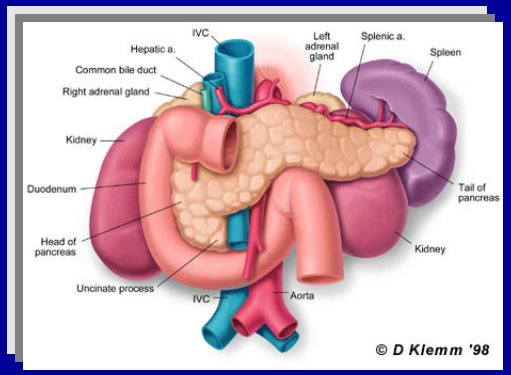
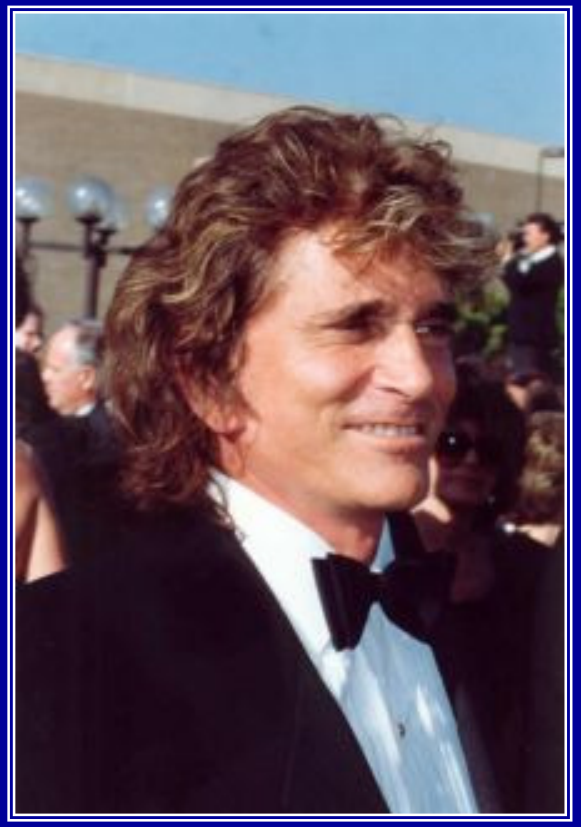
# Advances and Novel Approaches to the Treatment of Metastatic Pancreatic Cancer




**Philip A Philip, MD, PhD**

**Karmanos Cancer Institute**

**Detroit**

**“Successful” resection of pancreas cancer in 2006**

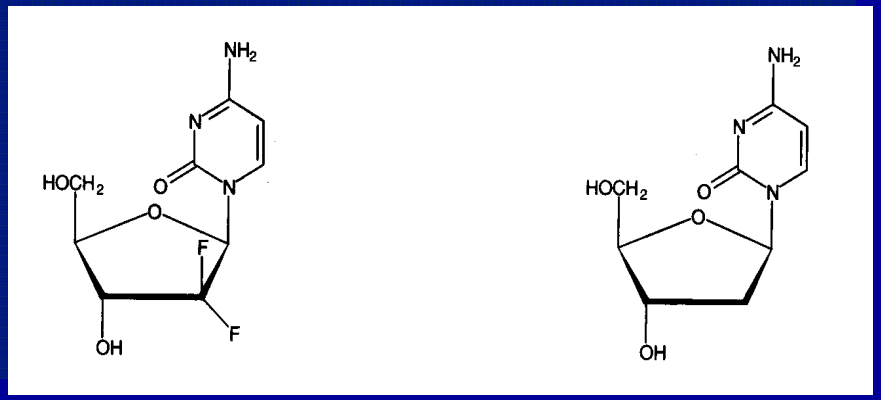
**Died of metastatic disease in 2007**

**Died < 6 months from diagnosis**

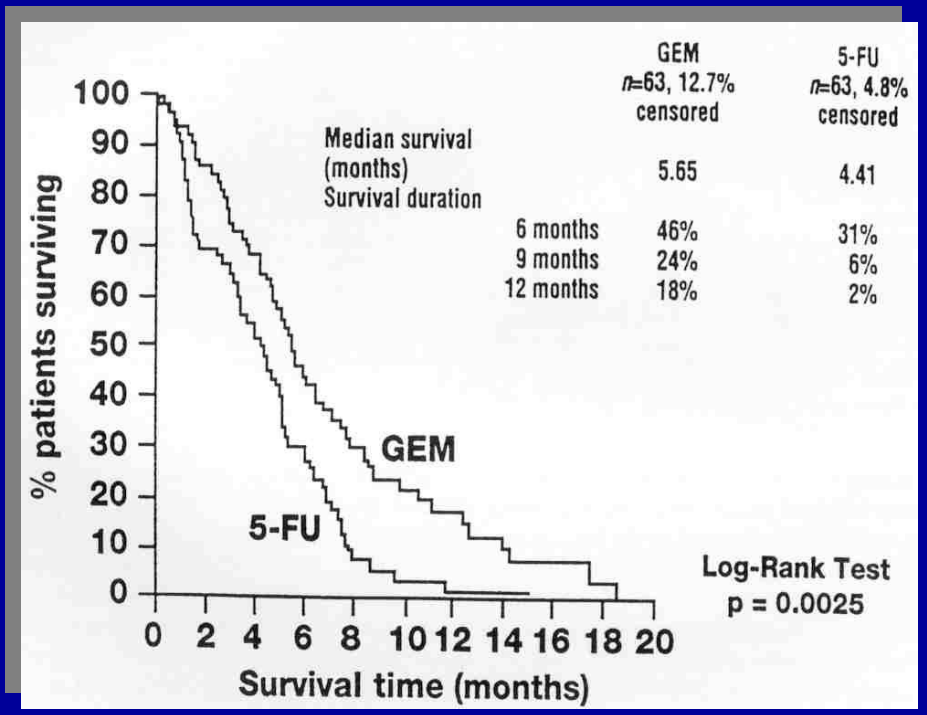
# Stages of Pancreas Cancer

| Stage | % of patients | Median Survival in months |
|---|---|---|
| Localized/Resectable | 10-15 | 14-20 |
| Localized/unresectable | 30-40 | 8-10 |
| Metastatic | 45-65 | 4-6 |

# Gemcitabine




**Gemcitabine** **deoxycytidine**



# 10 years later

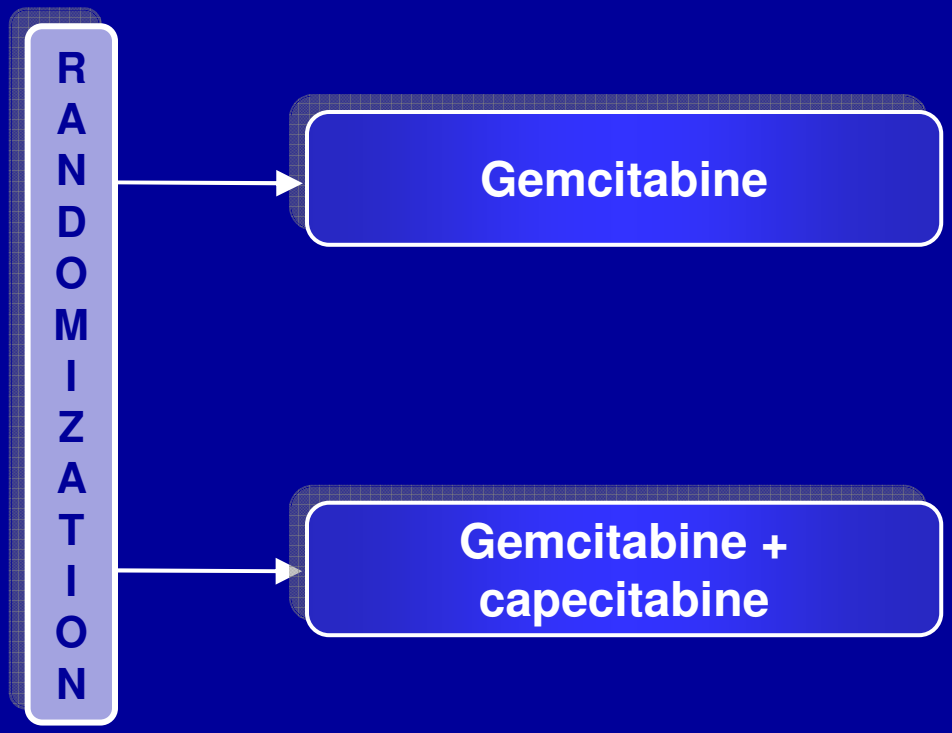
# +

# > 12 Phase III studies

# Phase III Trials of Gemcitabine Combinations in Pancreatic Cancer

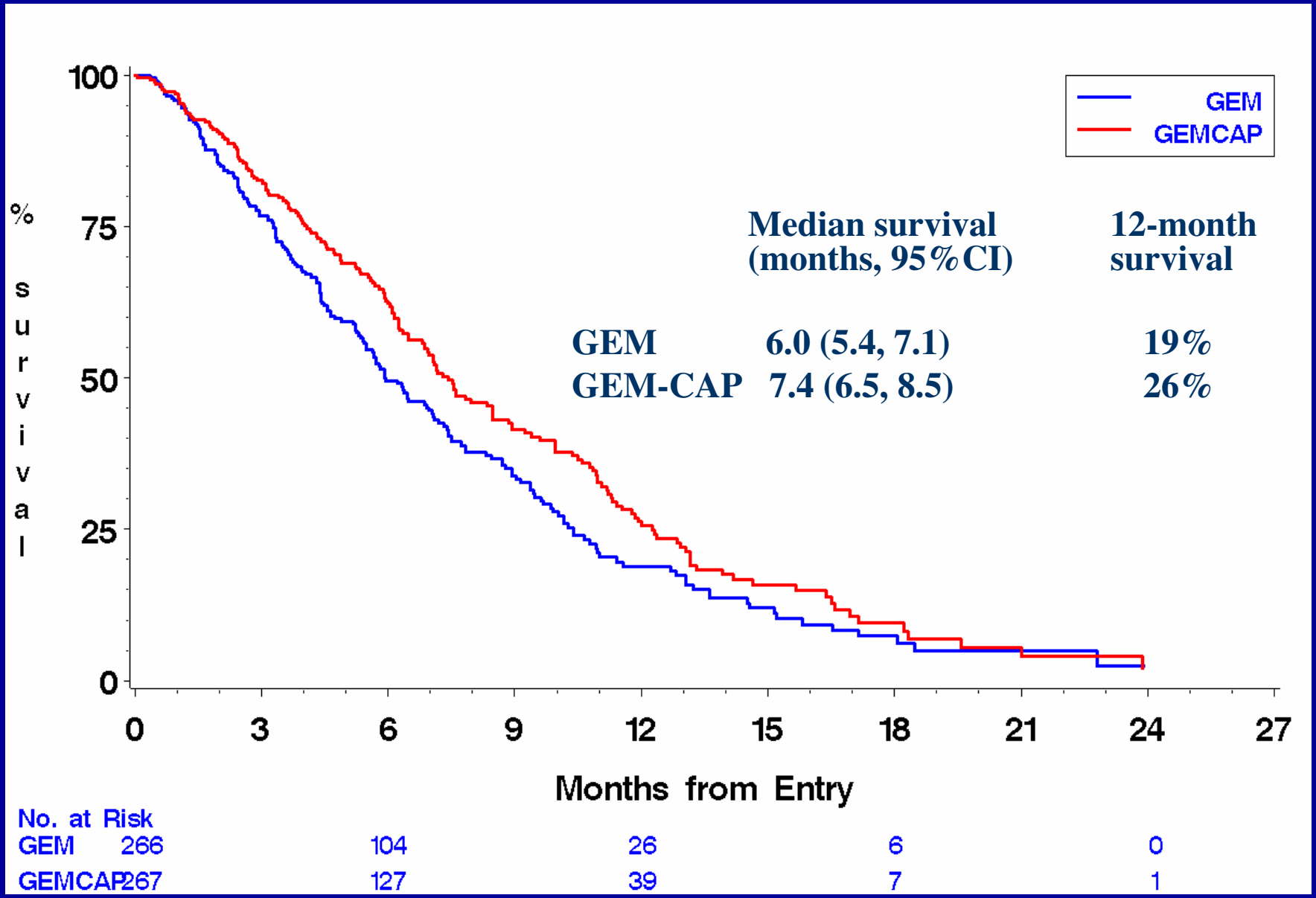
| Author | Phase III Agents Studied | Total Patients | Median Survival | 1-Year Survival | Progression-Free Survival |
|---|---|---|---|---|---|
| Burris[6]<br>1997 | GEMZAR vs<br>5-FU | 126 | 5.7 months*<br>4.2 months | 18%<br>2% | 2.3 months*<br>0.9 months |
| Van Cutsem[1]<br>2002 | GEMZAR + placebo vs<br>GEMZAR + R115777 | 688 | 6.1 months<br>6.4 months | 24%<br>27% | 3.6 months<br>3.7 months |
| Berlin[2]<br>2002 | GEMZAR vs<br>GEMZAR + bolus 5-FU | 327 | 5.4 months<br>6.7 months | < 20% both arms | 2.2 months<br>3.4 months |
| Moore[3]<br>2003 | GEMZAR vs<br>BAY12-9566 | 277 | 6.6 months*<br>3.7 months | 25%<br>10% | 3.5 months*<br>1.7 months |
| Bramhall[4]<br>2001 | GEMZAR vs<br>Marimastat 25 mg. | 414 | 5.6 months<br>4.2 months | 19%<br>20% | 3.8 months<br>1.9 months |
| Bramhall[5]<br>2002 | GEMZAR + placebo vs<br>GEMZAR + Marimastat | 239 | 5.5 months<br>5.5 months | 17%<br>18% | 2.1 months (TTF)<br>3.6 months |
| Colucci[7]<br>2002 | GEMZAR vs<br>GEMZAR + cisplatin | 107 | 5.0 months<br>7.5 months | 11%<br>11% | 2.0 months (TTP)<br>5.0 months* |
| Heinemann[8]<br>2003 ASCO | GEMZAR vs<br>GEMZAR + cisplatin | 192 | 6.0 months<br>7.6 months | Not Reported | 2.5 months (TTP)<br>4.6 months* |
| Rocha Lima[9]<br>2003 ASCO | GEMZAR vs<br>GEMZAR + irinotecan | 342 | 6.6 months<br>6.3 months | 22%<br>21% | 3.0 months (TTP)<br>3.5 months |

# Phase III trial of gemcitabine versus gemcitabine plus capecitabine




Cunningham et al, ECCO, 2005

# Overall survival

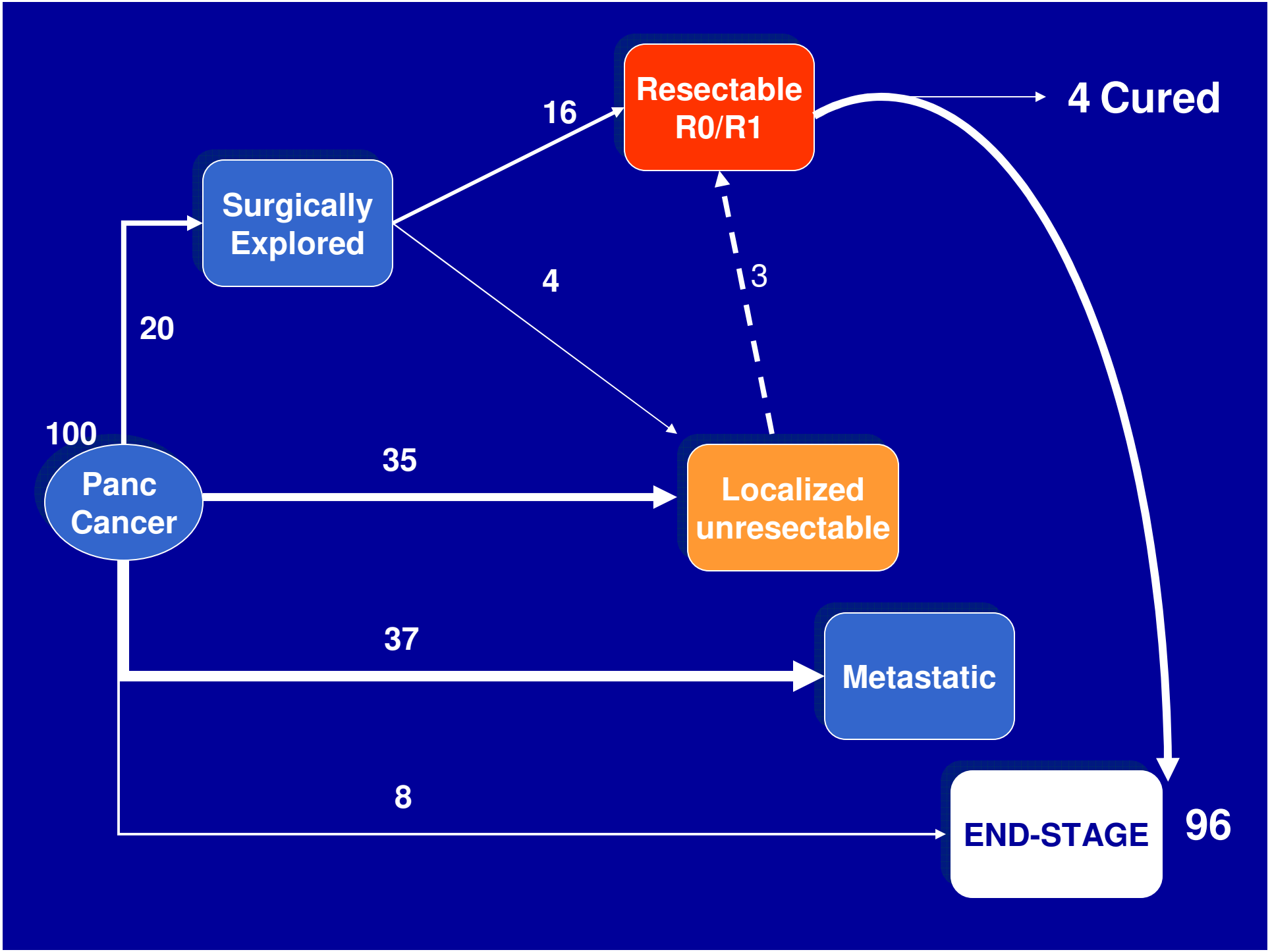



| | Median survival (months, 95% CI) | 12-month survival |
|---|---|---|
| GEM | 6.0 (5.4, 7.1) | 19% |
| GEM-CAP | 7.4 (6.5, 8.5) | 26% |

Cunningham et al, ECCO, 2005

# Summary of cytotoxic therapy

- Gemcitabine
  - Median survival 5.5 - 6 months
  - One year survival = < 20%
- No combination is better than gemcitabine in an “average” patient
- Subsets may benefit from an added drug
  - Platinums
  - Fluoropyrimidines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R0/R1
4 Cured
16
Surgically
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Cancer
35
Localized
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37
Metastatic
8
END-STAGE
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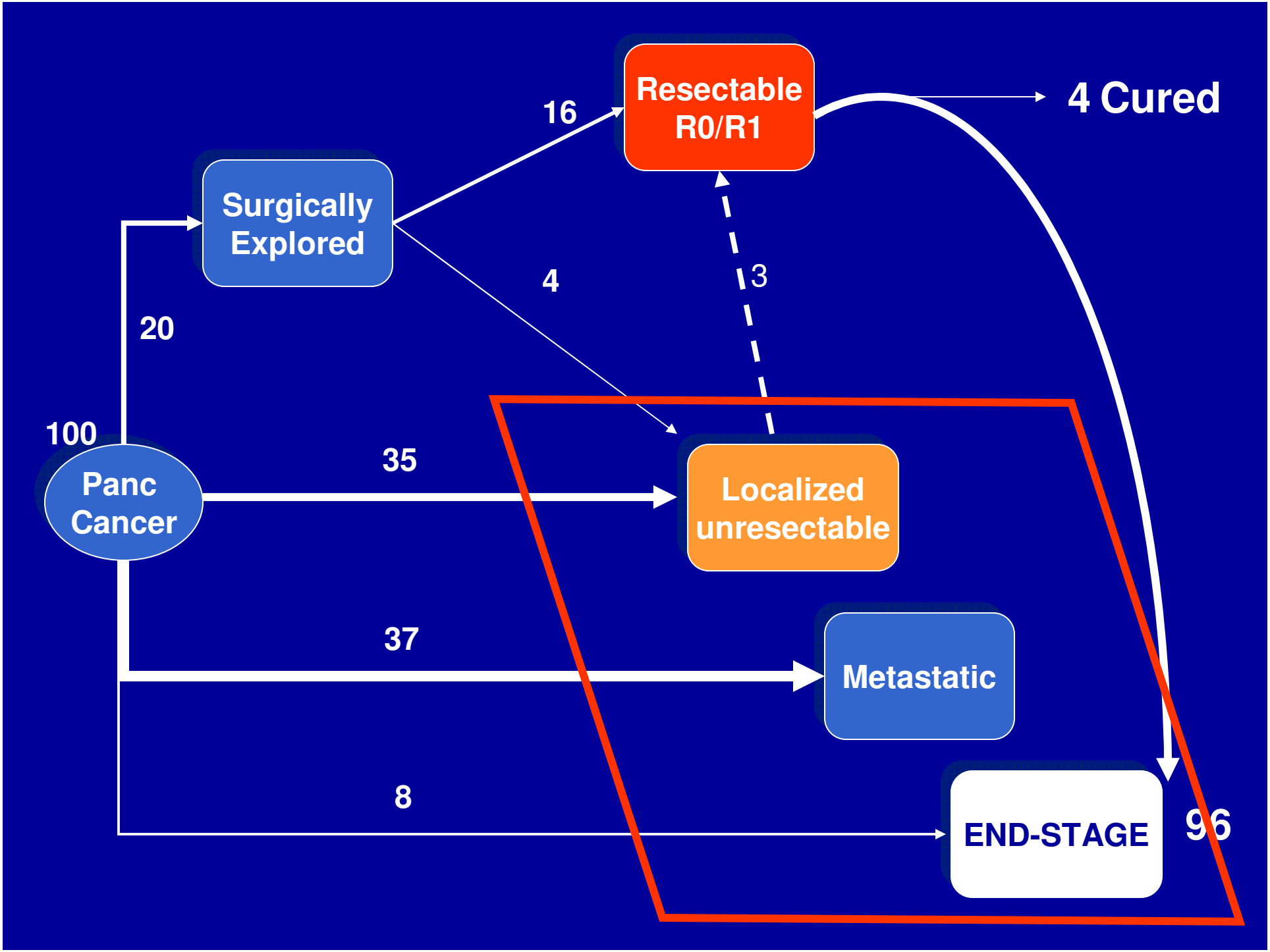
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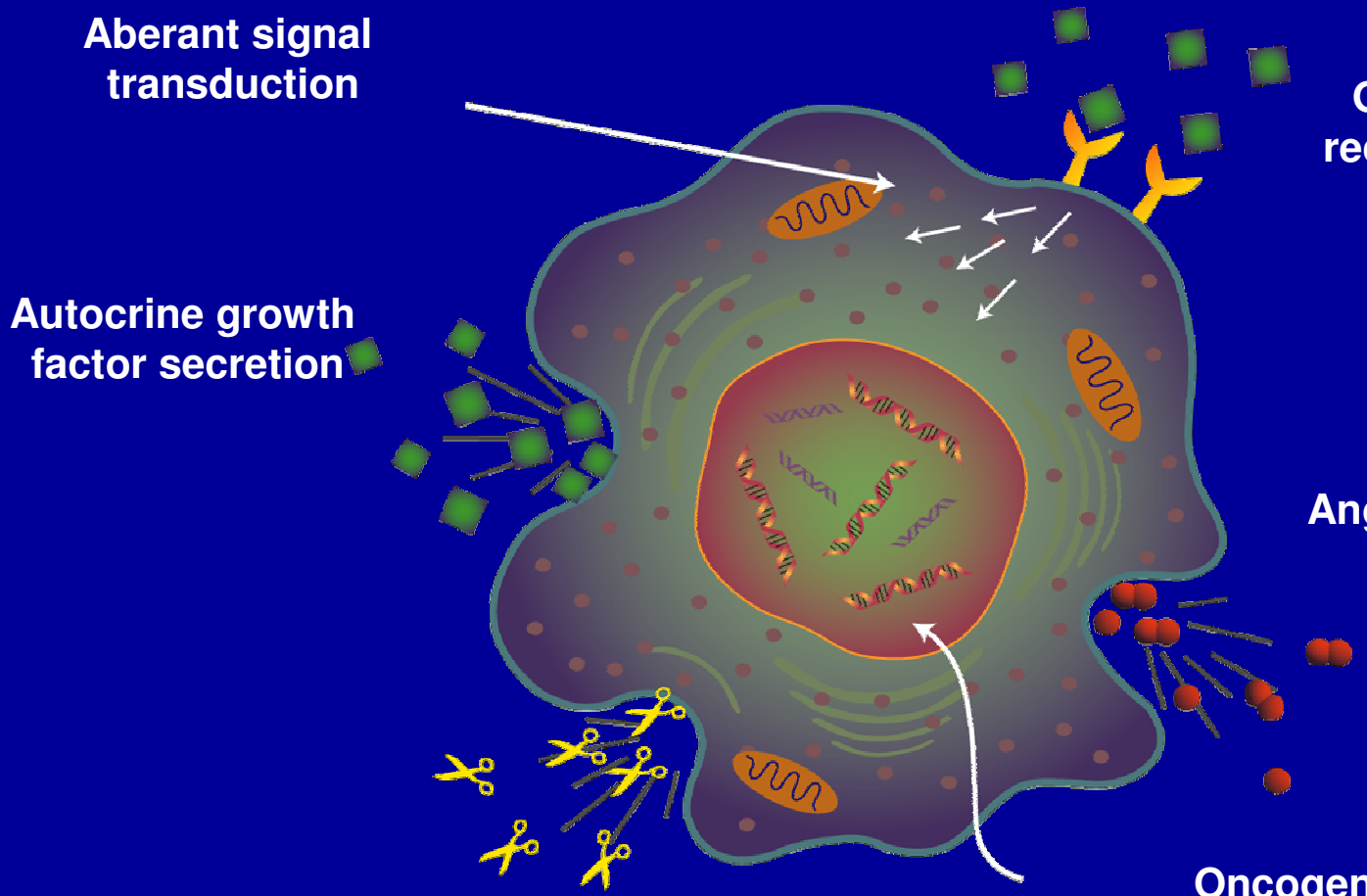
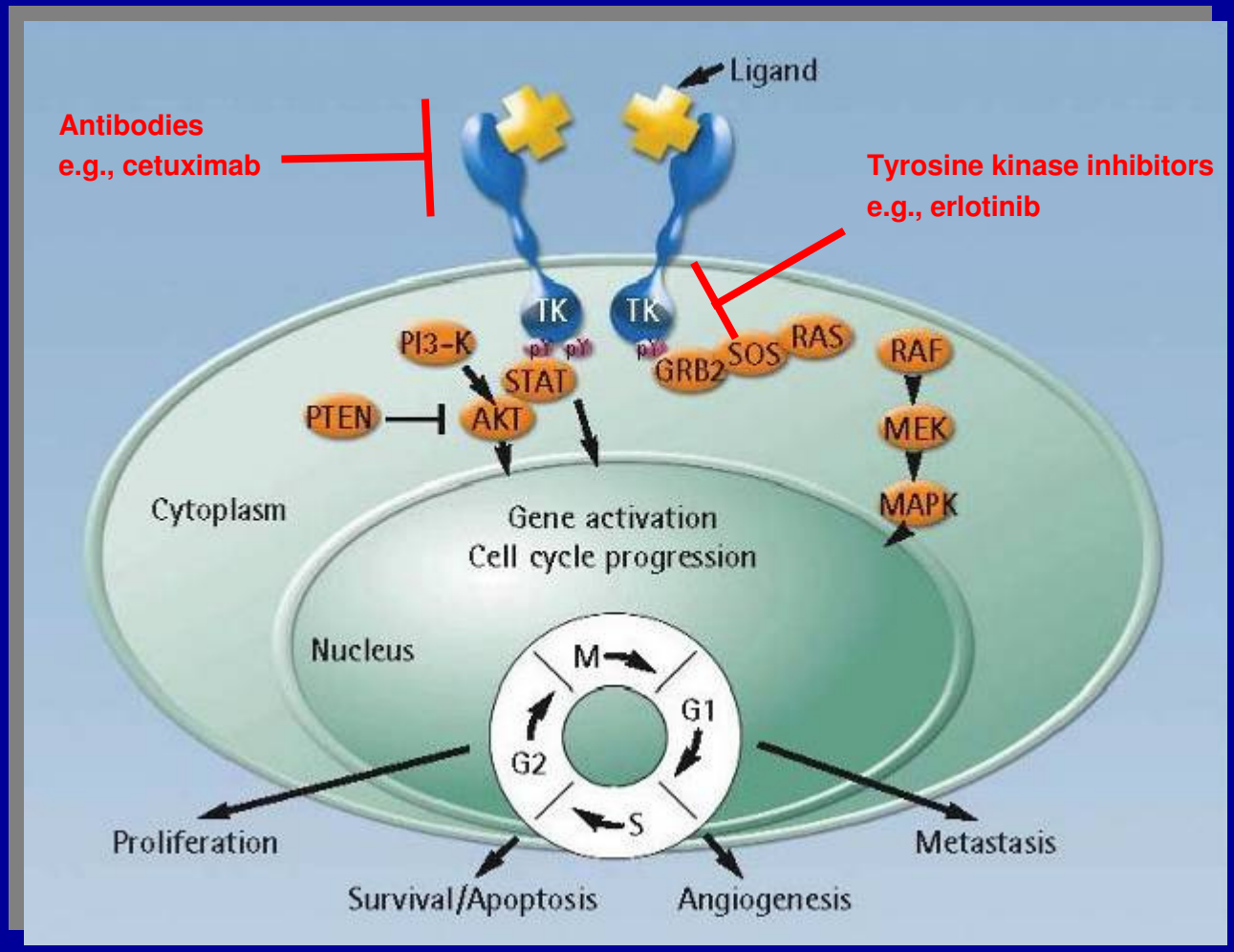
# Molecular Events in Cancer



# EGFR - Pathway

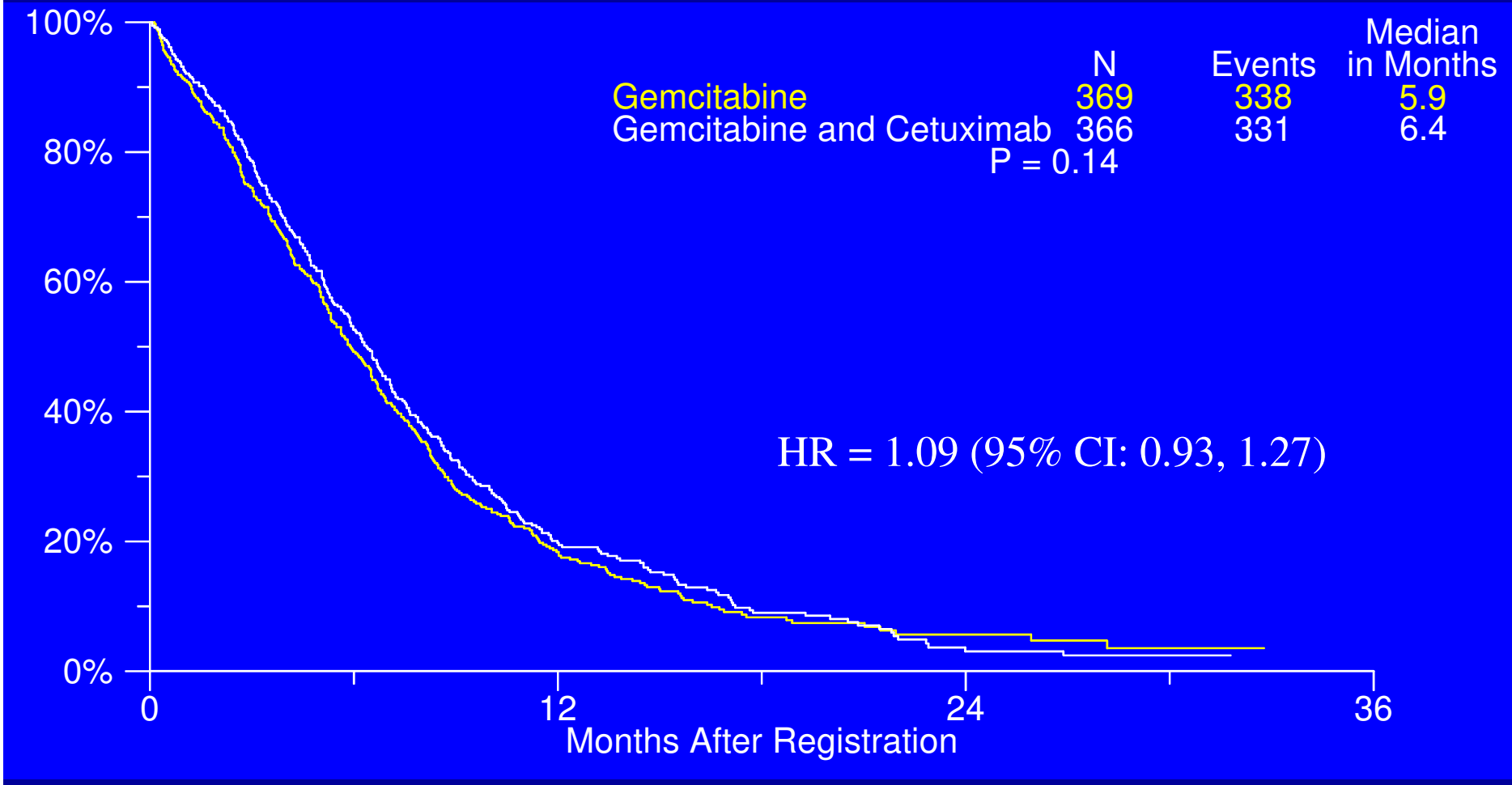


# The "validation" of EGFR as a target in pancreas cancer

- Pathway "activated" in a large proportion of human pancreatic cancers
- Prognostic significance of EGFR +/- ligand expression
- Pre-clinical activity of anti-EGFR drugs in vitro and in vivo

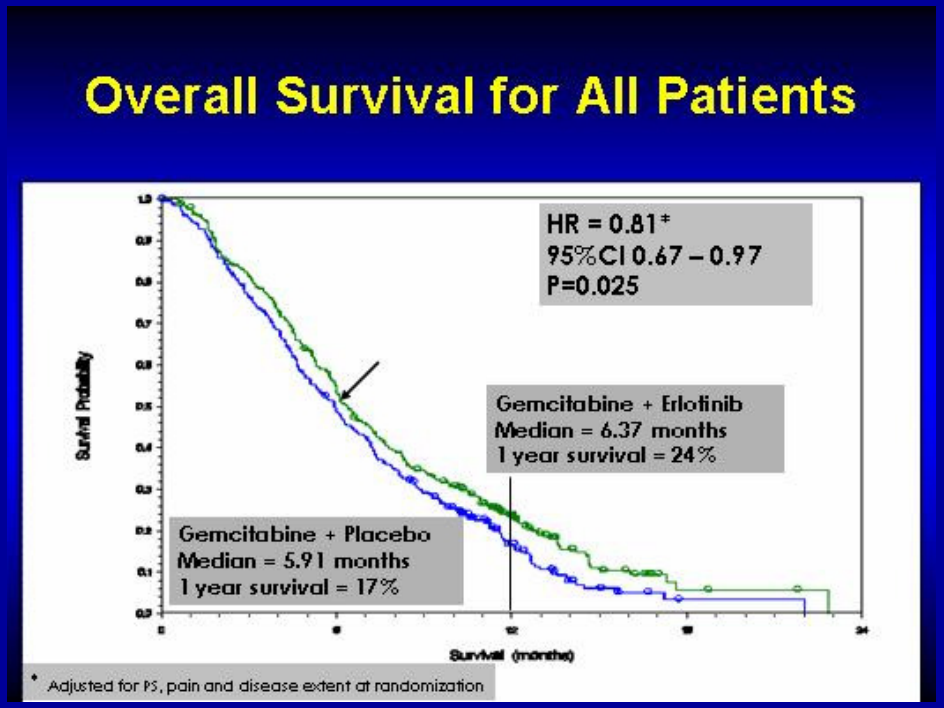
# Gemcitabine plus cetuximab: Survival

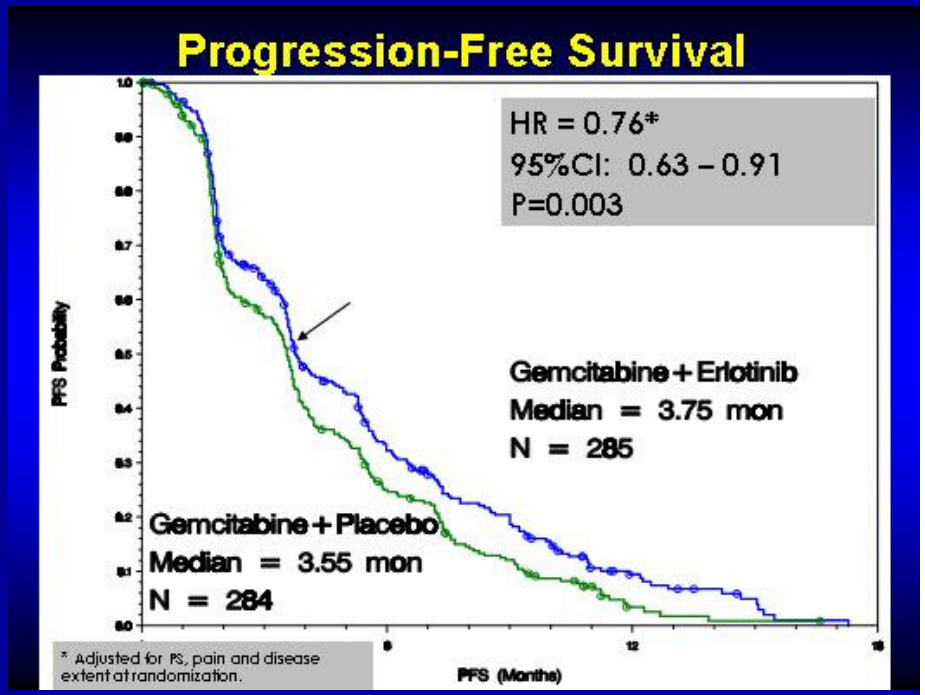
**N = 766**




Philip et al, ASCO, 2007

# Gemcitabine plus erlotinib: Phase III Trial



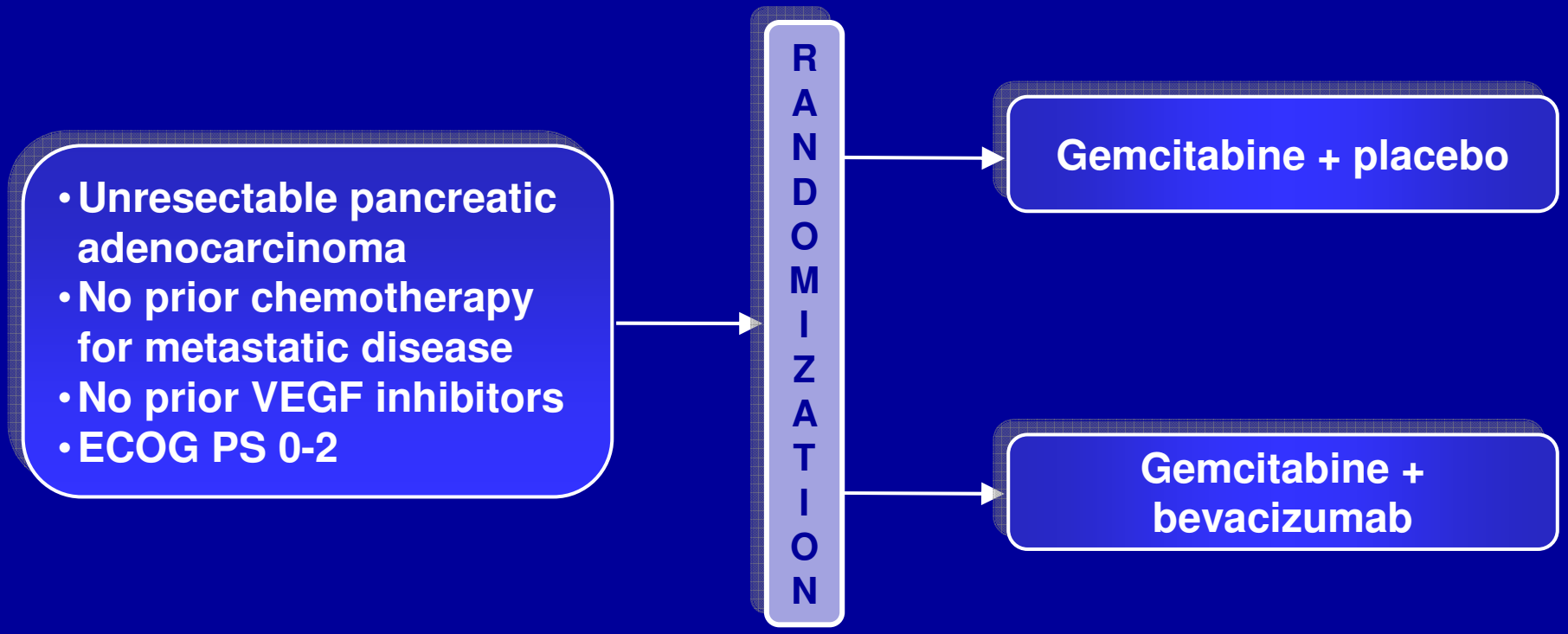




Moore et al, JCO, 2007

# EGFR blockade: what did we learn from >1,300 patients?

- Erlotinib adds a very small benefit
- mAb unlikely to add benefit to gemcitabine
- Not yet determined
  - Single agent activity of an EGFR blocker
  - A predictive biomarker

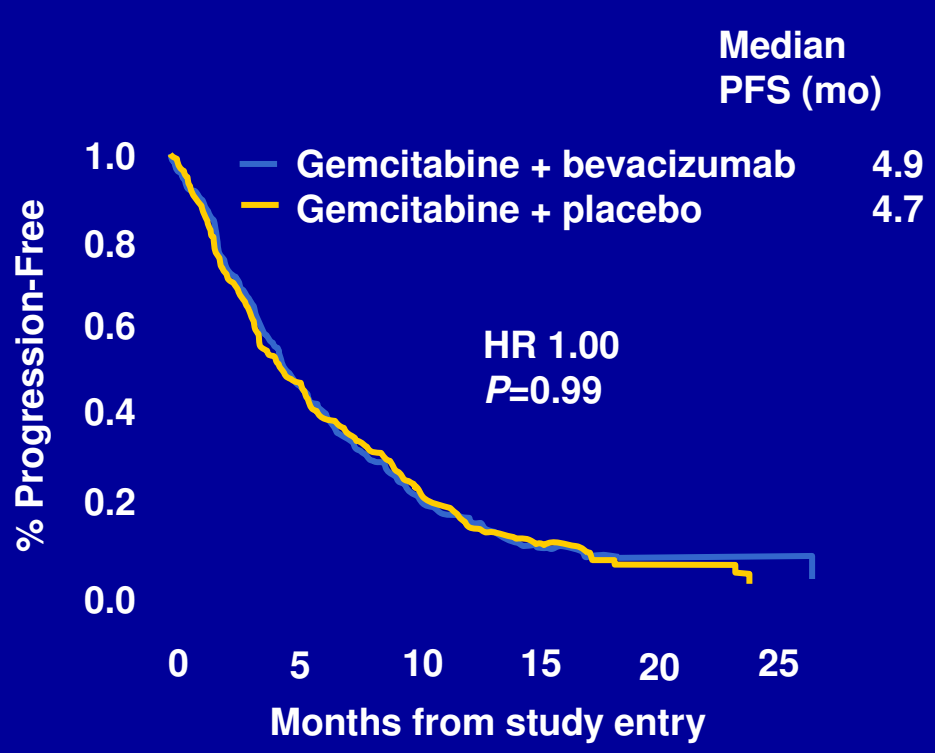
# Phase III Trial of Gemcitabine ± Bevacizumab in First-Line Metastatic Pancreatic Cancer

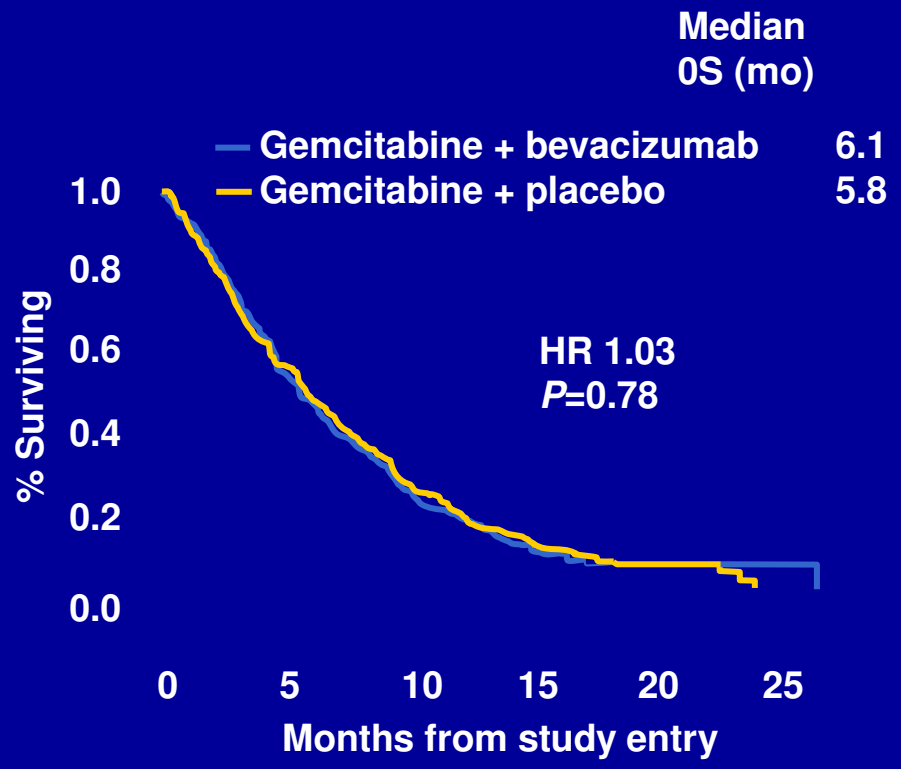



- **Primary end point: OS**

Kindler et al, ASCO 2007

# Phase III Trial of Gemcitabine ± Bevacizumab in First-Line Metastatic Pancreatic

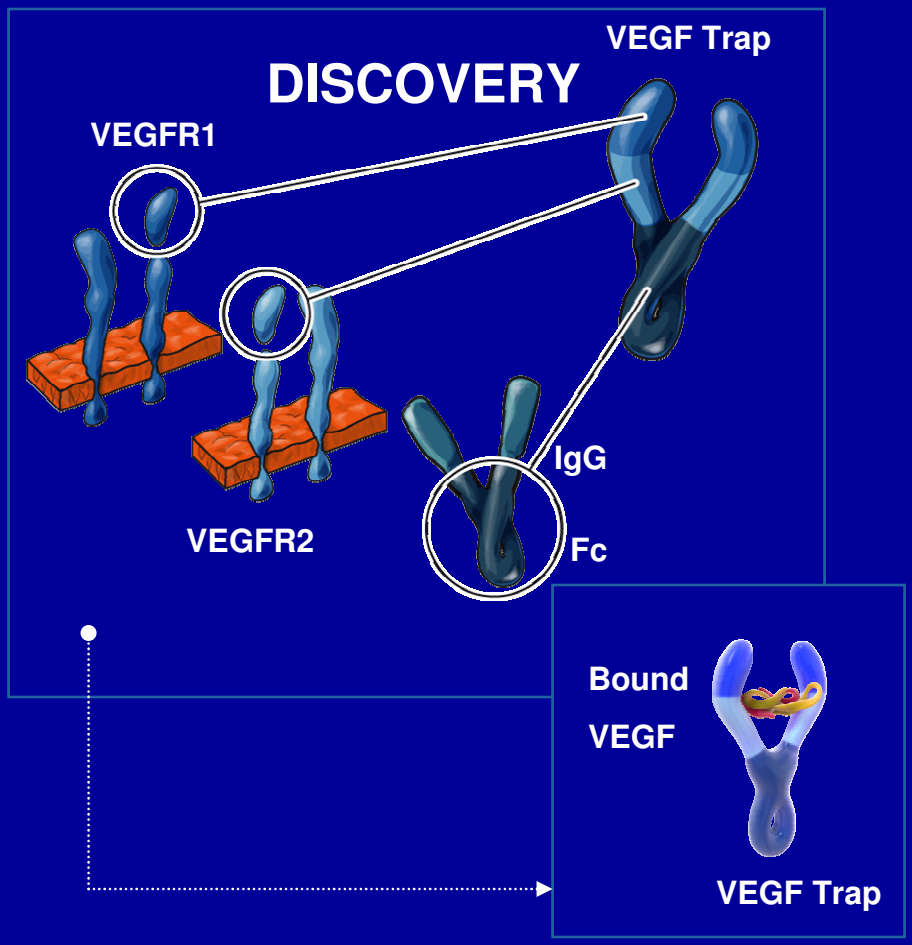


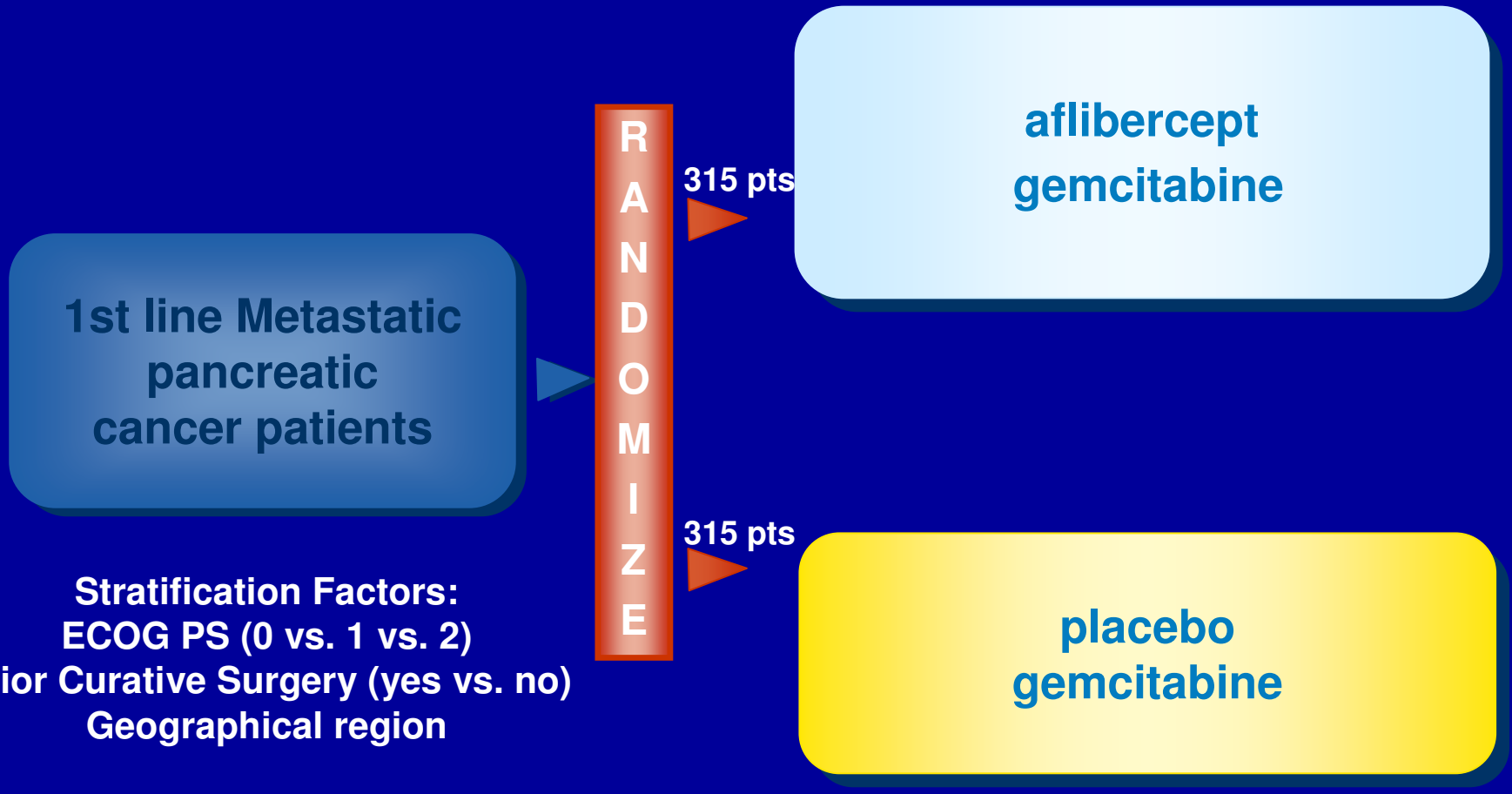

Kindler et al. ASCO, 2007. Abstract 4508.

# Aflibercept (VEGF trap)

- Recombinant fusion molecule of the human VEGF receptor extracellular domains and the Fc portion of human IgG1
- Increased affinity for VEGF compared to mAbs
  - Binds to VEGF-A, but also VEGF-B and PlGF
- Very well tolerated in early clinical trials



# Phase III 1st Line MPC




**Stratification Factors:**
**ECOG PS (0 vs. 1 vs. 2)**
**Prior Curative Surgery (yes vs. no)**
**Geographical region**

**140 centres**

Sponsored by Sanofi Aventis

# One versus multiple genes

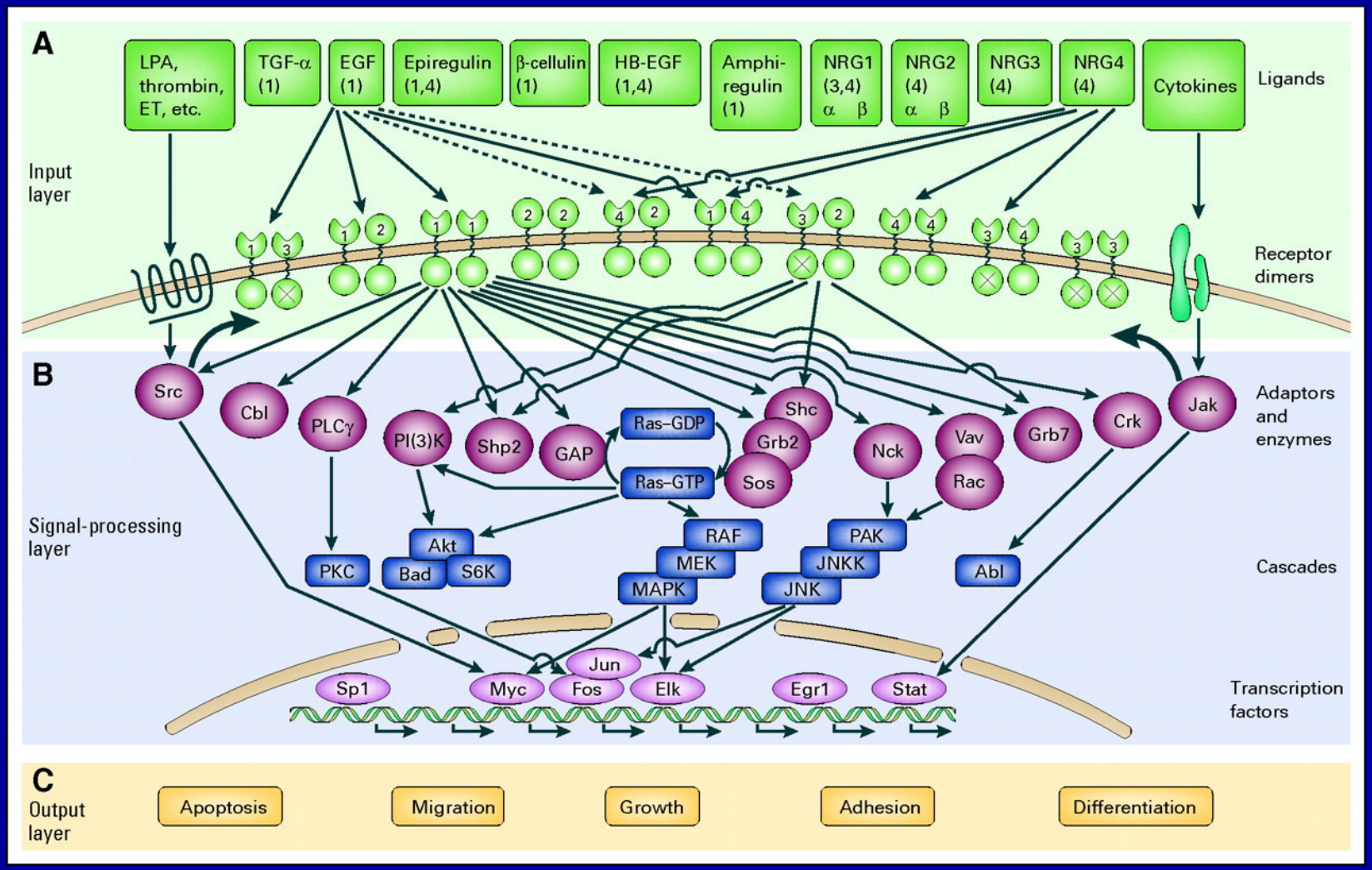
- **Single gene mutation**
  - Renal cancer
  - GIST
  - Her-2 + breast ca
  - EGFR mutated lung can
  - ER + breast cancer
  - APL
  - CML

30-80% single agent activity

- **Multigene mutations**
  - Colon cancer
  - Lung cancer
  - Breast cancer
  - Prostate cancer
  - Pancreas cancer

<10% single agent activity

# Redundancies and Cross Talks




Harari, P. M. et al. J Clin Oncol; 25:4057-4065 2007

# Genetic Events in Pancreatic Carcinogenesis

- **Oncogenes**
  - ***K-ras*** (~80%)
  - ***AKT2***
  - ***Cyclin D1***
  - ***Her-2***
  - ***MYB***
- **Xenobiotic-metabolizing enzymes**
  - ***CYPs***
  - ***GSTs***
- **Tumor suppressor genes**
  - ***p16 (95%)***
  - ***p53***
  - ***DPC4***
  - ***BRCA2***
  - ***p300***
- **DNA mismatch repair genes**
  - ***hMLH1***
  - ***hMSH2***

# Targeted therapy trials in pancreas ca

- M200
- Z-360
- Curcumin
- Isoflavone
- ARQ-501-212
- Sorafanib
- Flavopiridol
- Dasatinib
- Panitumumab
- Lapatinib
- Sunitinib
- Zactima
- Calcitriol
- Imatinib
- PTK787
- Enzastaurin
- Entracept
- AZD 0530
- Bevacizumab
- Cetuximab
- VEGF trap
- Axitinib

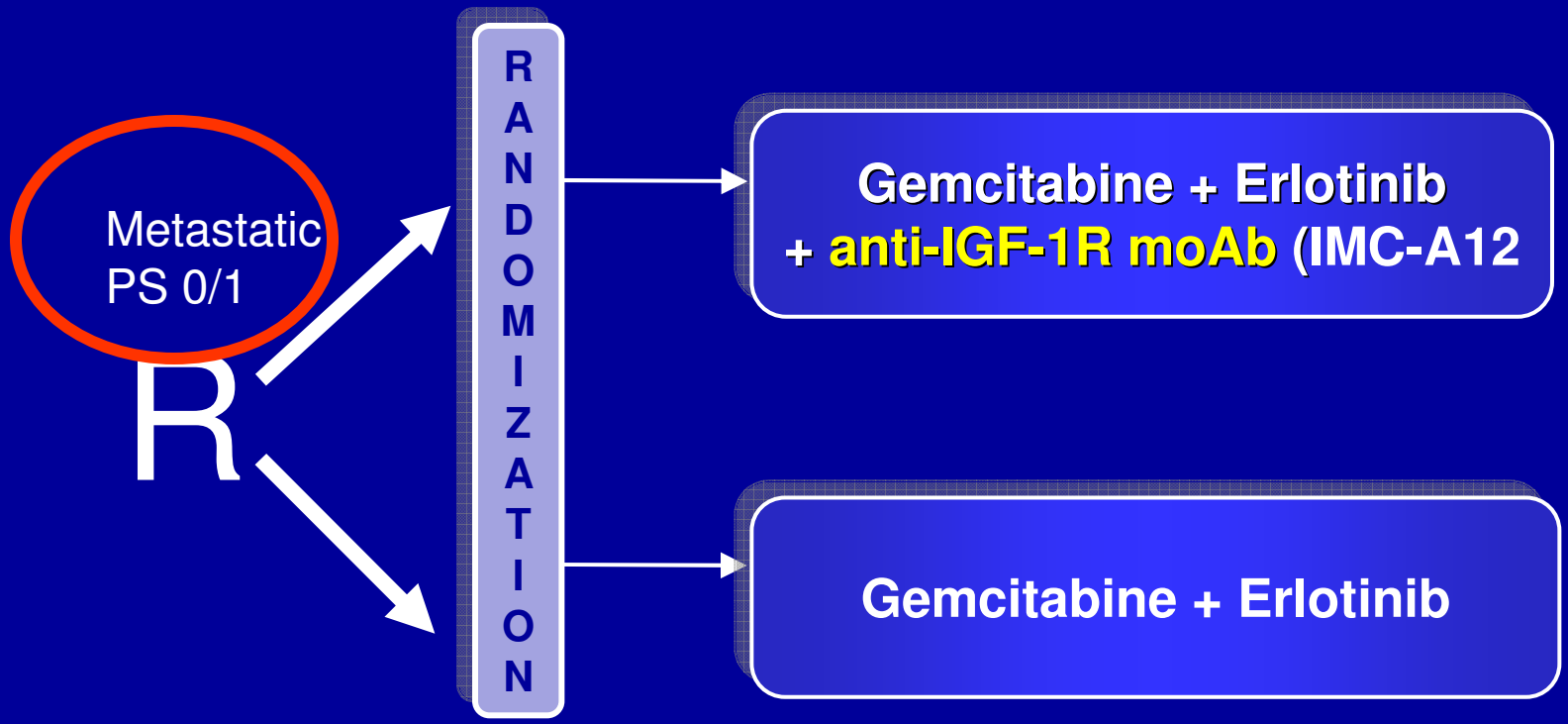
# Anti-EGFR based combinations

- EGFR plus VEGF
  - Bevacizumab + gemcitabine + erlotinib or cetuximab
  - University of Chicago
- EGFR axis “double hit”
  - Panitumumab + erlotinib + gemcitabine
  - NCCTG/Mayo

# Anti-EGFR based combinations (2)

- EGFR + src
  - Cetuximab + dasatinib + gemcitabine
  - CALGB concept
- HER family “double hit”
  - Gemcitabine + lapitinib
  - Brown University & Sarah Cannon
- EGFR + Akt/NFkB
  - Gemcitabine + erlotinib + genistein
  - Karmanos CC & MDACC

# SWOG's upcoming study: Randomized Phase II

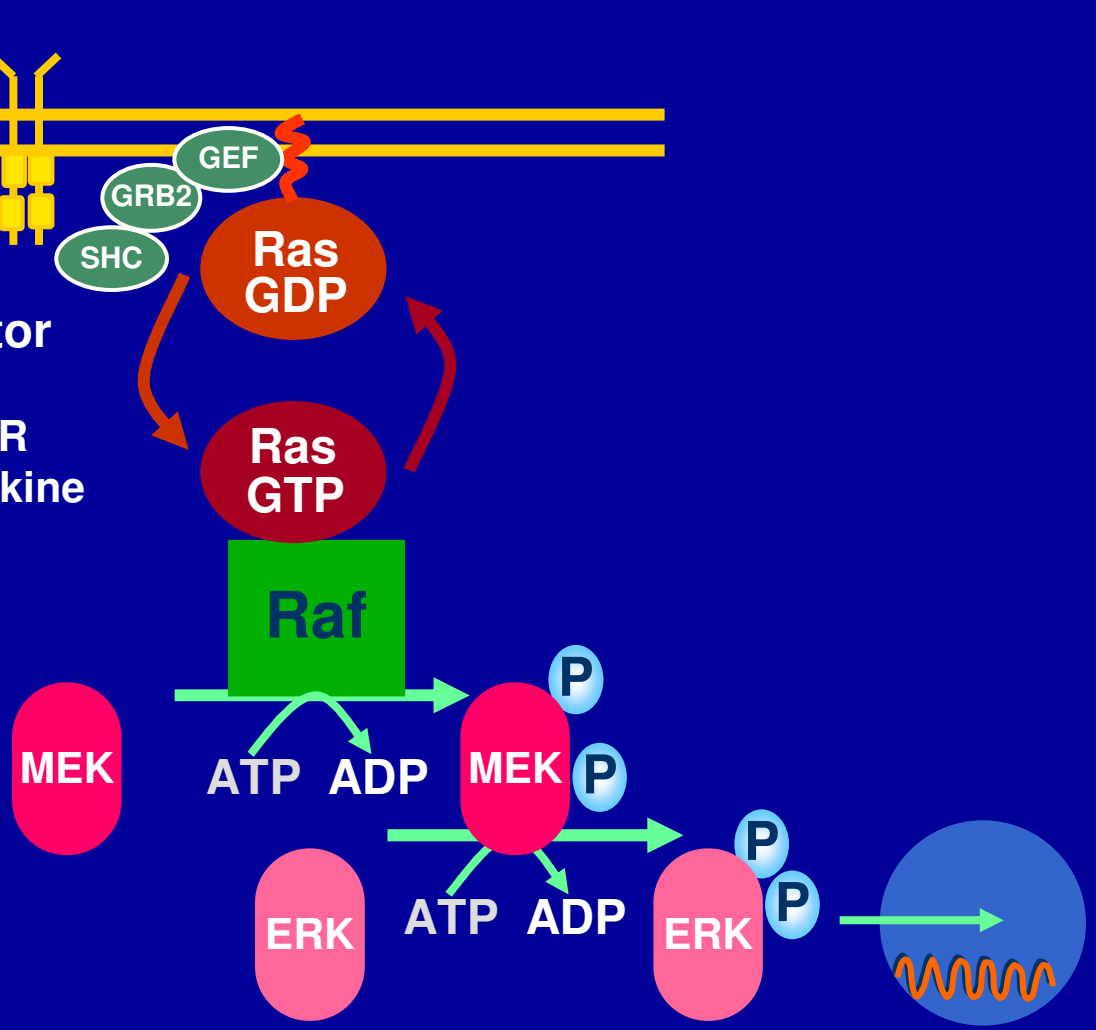



Sponsored by CTEP/ImClone

# Ras status: Potential determinant of anti-EGFR treatment outcome

**Extracellular signals**
- Hormones
- Growth factors
- Differentiation factors
- Tumor-promoting substances

**Receptor**
- RTK
- GPCR
- Cytokine



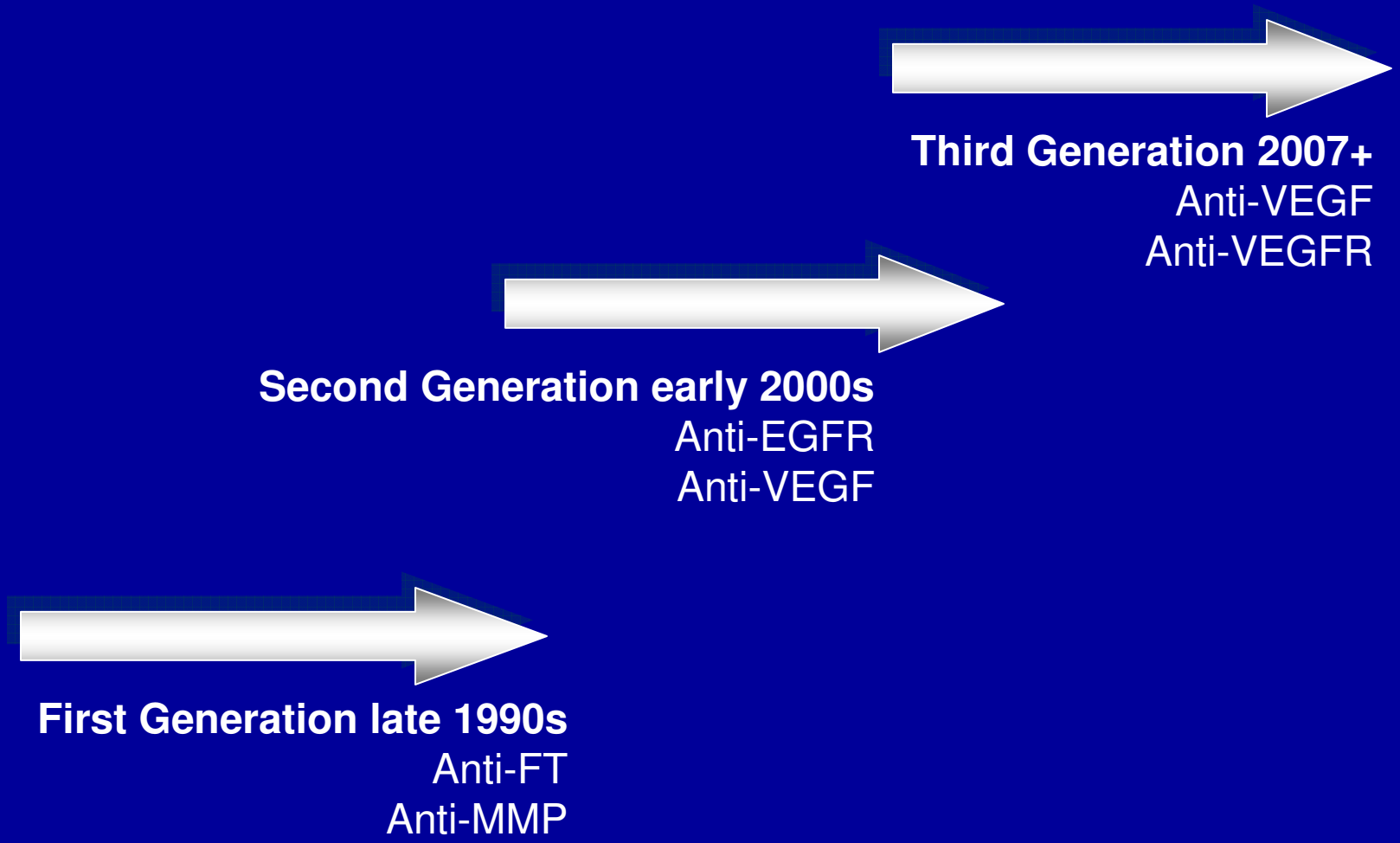
# The challenges of combination targeted therapies

- **Empericism versus good science**
- **Development of models**
- **PK/PD interactions**
- **$$$$$$$ versus added benefit**
- **PHARMA, CTEP, and FDA**

# Placing biologics on the best cytotoxic platform(s)

- *Cytotoxics with some activity*
  - S-1, capecitabine (Japan, EU)
  - Ixabepilone (SWOG)
  - FOLFOX/XELOX (EU)
  - Nab-paclitaxel (Phase I)
- *Do we need a cytotoxic platform?*

# March of the Phase III Studies of Gemcitabine +/- target X



# PRESENT

- Conventional cytotoxic therapy has minimal impact on pancreas cancer
- One-drug-single-pathway approach is unlikely to produce a major impact
- Combinations of targeted agents are currently in clinical trials

# FUTURE

- To discover science-driven “combinations”
- To understand treatments fail
- Refine patient “selection”
  - Clinico-pathol (PS, tumor extent, histol)
  - Molecular markers


BARBARA ANN
KARMANOS
CANCER INSTITUTE