)	5.8	6.1	1.03	0.78
PFS (months)	4.9	4.7	1.0	0.99
Response (%)				
CR + PR	11	10		
SD	36	31		

**Phase II : 8.7 mos median survival; 5.8 mos PFS
67% tumor control rate (PR+SD)**

Kindler HL et al. J Clin Oncol

Axitinib (TKI – VEGF, PDGF, c-kit) Phase II: key outcomes

	GEM +axitinib (n=69)	GEM (n=34)	HR	p
Median survival (months)	6.9	5.6	0.74	>0.10
PFS (months)	4.3	3.7	0.65	>0.10
Response (%)				
CR + PR	0	7		
SD	53	59		

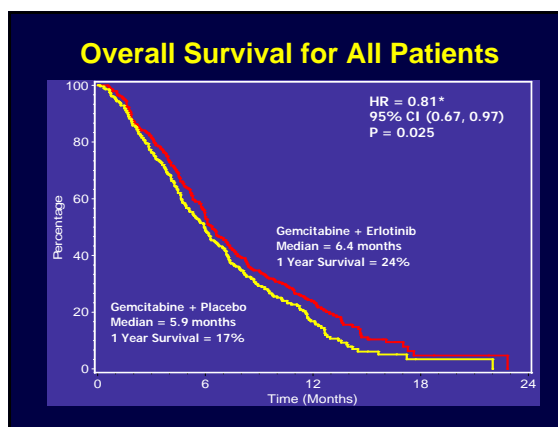
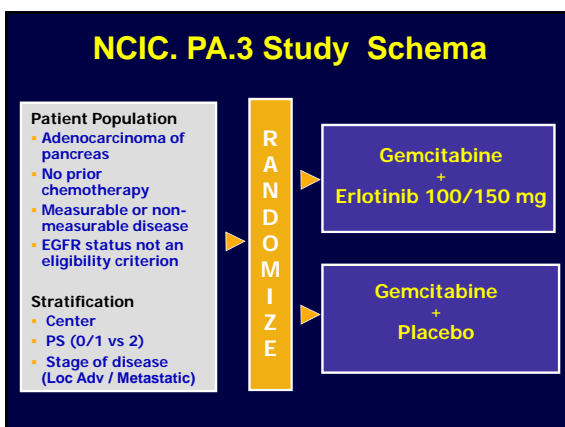
Phase III trial N=596 underway. ECOG PS 0/1 only.

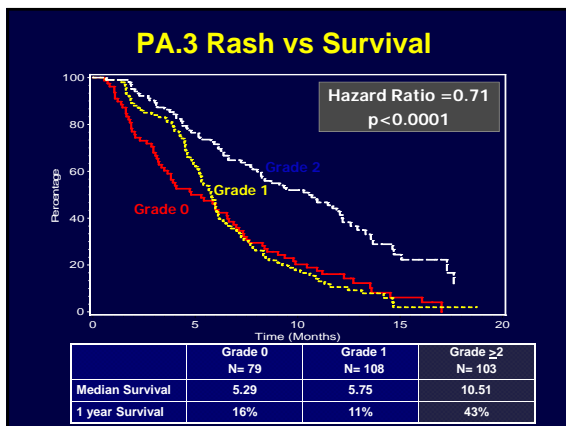
Feb 2 2009, 11:24 AM EST

Pfizer Halts Phase III Trial with Pancreatic Cancer Drug

GEN News Highlights

Pfizer is stopping Phase III development of axitinib for the treatment of advanced pancreatic cancer. The independent Data Safety Monitoring Board found no improvement in survival in patients treated with axitinib and gemcitabine compared to gemcitabine alone.

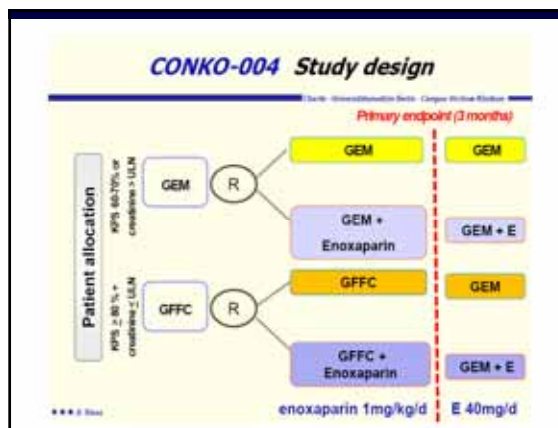
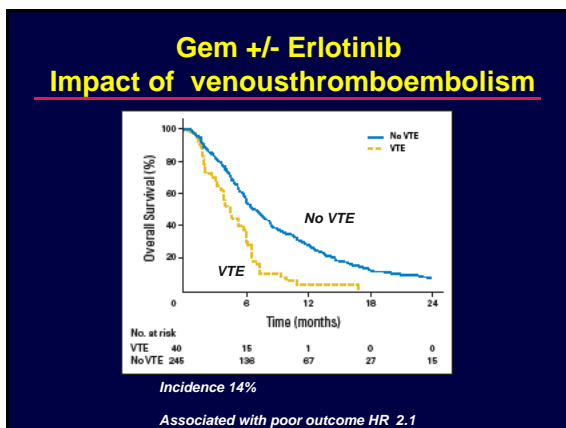




NCIC PA.3: K-ras, EGFR & Survival

- N= 569; 146 adequate specimens (26%)

	Gem + Erlotinib	Gem + Placebo	HR	P
K-ras WT (21%)	6.1 mths	4.5 mths	0.66	0.34
K-ras Mut (79%)	6.0 mths	7.4 mths	1.07	0.78
EGFR Pos (47%)	5.2 mths	5.2 mths	0.90	0.32
EGFR Neg (53%)	8.4 mths	6.7 mths	0.60	0.08



CONKO-004 VTE, Bleeding

Median follow-up 30.4 weeks

	E 8 (5.0 %)	O 22 (15.5 %)	Δ 10.5 %	p < 0.05
VTE				
Bleeding	E 10* (6.3 %)	O 15*# (9.9 %)	Δ 3.3 %	p = 0.6

Three letal bleedings (***)
 * 1 tumor-associated letal GI - bleeding, both in GFFC-treated pts. (12.4, 13.4 w)
 # 1 letal oesophageal hemorrhage in a Gem-treated pt. (16.7 w)

- ### The way forward in Clinical Research
- Test novel targets and combinations in the phase II setting.
 - No phase III studies without a clear signal from phase II.
 - Separate studies for locally advanced and metastatic disease.
 - Translational research is critical!!
 - Routine tissue collection in trials
 - We need to understand a lot more about biology