

# *Putting drug development into practice for Pancreatic Cancer:*



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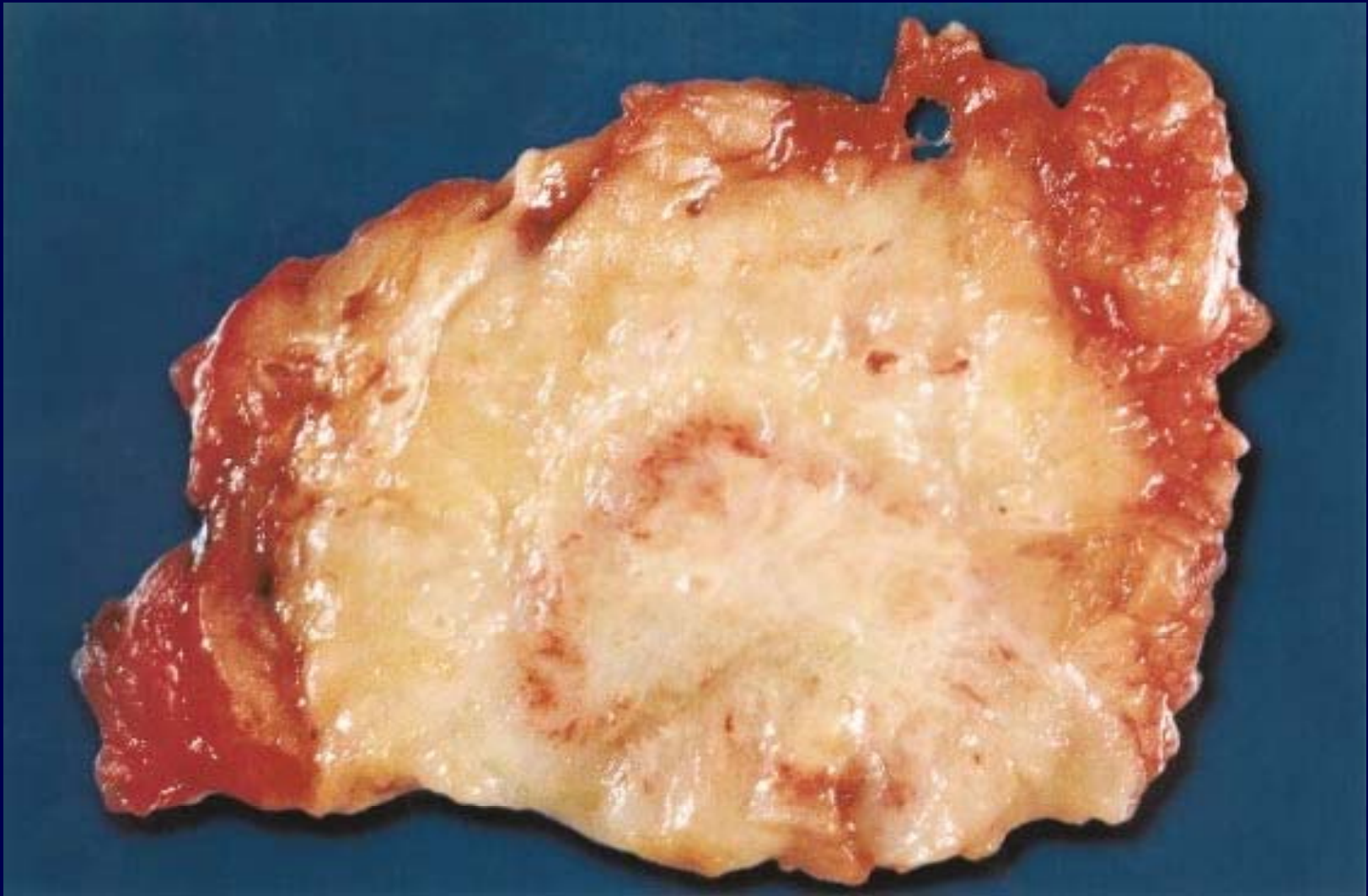
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# *My Mentors*





*Pancreatic Cancer – Ductal Adenocarcinoma*

# **Pancreatic cancer: a major therapeutic challenge**

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- **Major health burden**
  - fourth leading cause of cancer death in Canada
  - Affects over 3000 Canadians annually
- **Fatal disease with 98% mortality rate<sup>1,2</sup>**
  - overall survival rate is among the shortest of any solid tumour
- **Poor prognosis**
  - usually locally advanced or metastatic at diagnosis
  - most patients unsuitable for surgery

# Gemcitabine

## Registration Study in Pancreatic Cancer

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

† 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

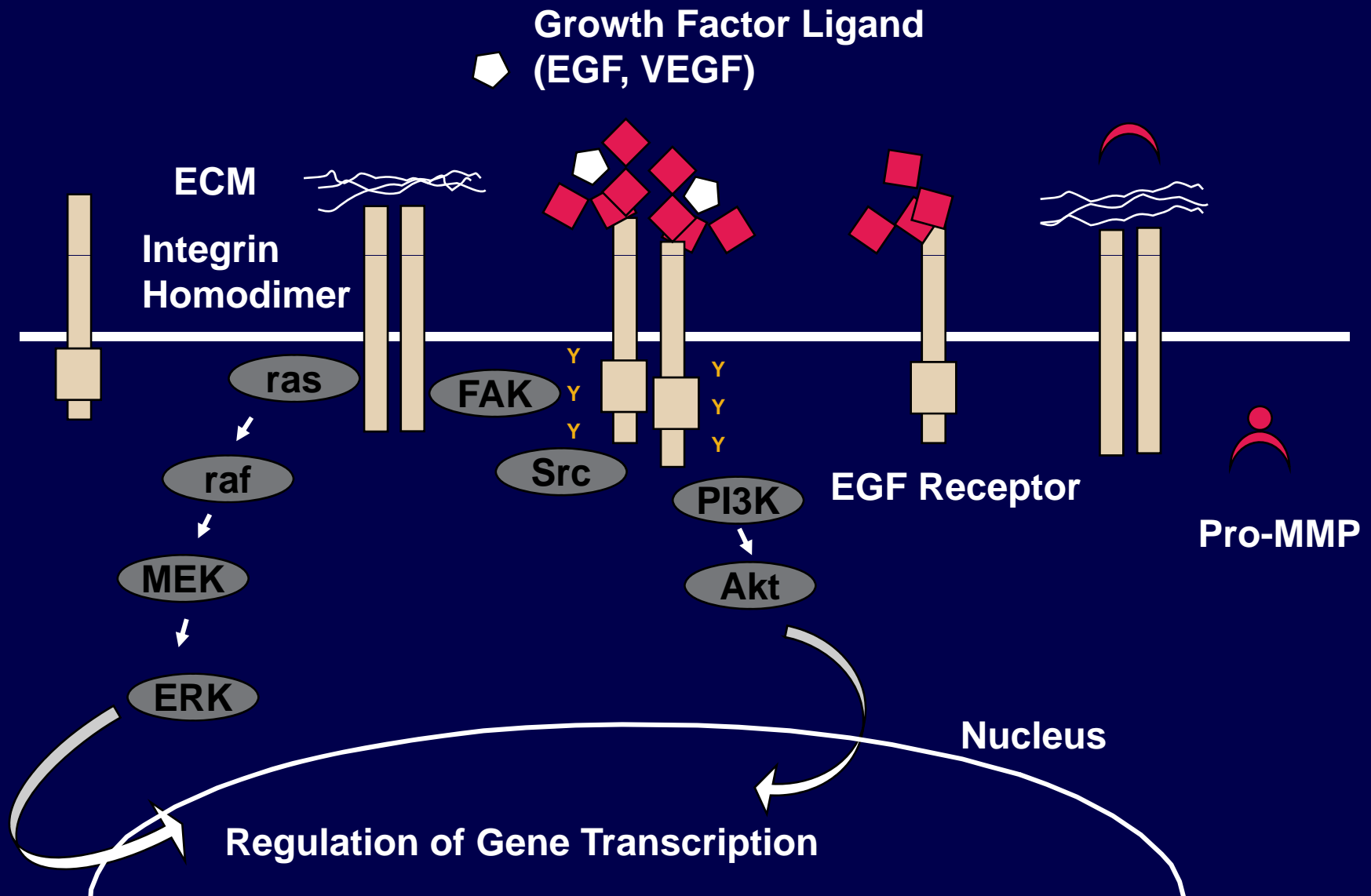
## Randomised phase III trials in pancreatic cancer (median overall survival in months)

	Gem	Gem + X	p value
<i>Gem ± exatecan (Abou-Alfa, JCO 2006)</i>	6.2	6.7	NS
<i>Gem ± CPT-11 (Rocha-Lima, JCO 2006)</i>	6.6	6.3	NS
<i>Gem ± pemetrexed (Oettle, Ann Oncol 2006)</i>	6.3	6.2	NS
<i>Gem ± 5-FU bolus (Berlin, JCO 2002)</i>	5.4	6.7	NS
<i>Gem ± capecitabine (Herrmann, JCO 2007)</i>	7.3	8.4	NS
<i>Gem ± 5-FU/LV (Riess, JCO 2005)</i>	6.2	5.9	NS
<i>Gem ± capecitabine (Cunningham, ECCO 2005)</i> <i>(preliminary results)</i>	6.0	7.4	0.026
<i>Gem ± cisplatin (Heinemann, JCO 2006)</i>	6.0	7.5	NS
<i>Gem ± oxaliplatin (Louvvet, JCO 2005)</i>	7.1	9.0	NS
<i>Gem ± oxaliplatin (Poplin, ASCO 2006)</i>	4.9	5.9	NS

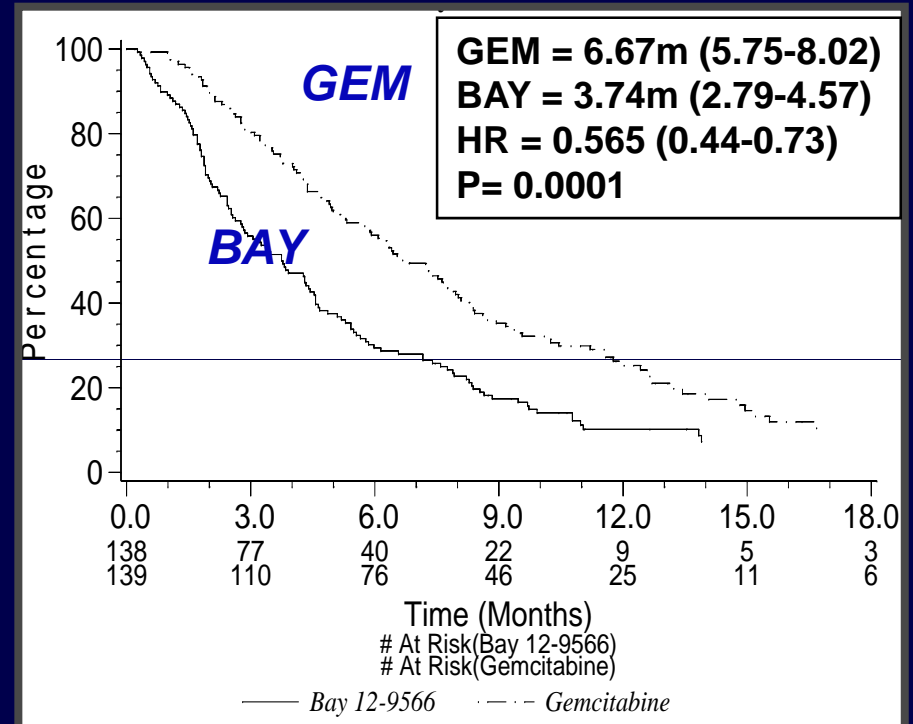
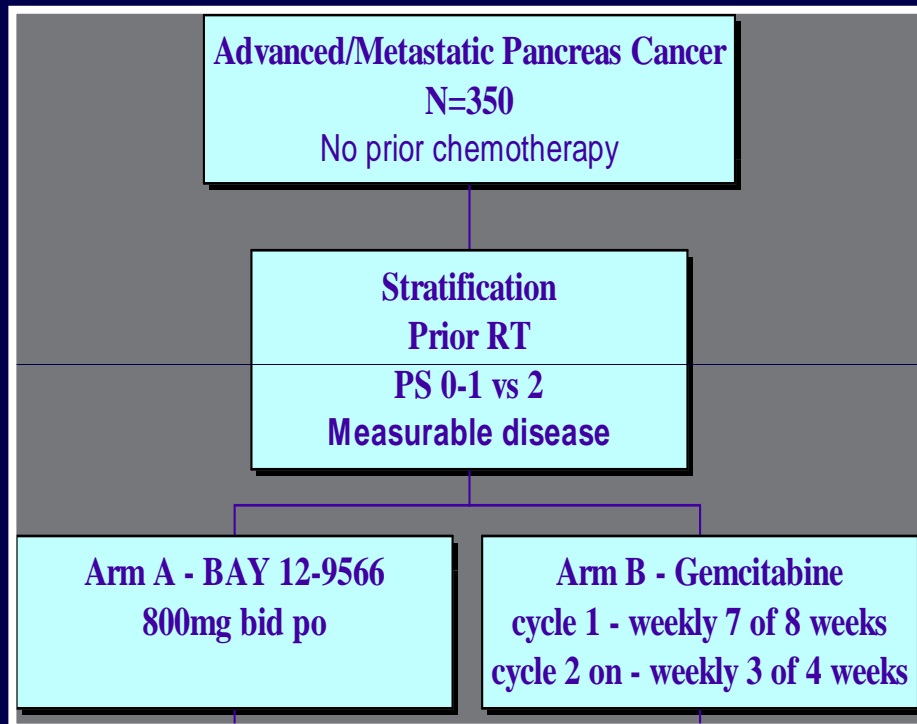
# Some key molecular abnormalities in Pancreatic Cancer

Oncogene	Relevance
<b>K-ras</b>	<ul style="list-style-type: none"> <li>● Noted in 75% to 90% of cases</li> <li>● 'Signature' defect of pancreatic cancer</li> </ul>
<b>Sonic Hedgehog</b>	<ul style="list-style-type: none"> <li>● Crucial role in embryological signaling</li> <li>● Evolving role in pancreas cancer</li> </ul>
<b>AURKA</b>	<ul style="list-style-type: none"> <li>● Encodes Aurora-A kinase</li> <li>● Overamplification - chromosomal instability</li> </ul>
Suppressor	Relevance
<b>CDKN2A/p16</b>	<ul style="list-style-type: none"> <li>● Normal function induces cell cycle arrest</li> <li>● Early event –enhances effect of K-ras</li> </ul>
<b>SMAD4</b>	<ul style="list-style-type: none"> <li>● Encodes transcription factor; lost in 50% cases</li> <li>● May also potentiate K-ras phenotype</li> </ul>
<b>p53</b>	<ul style="list-style-type: none"> <li>● Role in cell cycle arrest and apoptosis</li> <li>● Loss contributes to chromosomal instability</li> </ul>

# Pancreatic Cancer: Other Molecular Targets



# Gemcitabine vs MMPI: NCIC.PA1

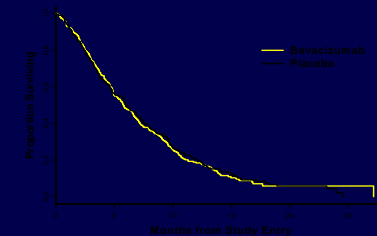


- ***Survival of untreated metastatic disease is short.***
- ***Salvage of patients with crossover not possible.***
- ***Gemcitabine needs to be included in all treatments.***

# 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)**

# NCIC. PA.3 Study Schema

## Patient Population

- Adenocarcinoma of pancreas
- No prior chemotherapy
- Measurable or non-measurable disease
- EGFR status not an eligibility criterion

## Stratification

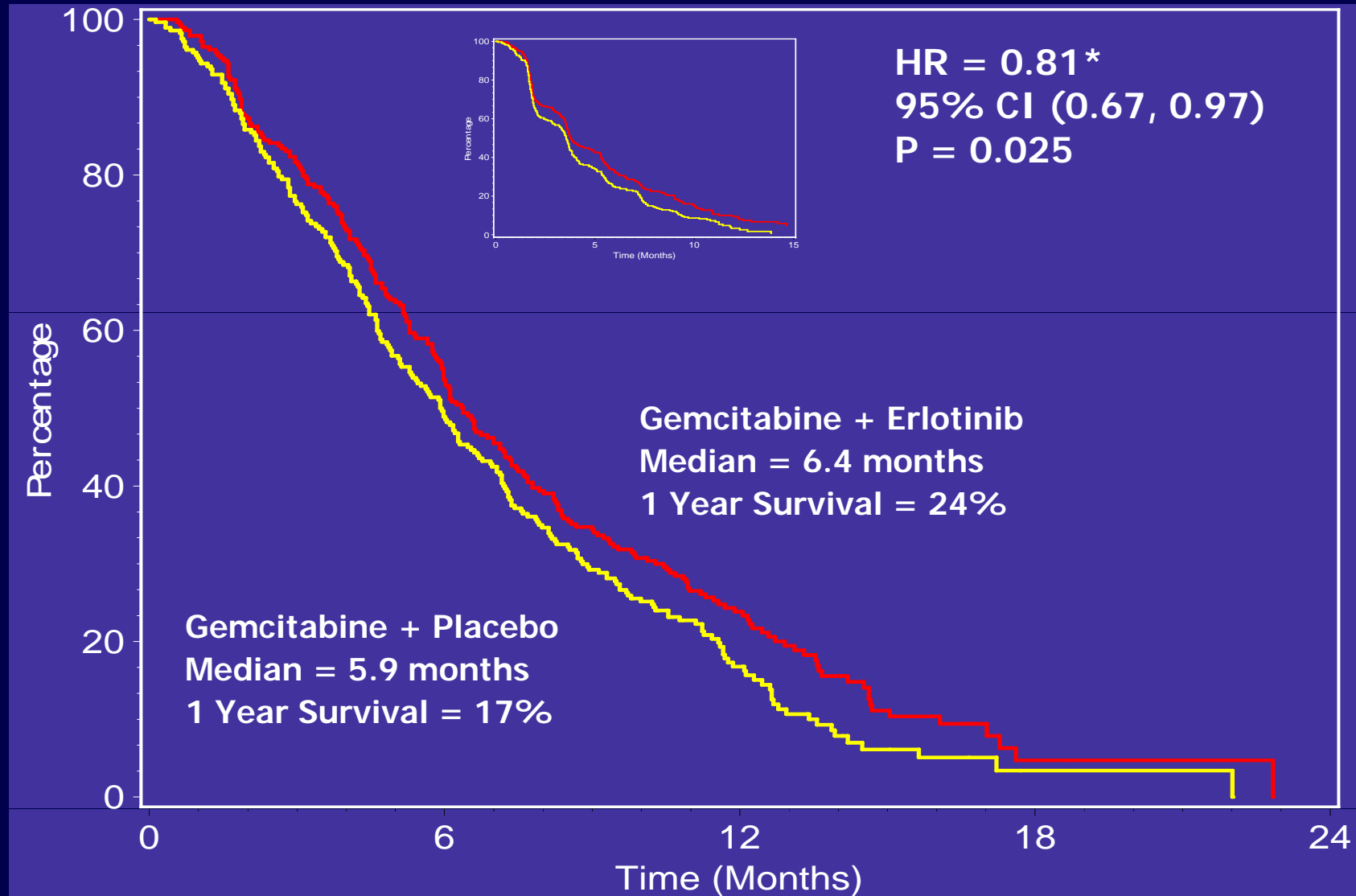
- Center
- PS (0/1 vs 2)
- Stage of disease (Loc Adv / Metastatic)

R  
A  
N  
D  
O  
M  
I  
Z  
E

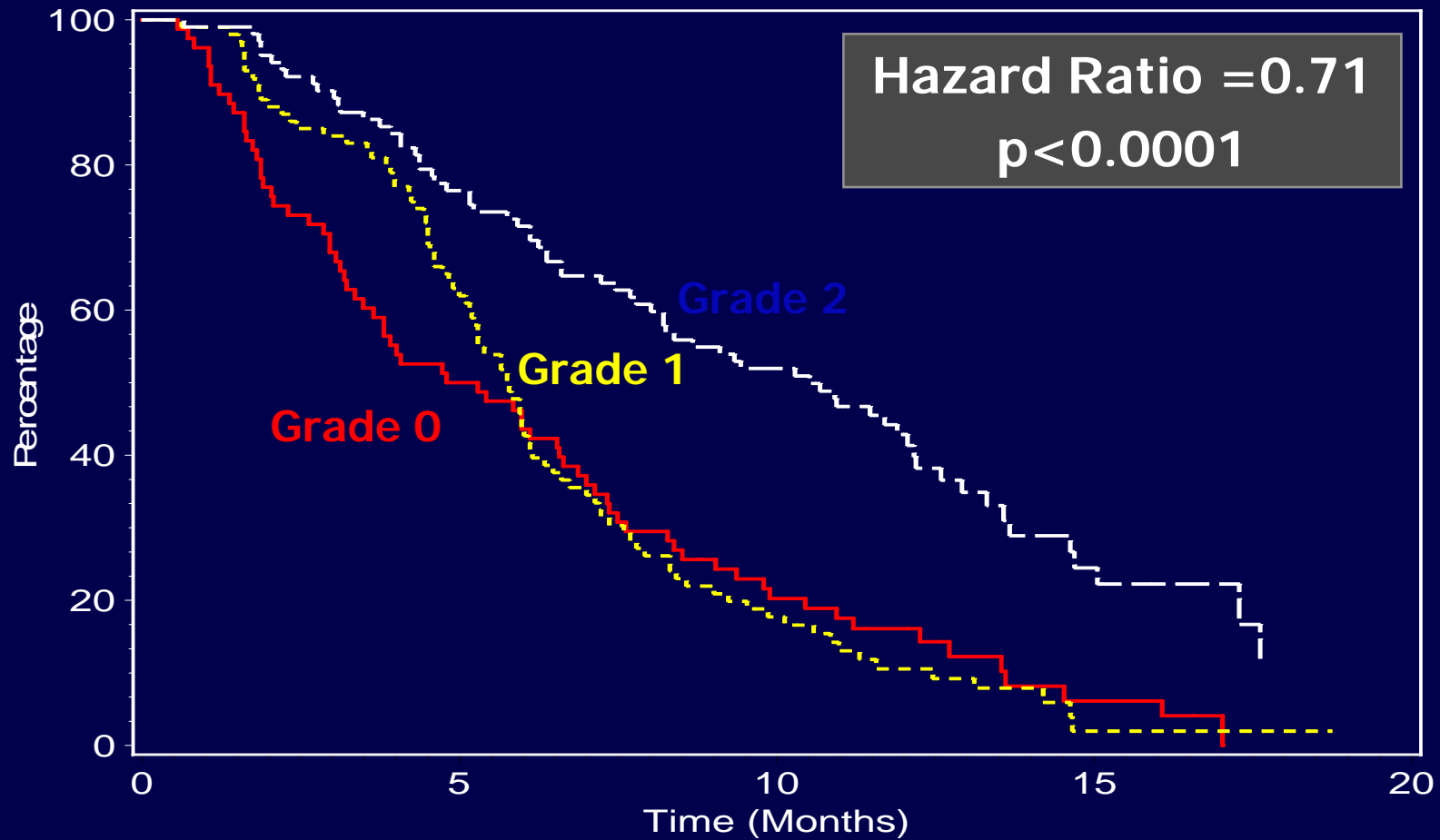
Gemcitabine  
+  
Erlotinib 100/150 mg

Gemcitabine  
+  
Placebo

# Overall Survival for All Patients



# PA.3 Rash vs Survival



	<b>Grade 0</b> N= 79	<b>Grade 1</b> N= 108	<b>Grade <math>\geq 2</math></b> N= 103
<b>Median Survival</b>	<b>5.29</b>	<b>5.75</b>	<b>10.51</b>
<b>1 year Survival</b>	<b>16%</b>	<b>11%</b>	<b>43%</b>

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

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

	Gem + Erlotinib	Gem + Placebo	HR	P
K-ras WT (21%)	6.1 mths	4.5 mths	<u>0.66</u>	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	<u>0.60</u>	0.08

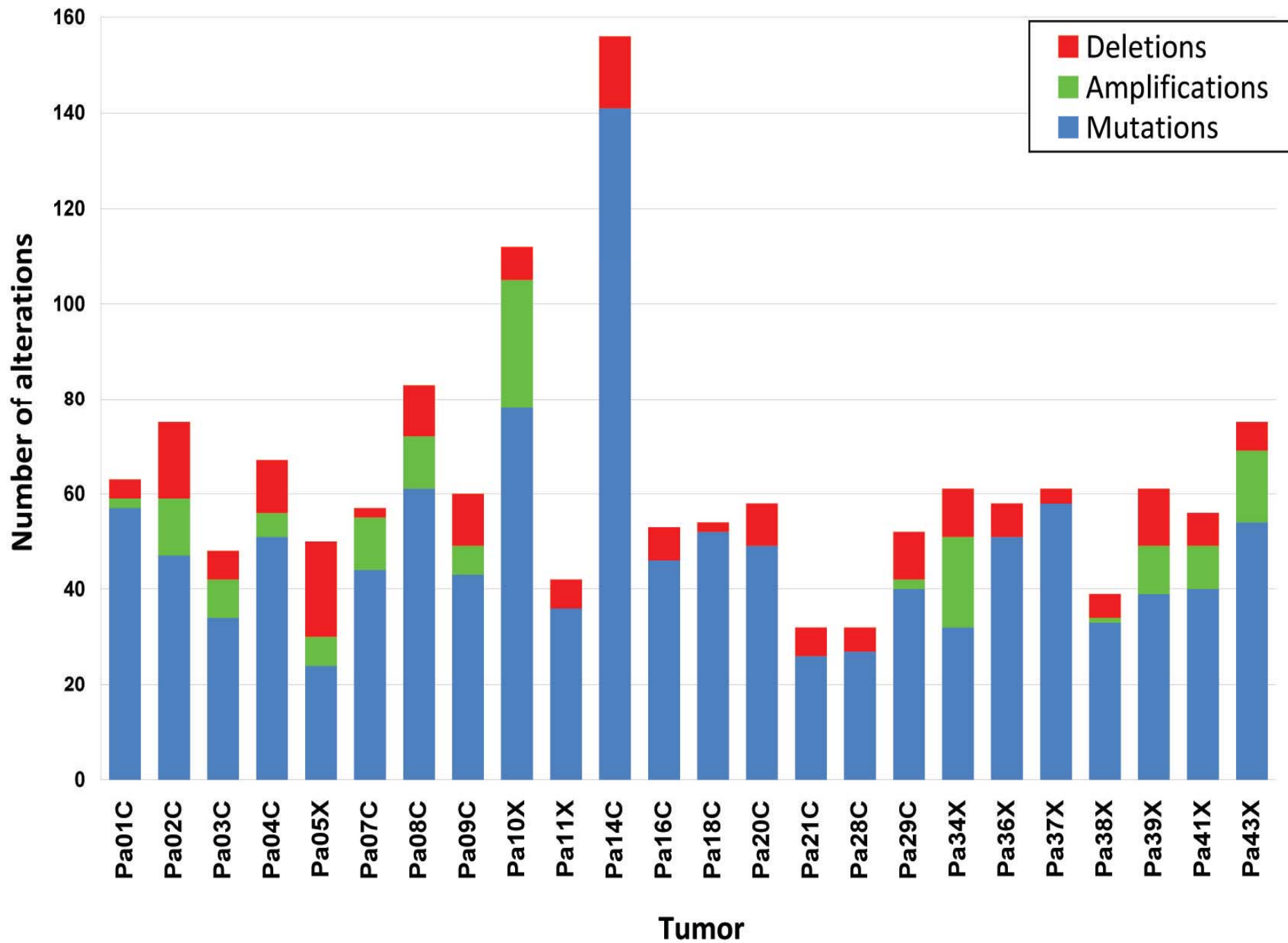
# Going forward

## Understanding the genetics.

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- 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*



# Drug Development – the future

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- **This is not CML or GIST.**
- **Targeting individual pathways such as EGFR, hedgehog less likely to be successful than focussing on downstream effects.**
- **Multiple agents likely to be needed.**
- **Therapy needs to be individualized**
- **We need to link biology and genomics with therapy to move forward.**