



# Pancreatic Cancer

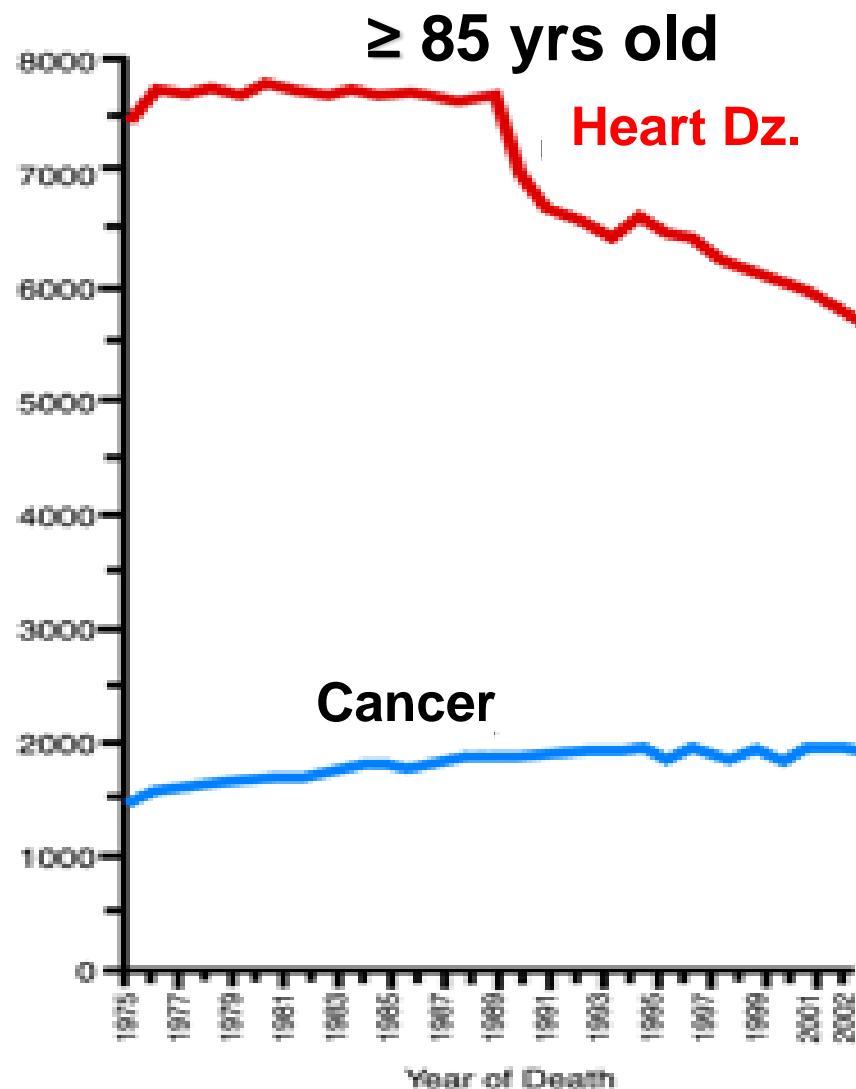
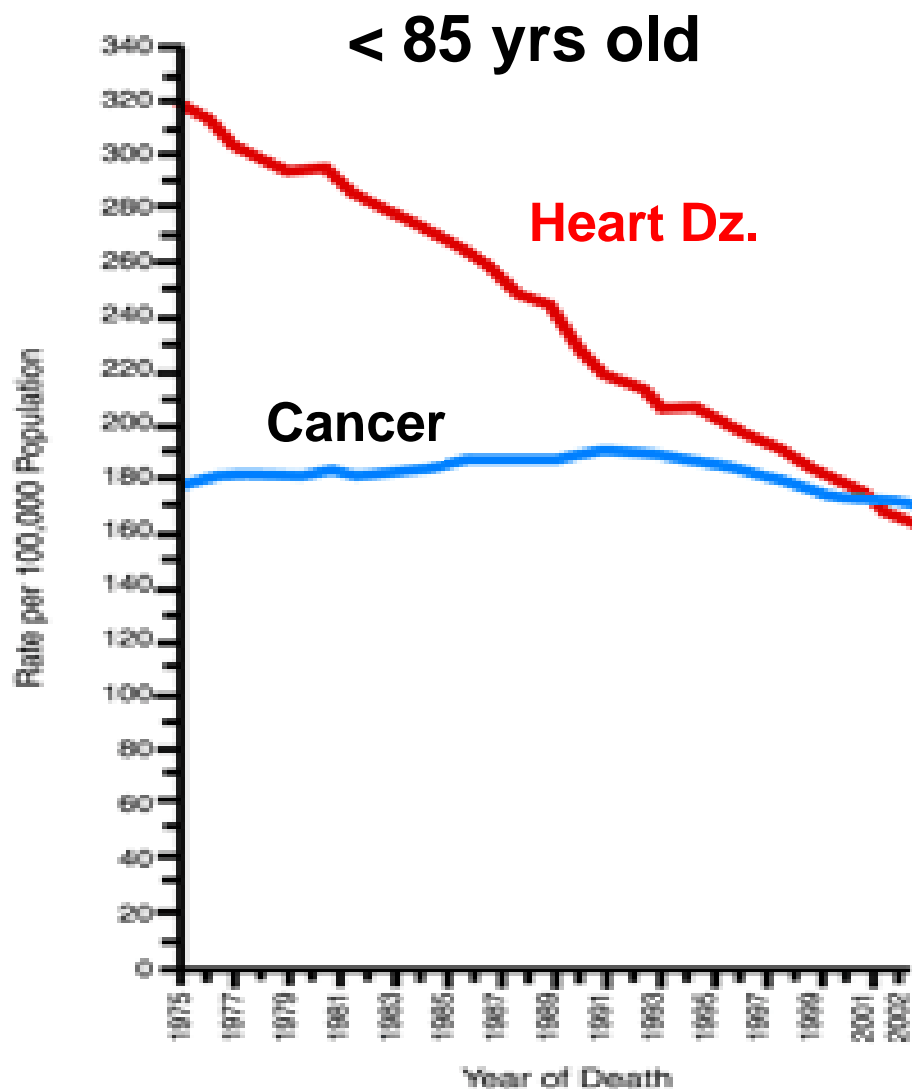
Weijing Sun, MD  
University of Pennsylvania  
Cancer Center



# Death Rates from Cancer and Heart Disease (<85 yrs. vs. ≥ 85 yrs Old)



Jemal A et al. CA Cancer J Clin 2006; 56:106

<http://caonline.amcancersoc.org/cgi/content/full/56/2/106>





# 2009 Estimated US Cancer Deaths

## Estimated New Cases\*

			Males	Females			
Prostate	192,280	25%			Breast	192,370	27%
Lung & bronchus	116,090	15%			Lung & bronchus	103,350	14%
Colon & rectum	75,590	10%			Colon & rectum	71,380	10%
Urinary bladder	52,810	7%			Uterine corpus	42,160	6%
Melanoma of the skin	39,080	5%			Non-Hodgkin lymphoma	29,990	4%
Non-Hodgkin lymphoma	35,990	5%			Melanoma of the skin	29,640	4%
Kidney & renal pelvis	35,430	5%			Thyroid	27,200	4%
Leukemia	25,630	3%			Kidney & renal pelvis	22,330	3%
Oral cavity & pharynx	25,240	3%			Ovary	21,550	3%
Pancreas	21,050	3%			Pancreas	21,420	3%
<b>All Sites</b>	<b>766,130</b>	<b>100%</b>			<b>All Sites</b>	<b>713,220</b>	<b>100%</b>

## Estimated Deaths

			Males	Females			
Lung & bronchus	88,900	30%			Lung & bronchus	70,490	26%
Prostate	27,360	9%			Breast	40,170	15%
Colon & rectum	25,240	9%			Colon & rectum	24,680	9%
<u>Pancreas</u>	<u>18,030</u>	<u>6%</u>			<u>Pancreas</u>	<u>17,210</u>	<u>6%</u>
Leukemia	12,590	4%			Ovary	14,600	5%
Liver & intrahepatic bile duct	12,090	4%			Non-Hodgkin lymphoma	9,670	4%
Esophagus	11,490	4%			Leukemia	9,280	3%
Oral cavity & pharynx	10,180	3%			Uterine Corpus	9,780	3%
Non-Hodgkin lymphoma	9,830	3%			Liver & intrahepatic bile duct	6,070	2%
Kidney & renal pelvis	8,160	3%			Brain & other nervous system	5,590	2%
<b>All Sites</b>	<b>292,540</b>	<b>100%</b>			<b>All Sites</b>	<b>269,800</b>	<b>100%</b>

GI Cancer 25%

GI 130,000  
24%

GI cancer 22%



Singer Luciano Pavarotti



Actor Patrick Swayze

Supreme Court Justice  
Bader Ginsburg



# Pancreatic Adenocarcinoma

- Cure is rare and only seen in resected patients
- 15 - 20 % resectable tumors
  - 1/5 have longterm survival
  - 3 - 4% five year survival

# Risk Factors

- Cigarette Smoking                      RR = 1.3-5.6
- Dietary Fat/Chol/Meat              RR = ?
- Diabetes ( > 1 yr before)      RR = ~ 2.0
- Pancreatitis (Tropical, familial, chronic)
- Other factors



Normal PanIN-1A PanIN-1B PanIN-2 PanIN-3

Her-2/neu  
K-ras

p16

p53  
DPC4  
BRCA2

# Clinical Presentation

- Early Presentation: Non-specific
  - Fatigue
  - Weight loss
  - Mal-digestion
- Tumor location within pancreas
  - Compression of bile duct → jaundice (head lesions)
  - Compression splanchnic/mesenteric plexus → back pain or epigastric pain (body lesions)
  - Pancreatitis
    - Chronic
    - acute

# Clinical Management

I. Resectable Pancreatic Cancer

II. Locally Advanced, Unresectable Tumors

III. Metastatic Disease

## II. Locally Advanced Unresectable

- Radiographic evidence vascular encasement
- Peripancreatic lymphadenopathy within radiation port
- No evidence of distant metastatic disease (liver, lung, peritoneum)

### III. Metastatic Disease

- Disease characterized by pain, weight loss, poor energy.
- Single agent chemotherapy trials occasionally show RR > 15%, but none reproducibly.
- Benefits of combination? Role of biological agents?

# Terminology/Language

How much do we understand? Are we on the same page?

- *Stage; Early, late...*
- *Prognosis; Advanced vs. metastatic/Spread out...*
- *Cure, control, palliative...*
- *Treatment, Therapy...*
- Chemotherapy
- “Experimental”:  
Any therapy has not been proven to have “activity” or “benefit” in pancreatic cancer: as single agent or as ‘Combination, drugs may be approved for other diseases
- “Activity”:  
usually means tumor shrinkage or stabilization
- “Benefit”:  
patient feels better or lives longer and worth it (without terribly toxic).

# Chemotherapy

- 5-Fluorouracil
- Mitomycin C
- Doxorubicin
- Cisplatin
- *Gemcitabine*
- Docetaxel
- Irinotecan
- Oxaliplatin

# Gemcitabine in Pancreatic Cancer

- Gemcitabine (2', 2'-difluorodeoxycytidine)
  - To mono-, di- and tri-phosphated gemcitabine.
  - Diphosphated inhibits ribonucleotide reductase
  - Triphosphated competes with deoxycytidine triphosphate for incorporation into DNA.
  - **1<sup>st</sup> line for advanced pancreatic cancer since 1998**
    - **Superior to 5-FU** (Burris HA, et al J Clin Oncol. 1997 15:2403)
      - **RR: 23.8% vs. 4.8% (p=0.0022)**
      - **MS: 5.65mo. Vs. 4.41mo. (p=0.0025)**
      - **1-yr. survival: 18% vs. 2%**
  - Fixed-dose-infusion may increase clinic effect since phosphorylation is rate-limited (Tempero M J Clin Oncol. 2003 Sep 15;21(18):3402)

# 'Experimental' Therapy

**"All drugs are poisonous.  
Its only a matter of the dose."**

**The Third Defense, 1537**

# Experimental and 'Phase' of Study

- **Phase I:**
  - 'Safety Analyses' and 'Dose Finding' of New Drug (new testing on human based on preclinic and xenograft data)
  - MTD (maximal tolerable dose), DLT (dose-limited toxicity)
  - Activity → 'secondary'
- **Phase II:**
  - Activity assessment of new drugs in selected patient population and disease (pancreatic cancer)
- **Phase III:**
  - Comparison of new drug(s) with current 'standard' care regimen
- **Post-Marketing (Phase IV):**
  - Confirming the efficacy of newly approved drug (regimen) in larger population.

# 'Chemotherapy' vs. Target Therapy

- Cytotoxic (Traditional) Chemotherapy:
  - 'Poisoning' Tumor Cells – attack DNA, RNA, protein synthesis and function
  - Classes of drugs:
    - Synthetic chemicals
    - Semi-synthetic or Natural Products
  - **Toxicity:**  
**HOST EFFECTS: Cell Multiplication → many NL cells; particularly those with a rapid rate of turnover, Bone Marrow and Mucous Membrane...**
- Antibiotics, enzymes.
- Hormonal and biological agents

# Target Therapy

- Not intended to 'Kill' the tumor/cancer cell directly
- Rationally designed to attack 'pathway'/proteins within the tumor cells to prevent it from dividing and spread, or stimulate the programmed 'nature death' (apoptosis)
- Also work to change interactions between tumor cells and normal cells such as tumor's blood supply
- Side effects are different than cytotoxic chemotherapy : skin rash/reactions, vascular events,
- In some cancers, these drugs alone can work miraculously

# Experimental Principles

- Pancreatic Cancer is usually a systemic disease which tends to spread into the liver, lung, bone, and belly.
- Generally experimental drugs are given “systemically”.
  - Go through blood stream to Liver, Lung, Bone, Belly
- Preliminary drug testing is often offered to patients who have exhausted the standard regimens.

# Gemcitabine Combinations in Pancreatic Cancer

---

- Gemcitabine + 5-FU (IV or PO)
- Gemcitabine + Cisplatin
- Gemcitabine + Irinotecan or Rubitecan
- Gemcitabine + Docetaxel
- Gemcitabine + Oxaliplatin
- Gemcitabine + Target Oriented agents....

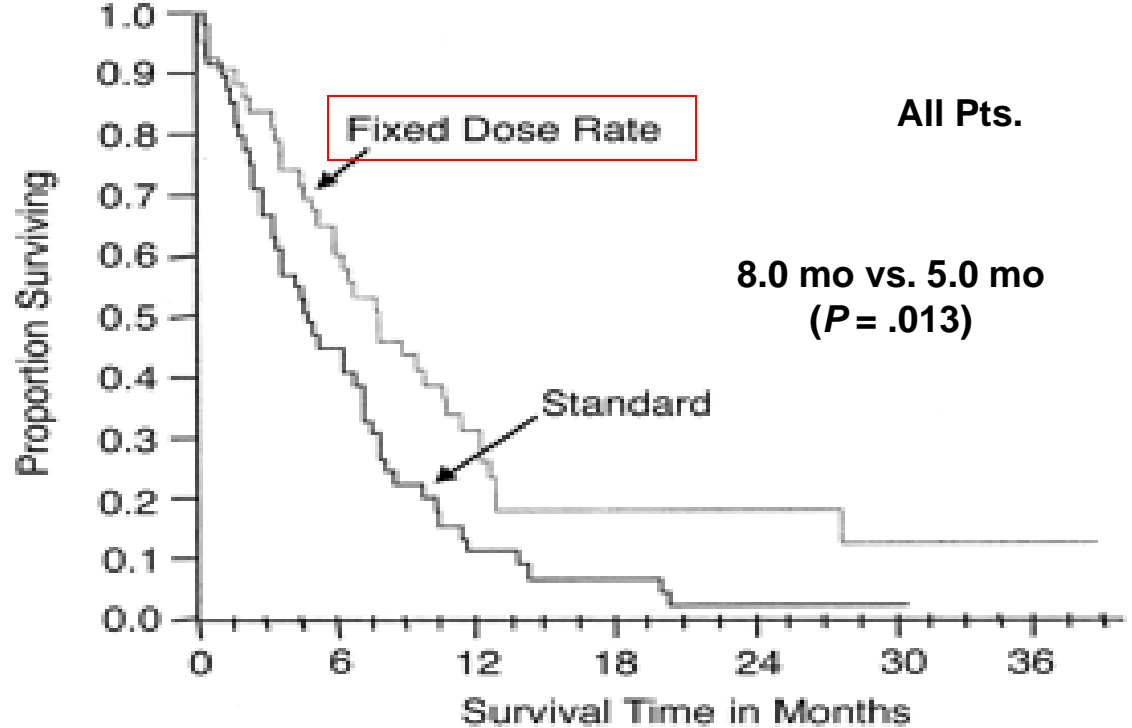
# Gem vs. FDR Gem

## Survival

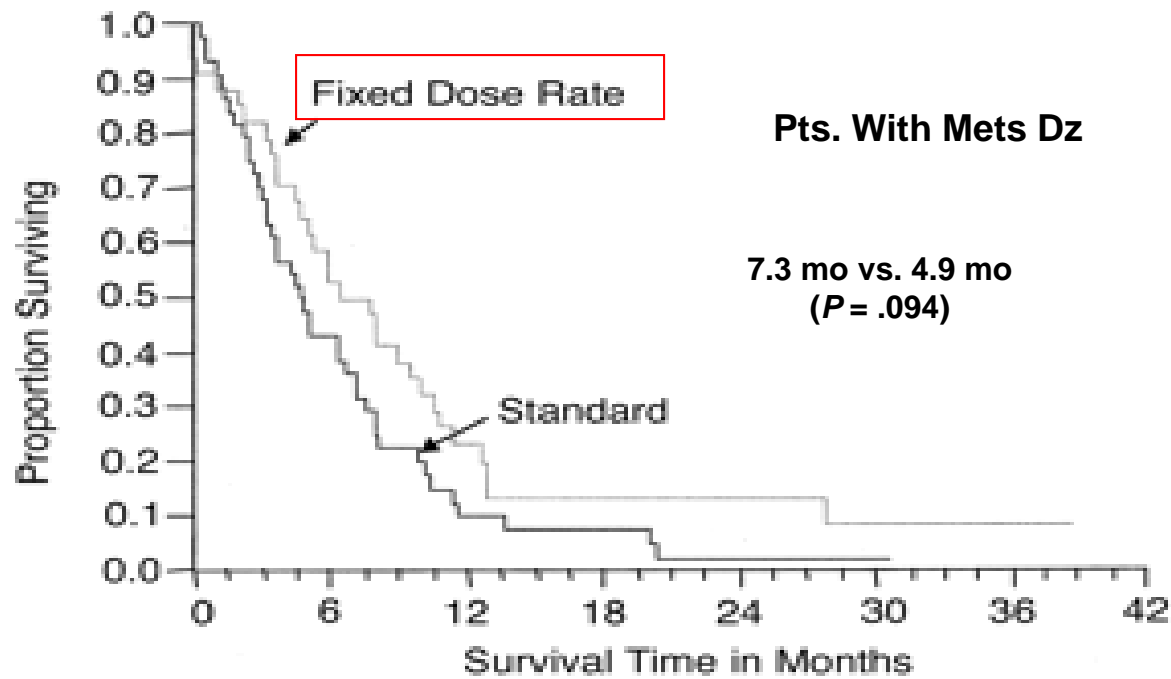
	Std.	FDR	<i>P</i>
1-Yr (%)	9	28.8	.014
2-Yr (%)	2.2	18.3	.007

JCO. 2003, 21(18):3402

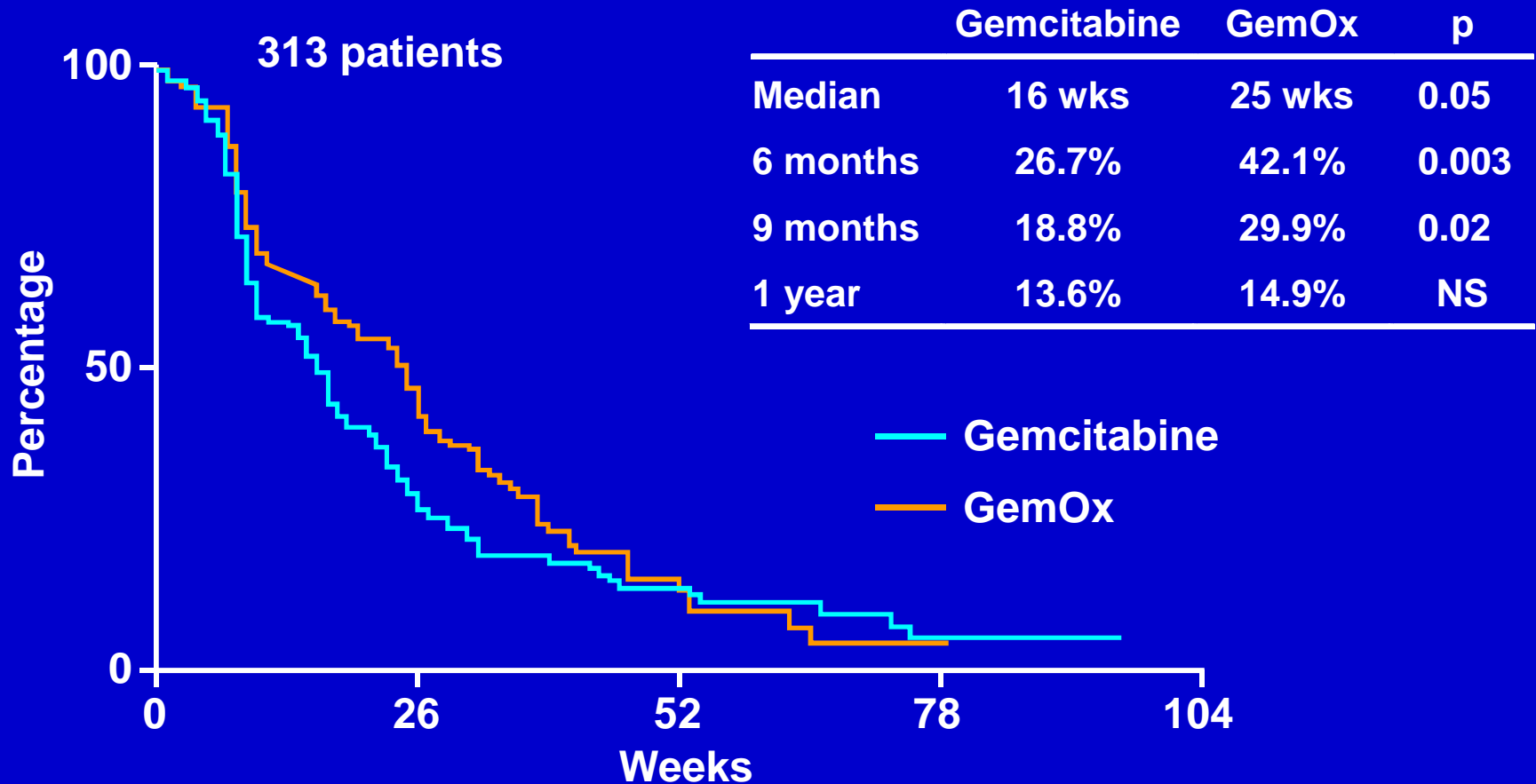
**A**



**B**

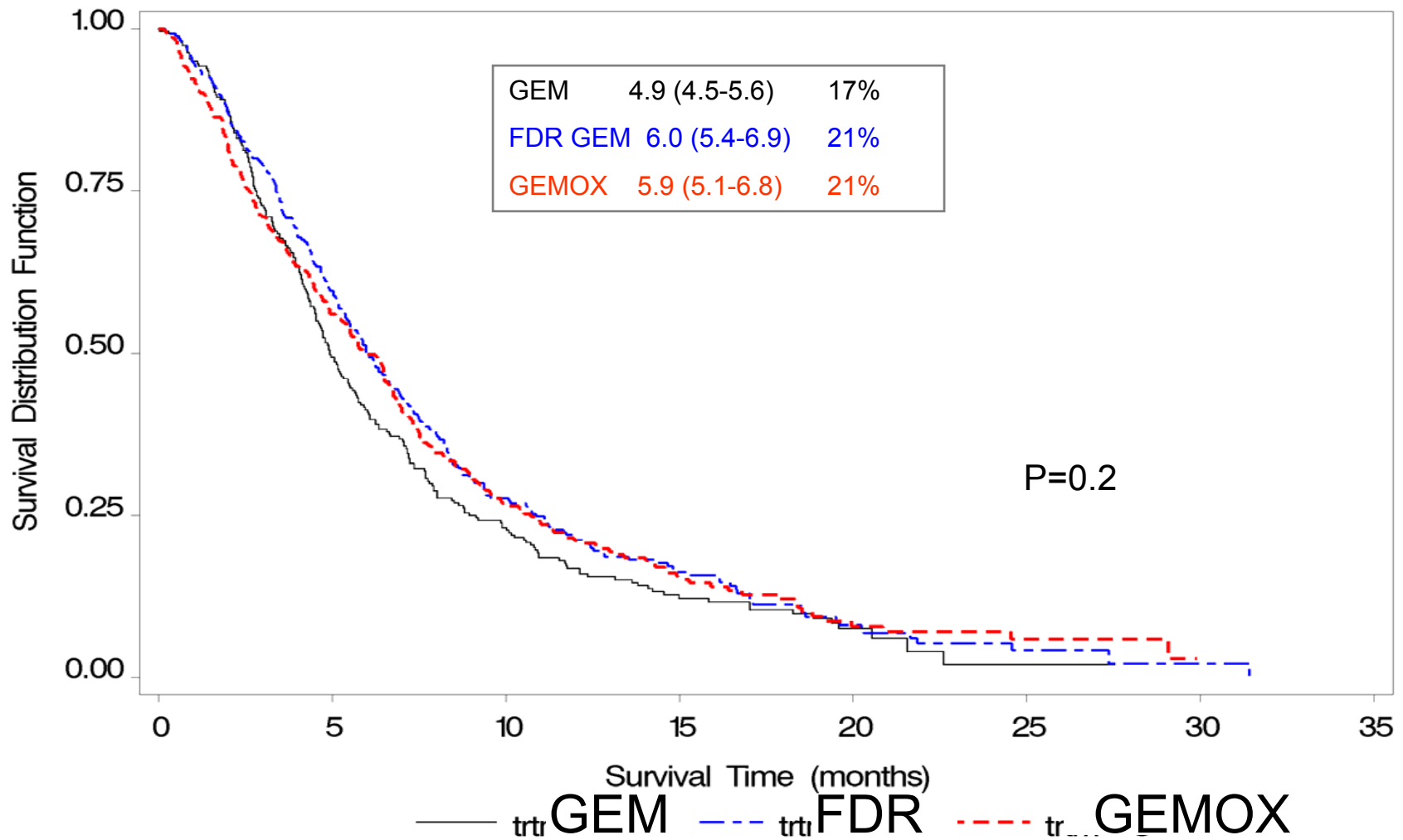


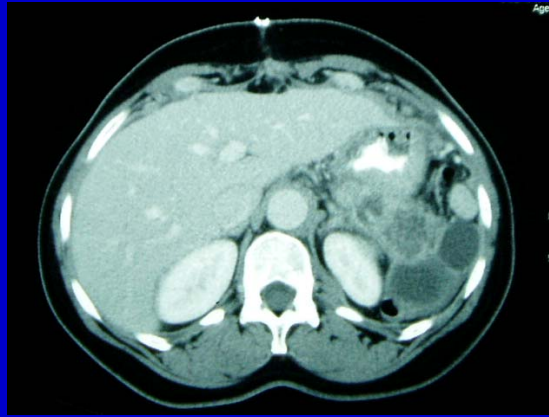
# Gem-GemOx study: Progression-Free Survival



# Survival by Treatment

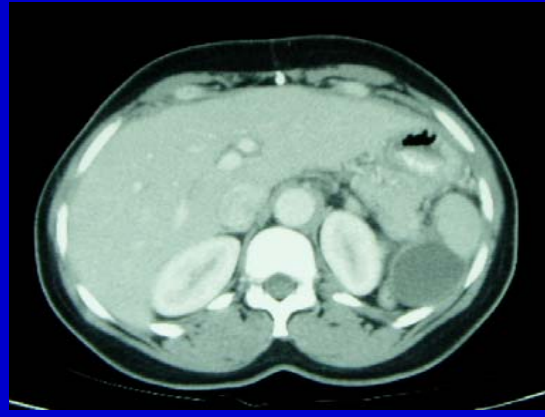
Overall Survival By Treatment





**Before Treatment**

**CA:19-9: 449**



**After 6 Cycles of Tx**

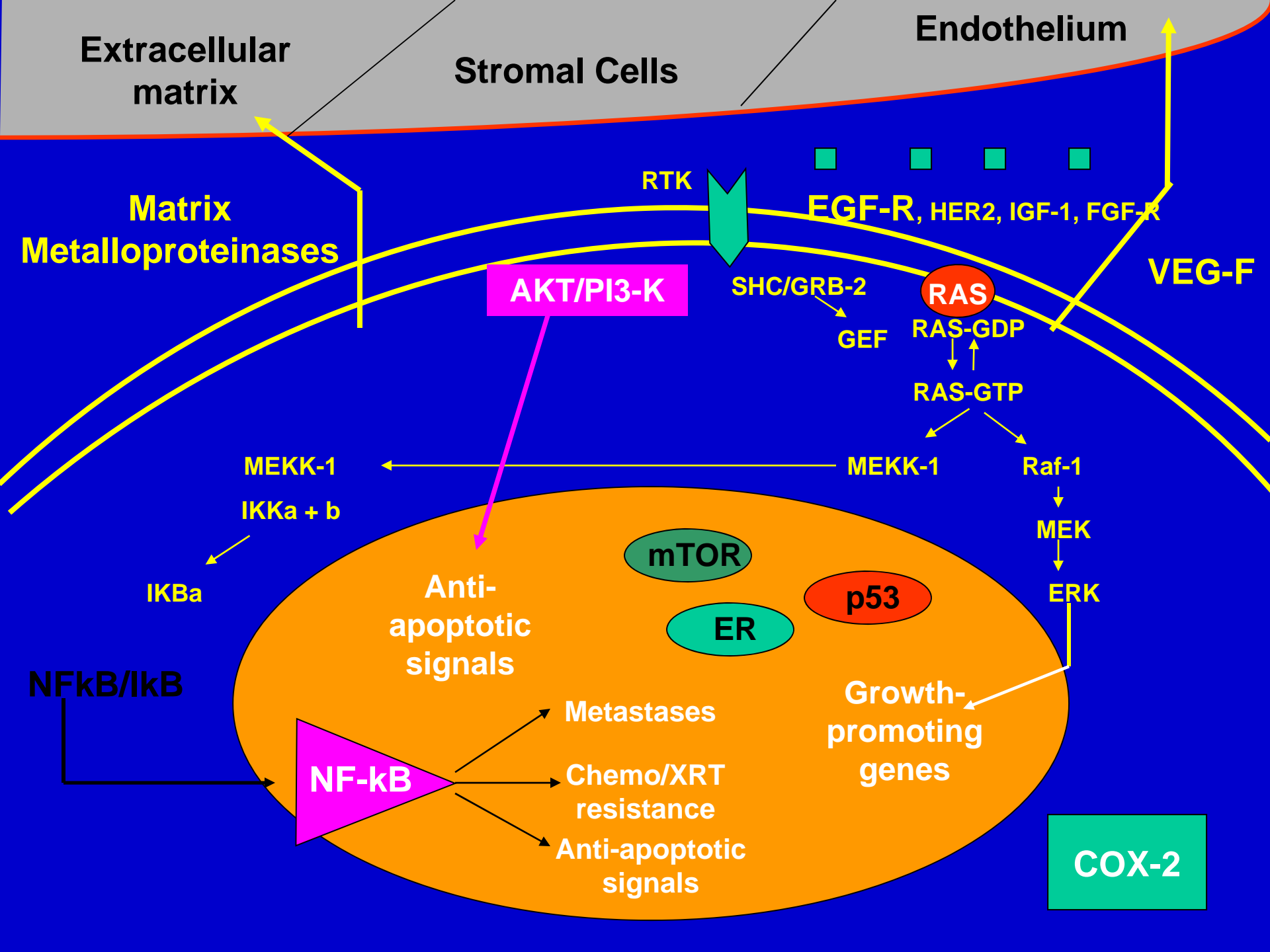
**CA:19-9: 19**



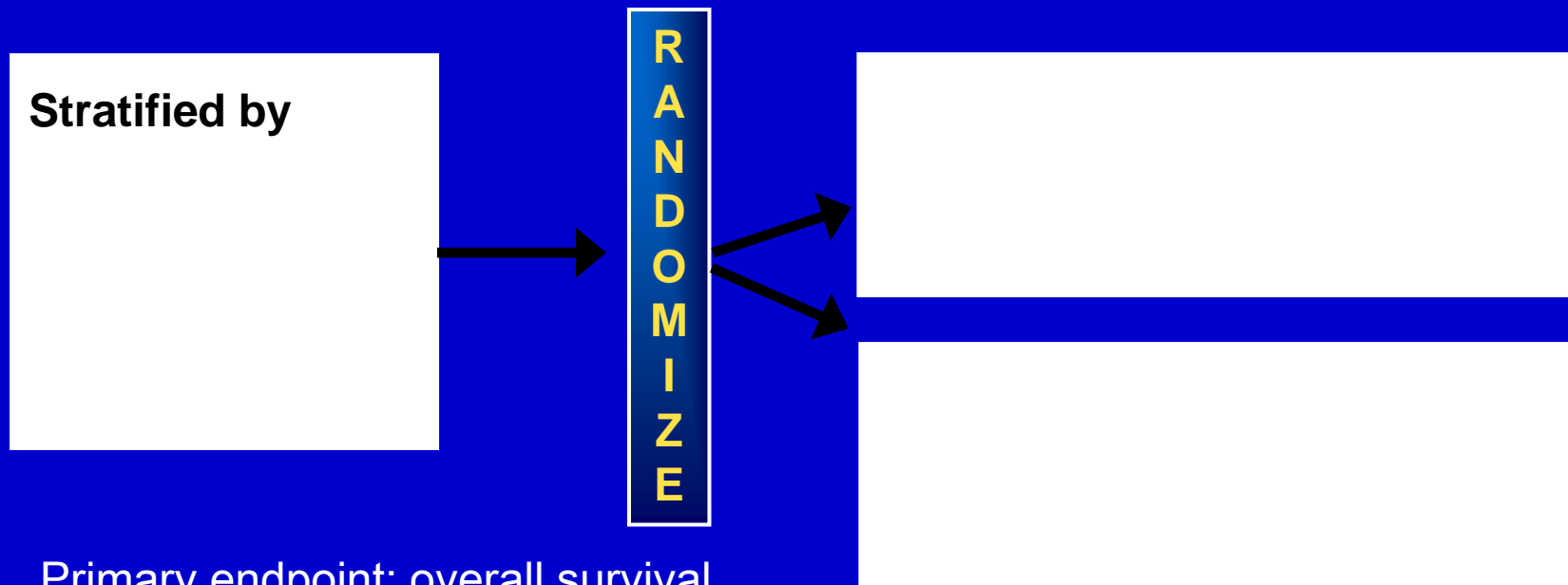
**After 22 Cycles of Tx**

**CA:19-9: NL**

**Gemcitabine and Irinotecan**



# NCIC PA.3: Treatment Schema



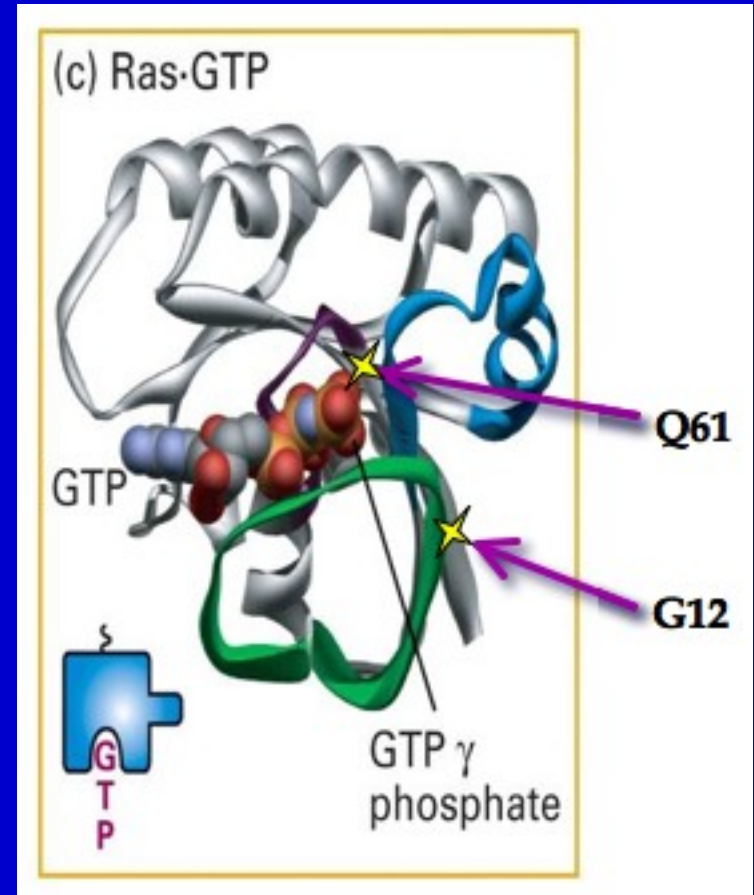
- Primary endpoint: overall survival
- Secondary endpoints: response rate and PFS
- Other endpoints: duration of response

\*A small proportion of patients (N=24 in each arm) received Erlotinib 150 mg/day.

PFS=progression-free survival.

# K-ras is an appropriate target for immunotherapy

- Missense mutation in *ras* oncogene in >90% of PanCA specimens
- Constitutively activates EGFR pathway
- Occurs early, and may be necessary, to malignant transformation of ductal cells



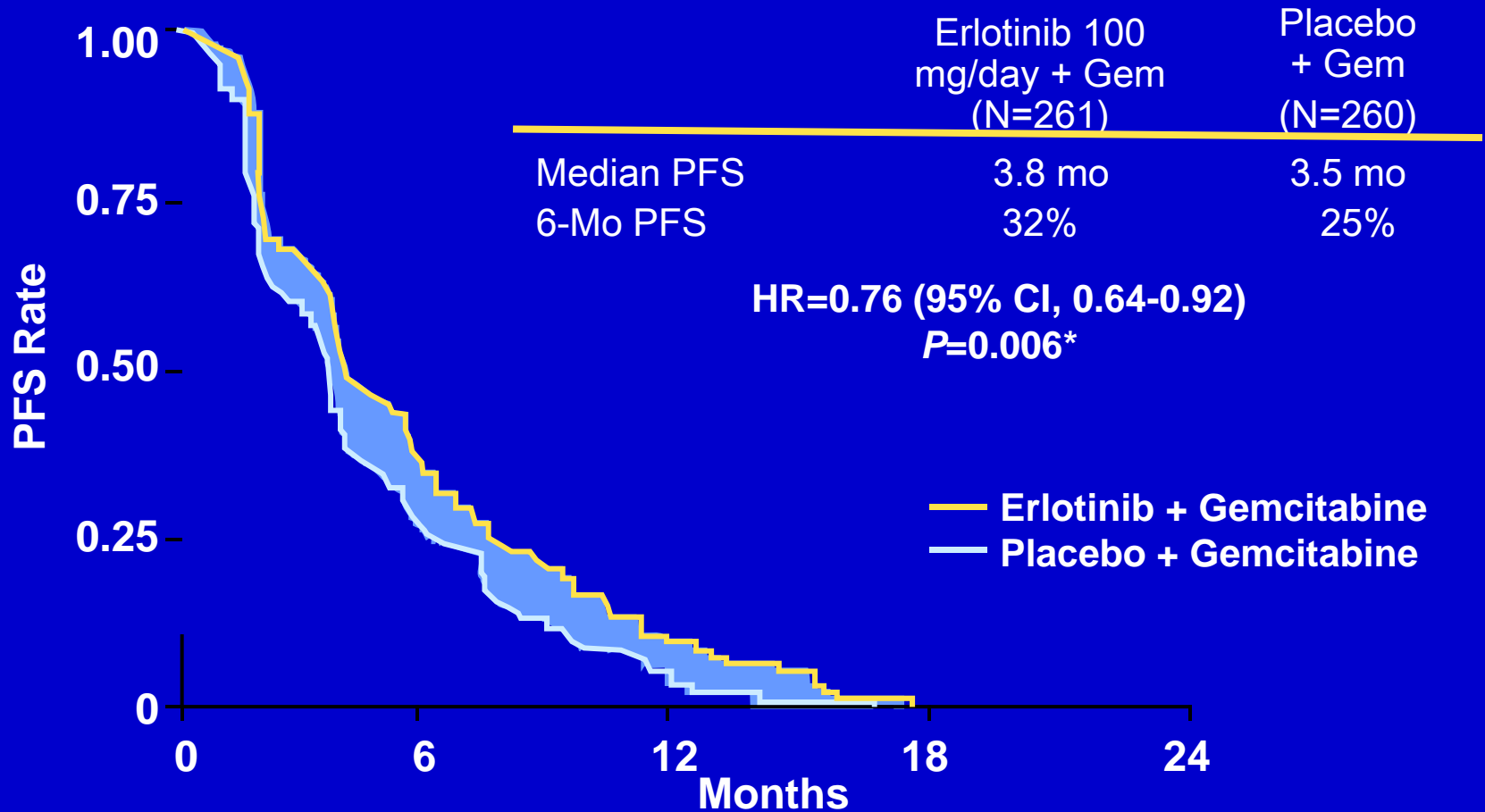
Almoguera *et al*, *Cell* **53**, 549 (1988).

Klimstra *et al*, *Am J Pathol* **145**, 1547 (1994).

DiGiuseppe *et al*, *Am J Pathol* **144**, 889 (1994).

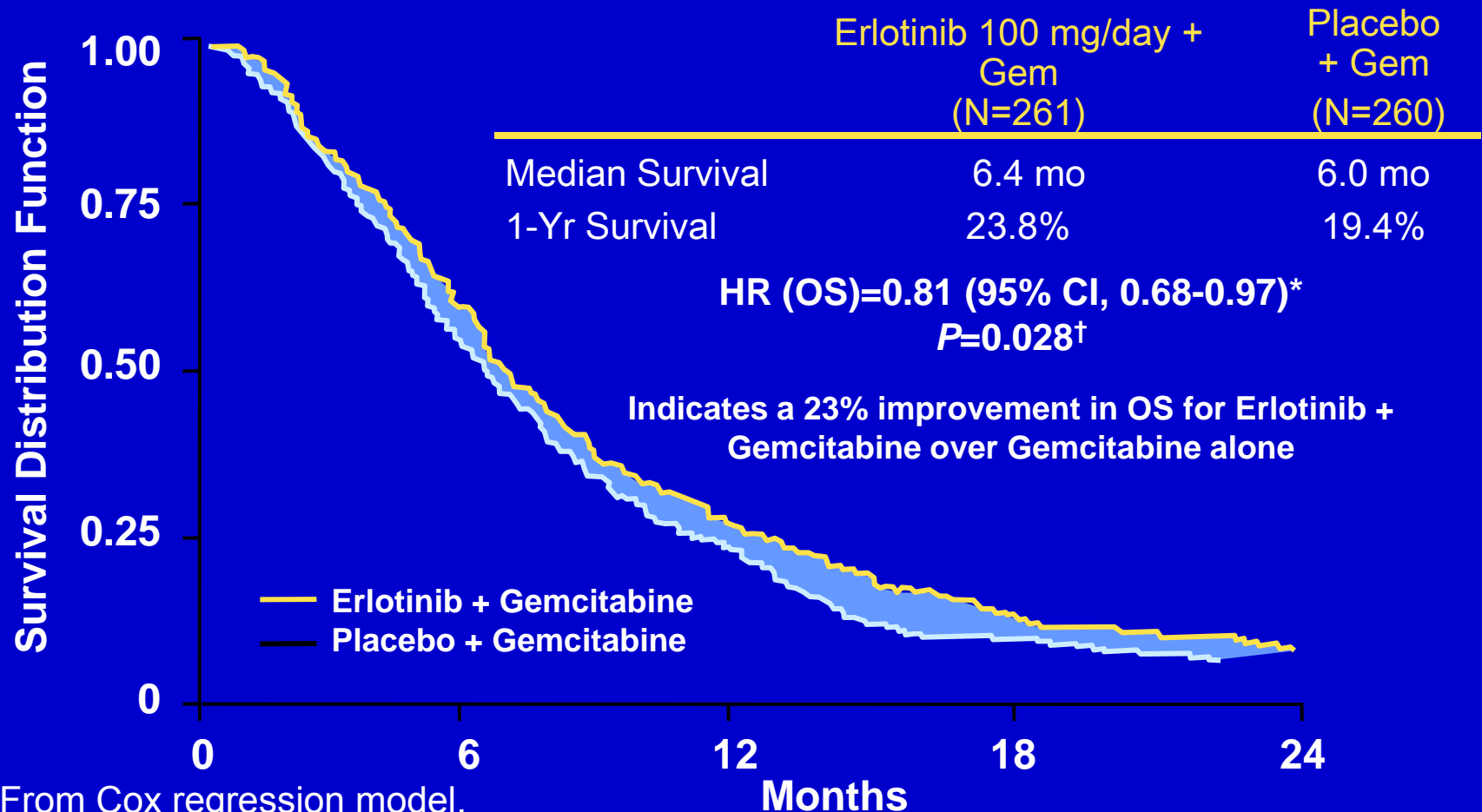
Hingorani *et al*, *Cancer Cell* **4**, 437 (2003)

# PA.3: Erlotinib Significantly Improved PFS



\*Adjusted for ECOG PS and extent of disease at randomization.

# PA.3: Erlotinib Significantly Improved Overall Survival

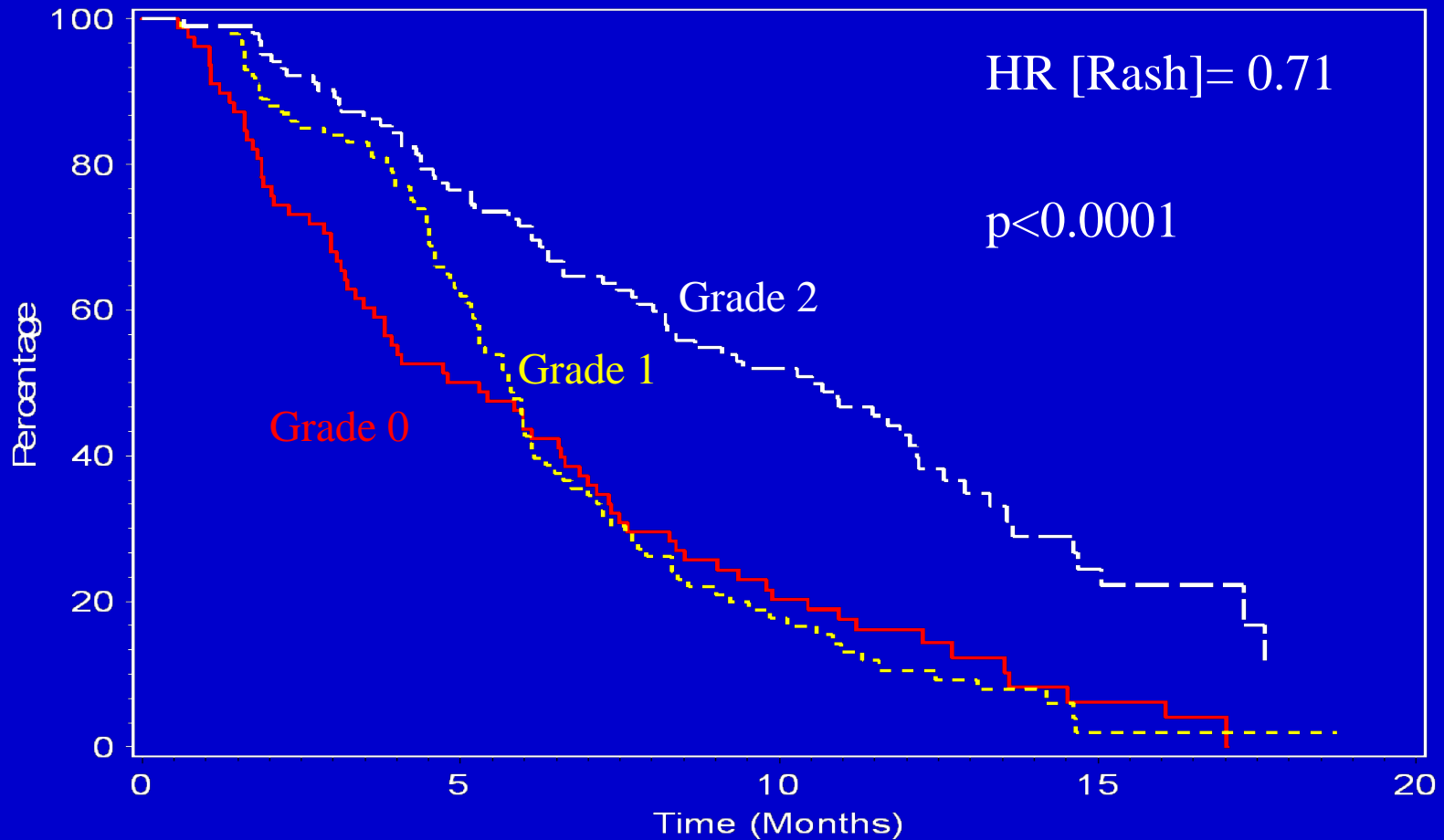


\*From Cox regression model.

†From 2-sided log-rank test.

HR=hazard ratio

# Severity of rash correlates with survival



	Grade 0 N= 79	Grade 1 N= 108	Grade $\geq 2$ N= 103
Median survival	5.29	5.75	10.51
1-yr survival	16%	11%	43%

# Exploratory Study of Curcumin

---

**Dose = 8 gm p.o. daily (16 tabs/day)**

## Objectives

- **Increase six-month survival**
- **Determine safety**
- **Assess effect on NF- $\kappa$ B, cytokines**

# Results of Exploratory Trial of Oral Curcumin

---

## Responses

**No. of Evaluable Patients = 21**

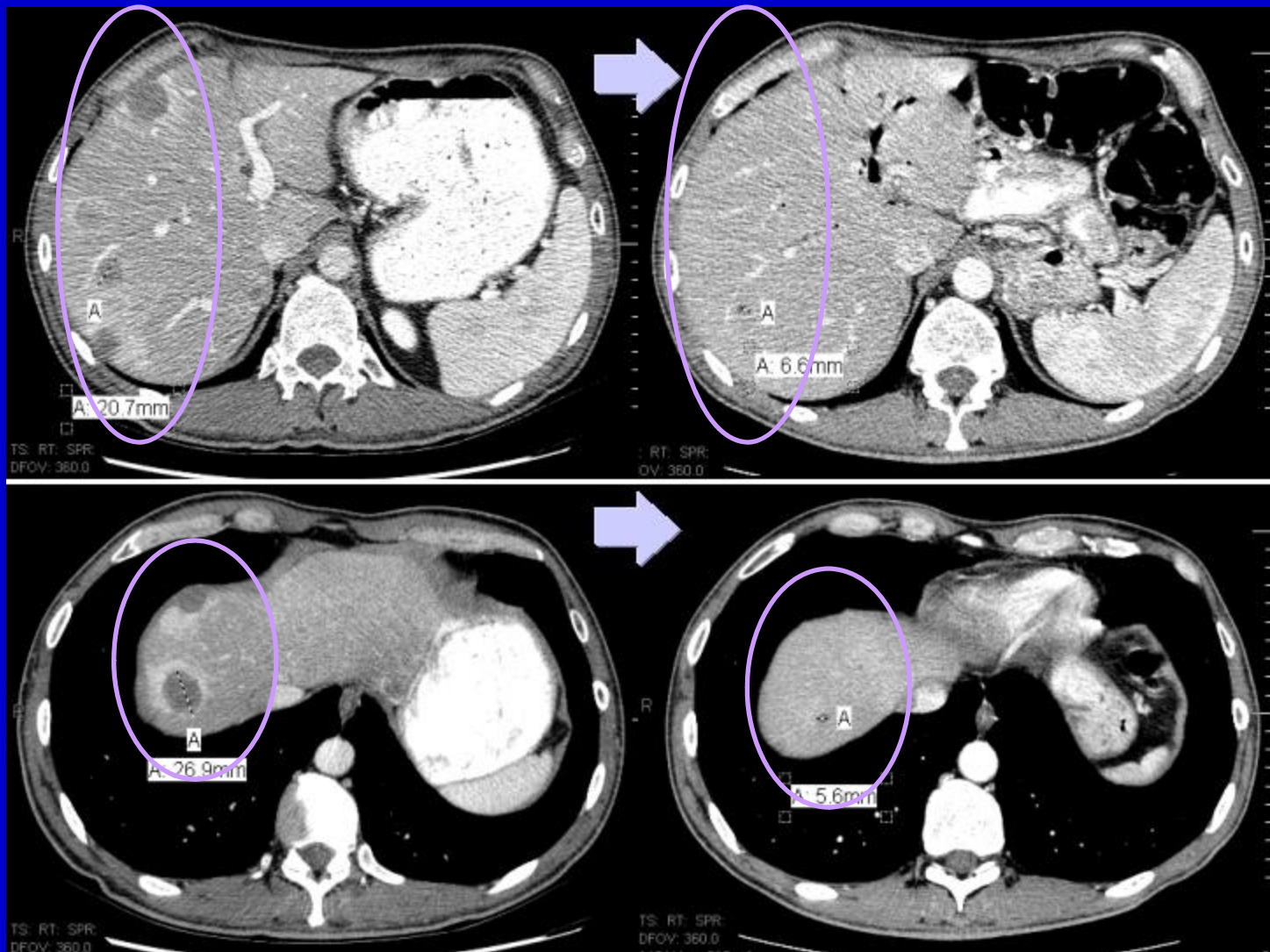
**Partial response = 1**

**Stabilized the tumor over six months:  
2 Patients: (8, 10+ months)**

## Side Effects

**None Evident!**

# Pancreatic Cancer Treated with Curcumin



Pre

Week 8

# Pancreatic Cancer Treated with Curcumin



**Pre**

**Week 8**

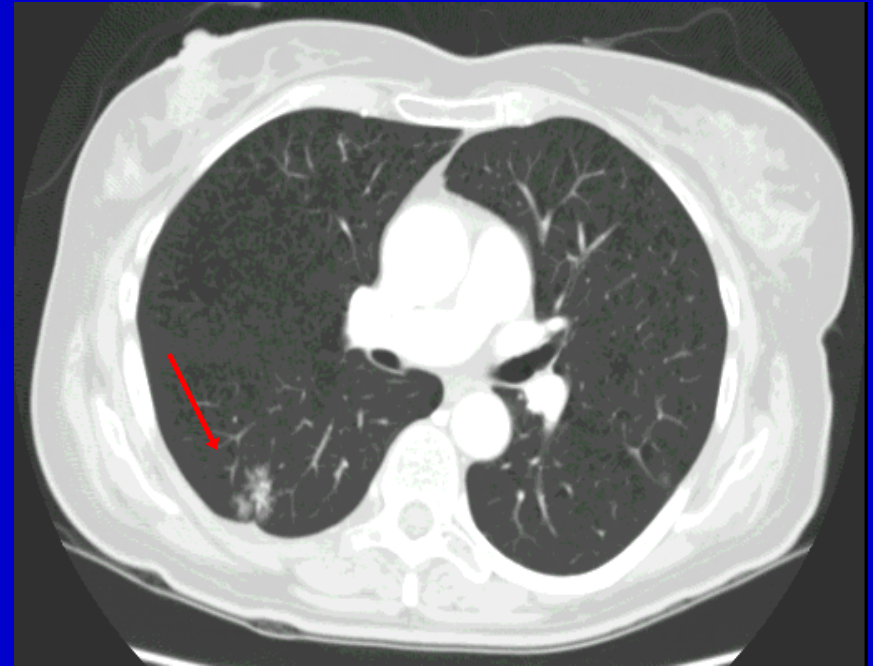
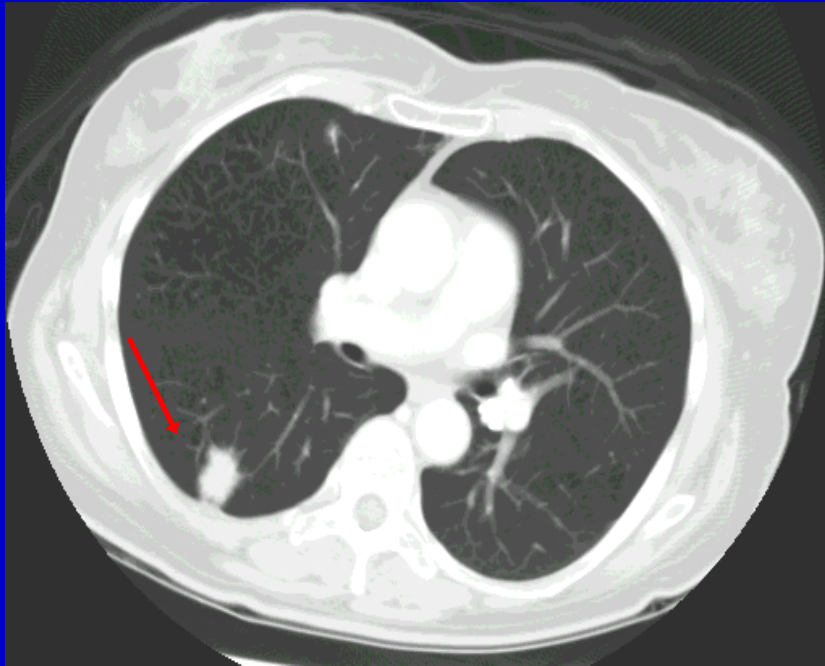
# Conclusions about Curcumin

- Works in the test tube and in mice at high conc.
- Non-toxic.
- Clearly worked to shrink tumor in 1 patient, but not long lasting.
- For almost all patients, very high oral doses of this drug did not lead to a concentration of drug high enough in the bloodstream to stop growth.
- Future plan: LIPOSOMAL Curcumin to allow for higher drug concentrations.

# Experimental Therapy with Sorafenib

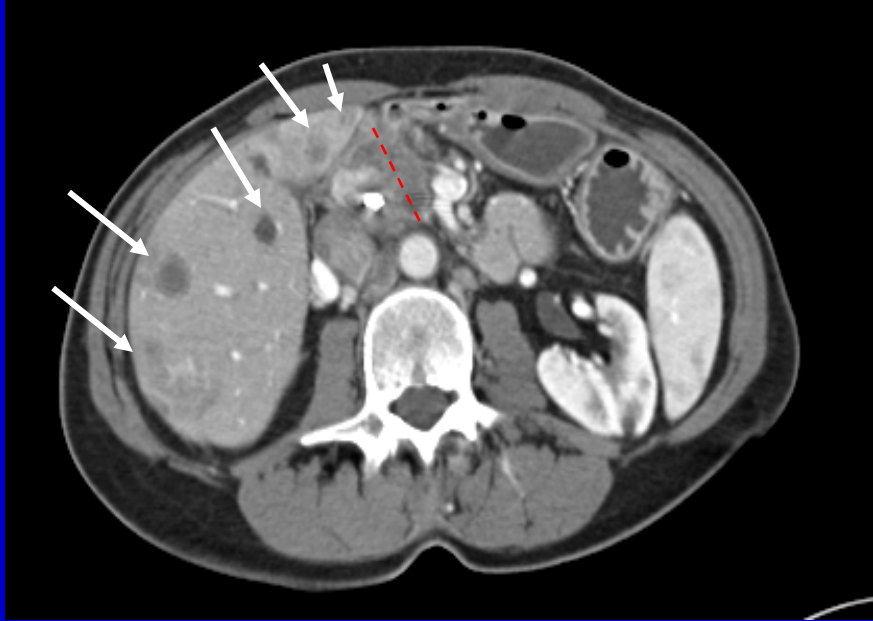
- Oral agent that inhibits the intracellular protein braf or raf-1.
- Has worked well and is approved for use in kidney/ liver cancer.
- The raf-1 pathway is activated in pancreatic cancer because of activation of the ras oncoprotein.
- Has worked in a few patients with pancreatic cancer.
- Experimental efforts Negative.

# Sorafenib *raf-1* Inhibitor



# Phase II Study: Gemcitabine + Lapatinib

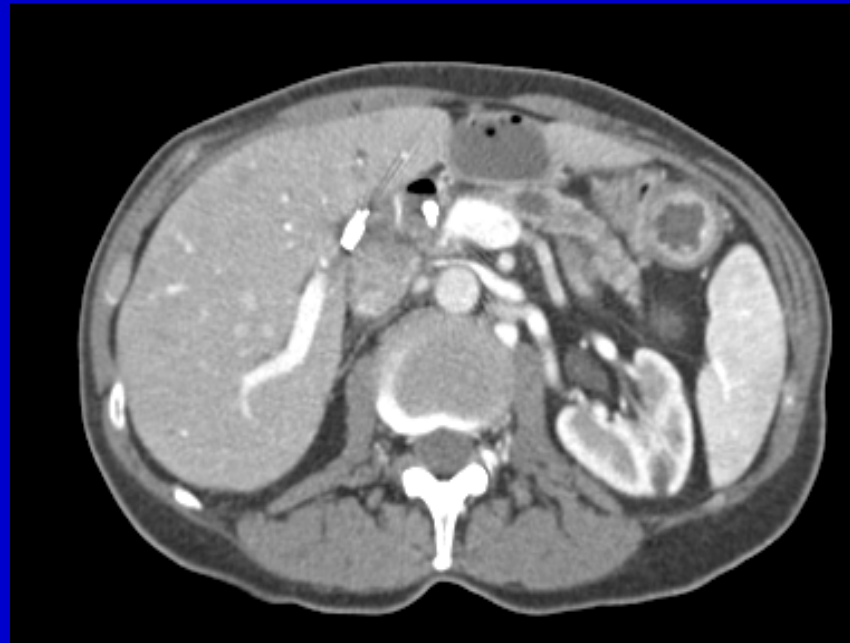
- Lapatinib:
  - Inhibits Her-2/ EGFR
  - Breast Cancer: effective for Herceptin failed cases.
  - FDA approved for Breast Cancer
- Pancreatic Cancer:
  - EGFR, Her-2 over expression
  - Erlotinib showed benefits



2/4/08

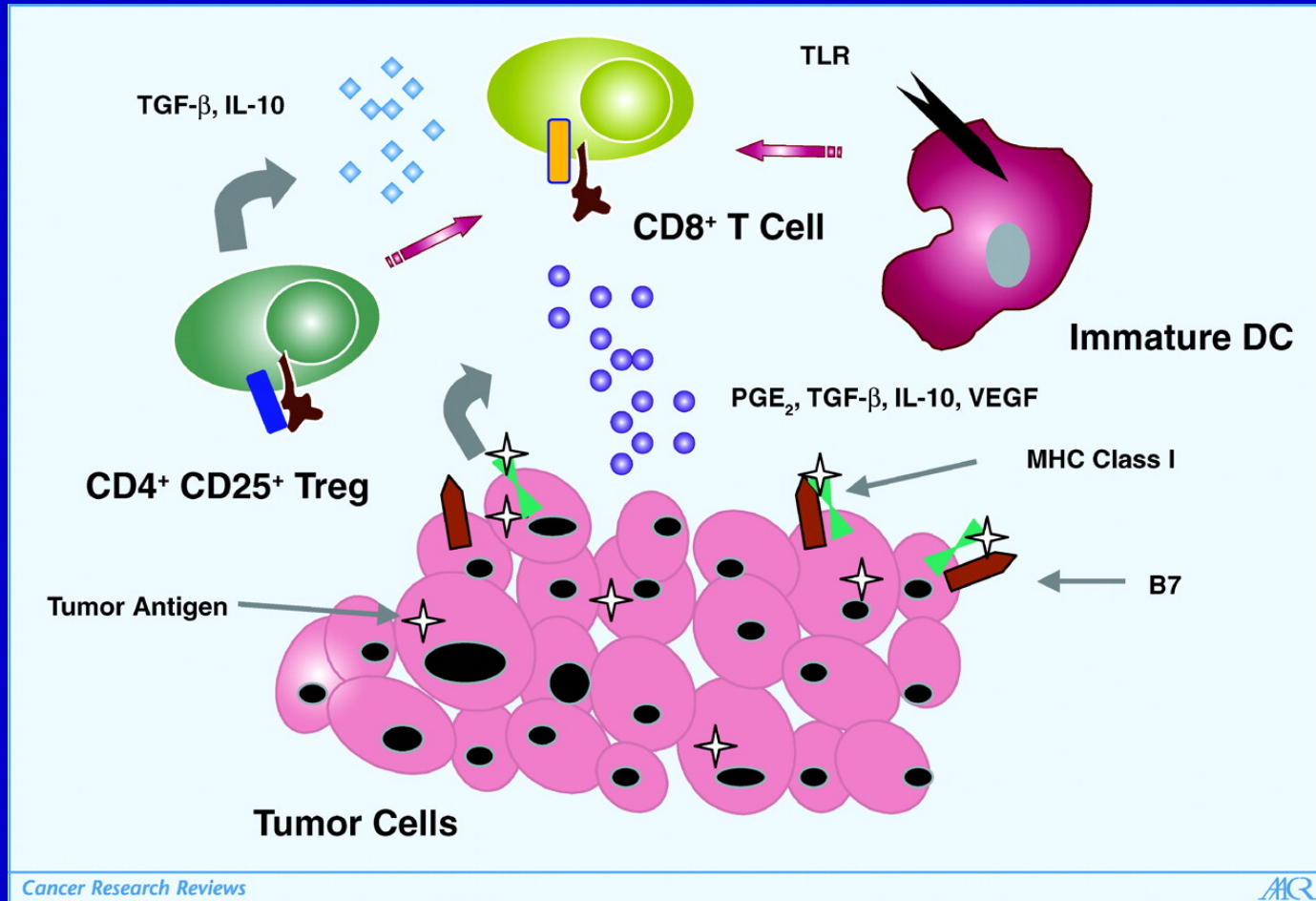


3/26/08



# Immunotherapy

# Numerous mechanisms active within the tumor microenvironment permit tumor cells to escape the lytic activity of activated CD8+ CTL



Emens, L. A. et al. *Cancer Res* 2005;65:8059-8064

# Re-establish Immunobalance and Chemoradiation Therapy

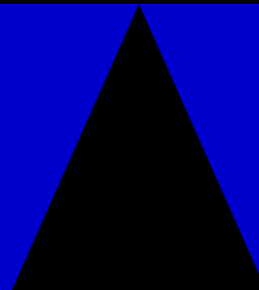
## Enhances antigen presentation by:

- Exposing antigens
- Enhancing MHC1 expression
- Enhancing DC maturation
- Engaging TLR's
- Converting Th2 to Th1 responses

## Facilitates Homeostatic proliferation

## Depletes Tregs

## Lymphodepletion

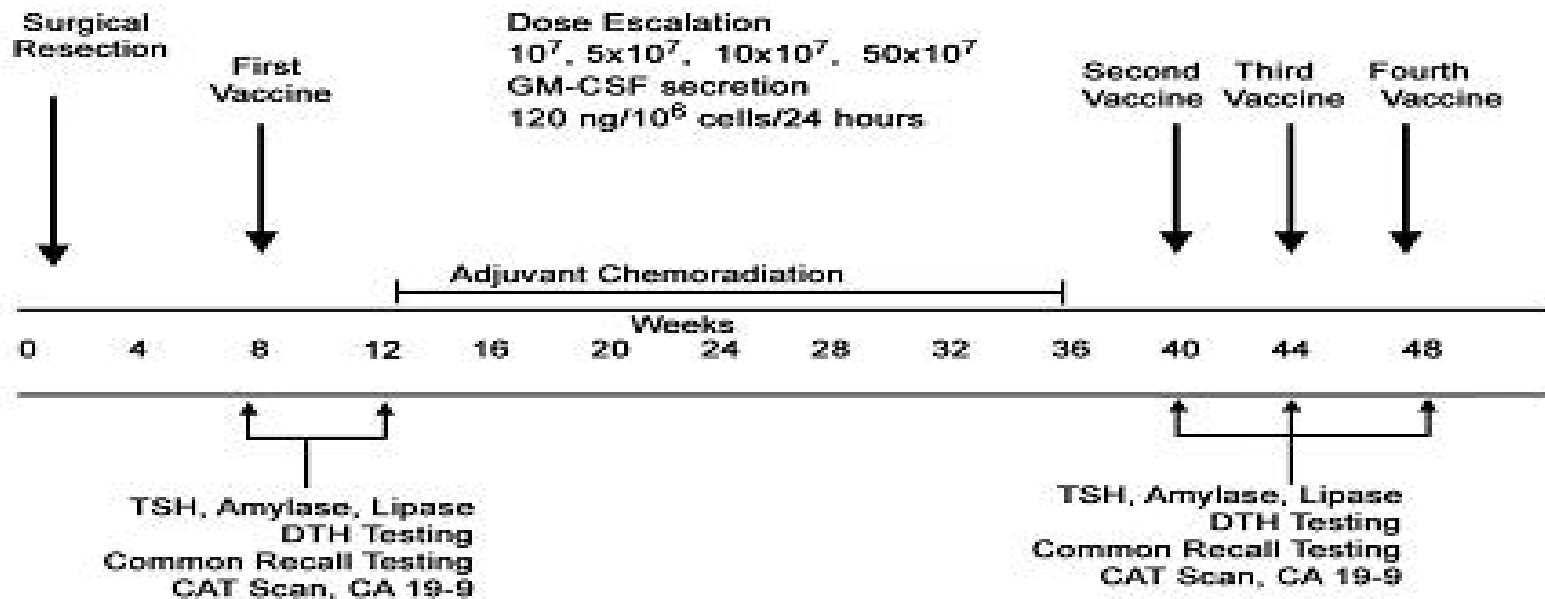


Correale *et al.*, *J Immunol* **175**, 820 (2005)  
Reits *et al.*, *J Exp Med* **203**, 1259 (2006)  
Plate *et al.*, *Cancer Immunol Immunother* **54**, 915 (2005)  
Nowak *et al.*, *Cancer Res* **62**, 2353 (2002)  
Powell *et al.*, *J Immunol* **177**, 6527 (2006)

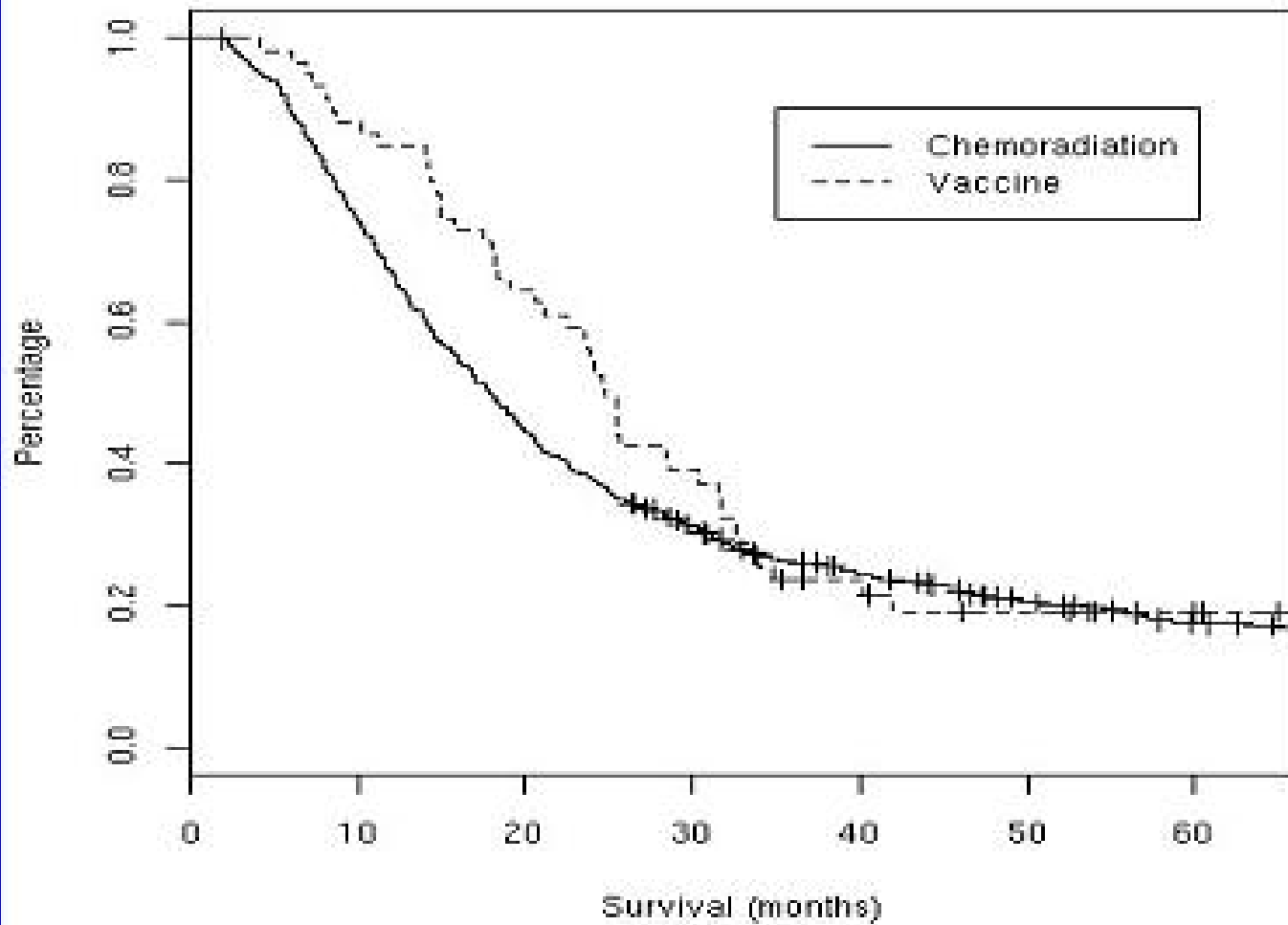
# Johns Hopkins Study

## Phase I Design

### Design of Protocol J9617: A Phase I Study of an Allogeneic GM-CSF Vaccine

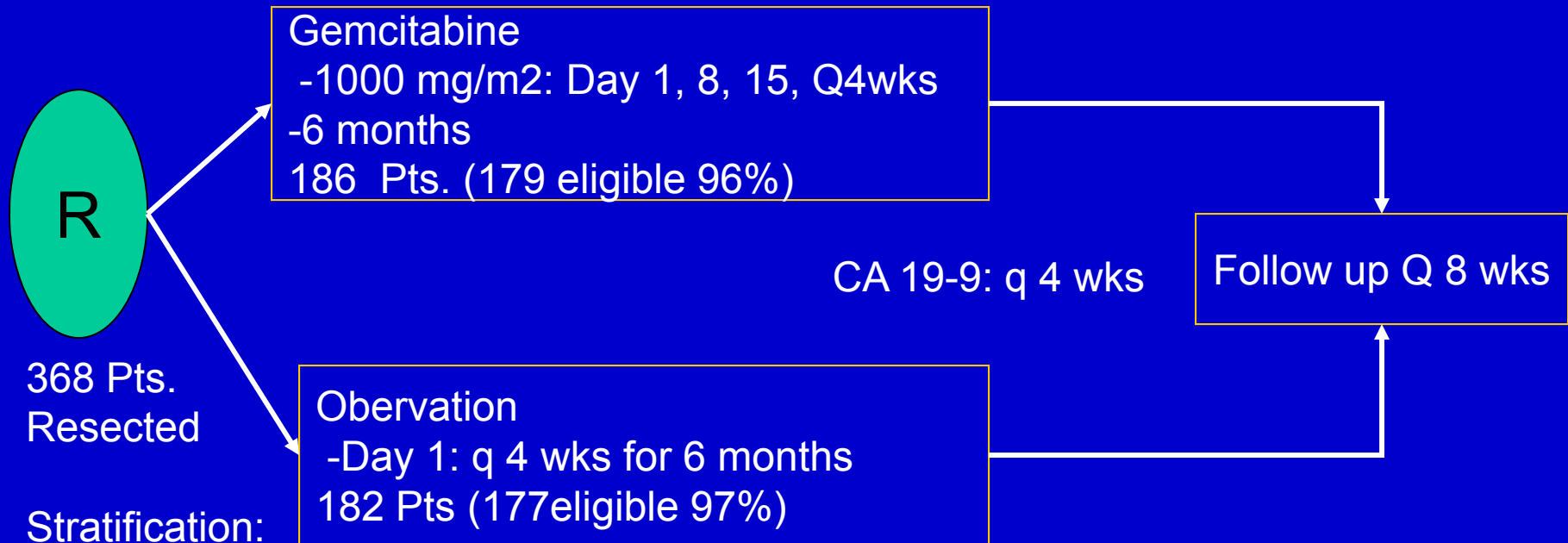


### Kaplan-Meier Overall Survival



# Phase III Randomized Adjuvant Chemotherapy with Gem vs. Obs. In Patients with Resected Pancreatic Cancer: CONKO 001

ASCO 2005:A4013



368 Pts.  
Resected

Stratification:  
R, T, N

- CA 19-9, CEA < 2.5 ULN
- Start within 6 wks after Op

- Primary endpoint: DFS, increase at least 6 months
- 2ndary: OS, Toxicity

# Phase III Randomized Adjuvant Chemotherapy with Gem vs. Obs. In Patients with Resected Pancreatic Cancer: CONKO 001

ASCO 2005:A4013

Median DFS		Gem	Obs	p
		14.21 months (95%CI 12.86-15.57)	7.46 months (95%CI 6.80-8.11)	<0.001
N	Negative	19.3	11.2	<0.05
	Positive	13.1	7.0	<0.05
R	R0	14.0	7.9	<0.05
	R1	14.5	5.5	<0.05

OS: Not ready for analysis yet!

# Trial's at Penn

- Gemcitabine + CD40 modulator
- Sorafenib + CPT-11
- Vaccine with Gem + XRT/5-FU, Gem as adjuvant setting)

# Supportive Care

- Nutrition Support:
  - Pancreasase
  - Calorie
- Pain Control
- Biliary Drain
- DVT
- Psycho-, Social Support

# Molecular Characterization Will Enable More Individualized Treatment

