# Treatment Approaches for Pancreatic Cancer

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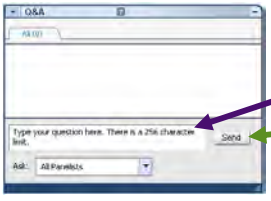


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# Treatment approaches for pancreatic cancer

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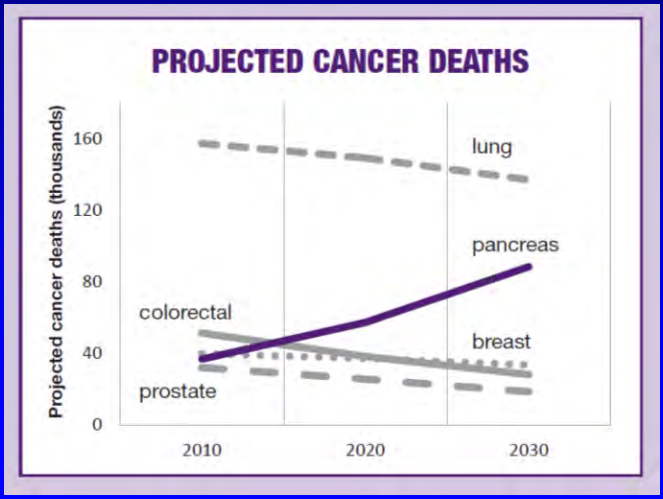
## Pancreatic cancer: A challenging disease

**Pancreas cancer:**

- **Has the lowest survival of *any* solid tumor**
  - Unfortunately, only 6% of all PC patients are cured
- **Is rarely diagnosed early, when it might be curable**
  - There are no effective screening tests
  - Vague early symptoms mimic other diseases
  - Nearby blood vessels allow it to spread quickly
- **Often doesn't respond to treatment**
  - It is resistant to many drugs
  - The dense stroma around the tumor acts as a barrier to protect the cancer cells from chemotherapy
  - We don't understand its biology well enough to develop more effective drugs

## Within this decade, pancreatic cancer is projected to become the 2nd leading cause of cancer death in the US




## Who gets pancreatic cancer?

**Incidence by gender in 2014:**

- 23,530 men
- 22,890 women

**Deaths by gender in 2014:**

- 20,170 men
- 19,420 women

**Age:**

- Most patients are between age 65 and 80 at diagnosis

**Race:**

- In the US, African-Americans are more likely to develop PC than Caucasians

# Risk factors

**Tobacco smoking**

- >30% of PC cases are due to smoking

**Pancreatitis** (5% of PC cases)

- Familial >> Acquired

**Increasing age**

**Weaker association:**

- Post-gastrectomy, post-cholecystectomy
- Diet: high fat intake, high meat intake
- Diabetes
- Industrial carcinogens

**Family History** (5-10%)

# Familial (inherited) syndromes

| Familial Syndrome | Genetic abnormality |
|---|---|
| Peutz-Jaegers | STK11/LKB1 |
| Familial pancreatitis | PRSS1, SPINK1 |
| FAMM | CDKN2A |
| HNPCC | hMLH1, hMSH2 |
| Hereditary breast-ovarian syndrome | BRCA1, BRCA2, PALB2 |
| Cystic fibrosis | CFTR |
| FAP | APC |
| Ataxia-telangiectasia | ATM |
| Li-Fraumeni | p53 |
| Familial pancreatic cancer | unknown |

## What are the most common symptoms at diagnosis?

- pain
- jaundice
- weight loss
- decreased appetite
- depression
- nausea/vomiting
- blood clots
- itching
- fatigue
- new onset diabetes

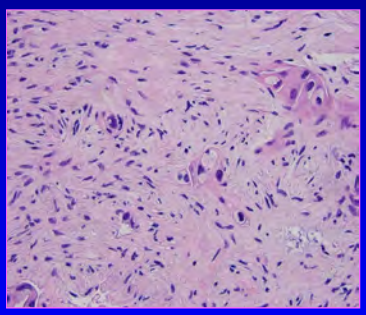
## If it looks like pancreas cancer on a scan, why is a biopsy required? Because knowing the pathologic type of pancreas cancer determines treatment options

**Exocrine carcinoma**

- Adenocarcinoma
  - >90% of PC
- Acinar

**Pancreatic neuroendocrine carcinoma (PNET): < 5%**

- Important to distinguish
- More indolent



Pancreatic adenocarcinoma demonstrating a prominent desmoplastic stromal reaction

## Staging pancreas cancer

- The stage of a cancer refers to the extent of the disease at diagnosis
- Stage is one of the most important factors for deciding treatment options and determining a patient's prognosis
- Stage is determined by CT scan, endoscopic ultrasound, biopsy, and physical examination. Sometimes stage is determined at surgery

## What is the TNM staging system?

- TNM staging is a standard way to determine how much a cancer has spread

The 3 elements are T, N, and M

- T: Indicates the size of the tumor in the pancreas and whether it has grown into nearby organs
- N: Indicates spread to lymph nodes
- M: Indicates spread to other organs
  - the most common sites of spread are the liver, lungs, or abdominal cavity (peritoneum)

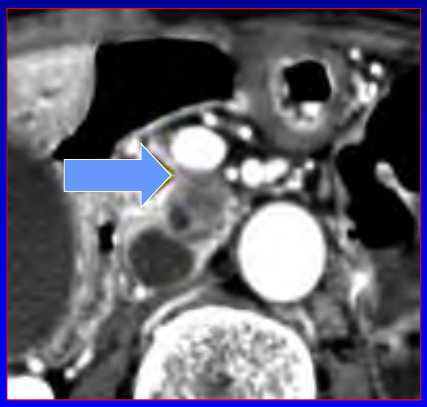
## TNM staging for pancreatic cancer

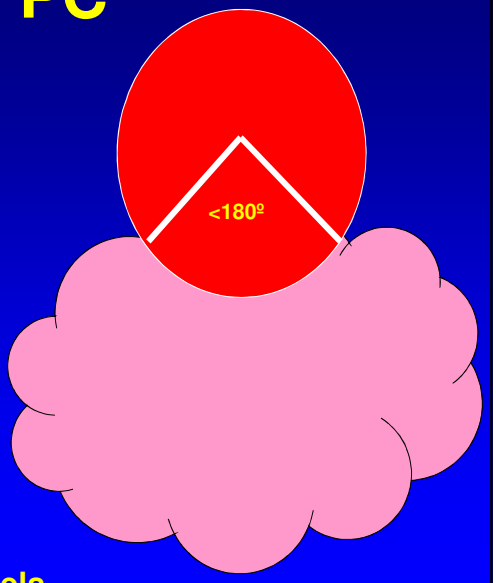
| Stage | TNM | Description |
|---|---|---|
| IA | $T_1N_0M_0$ | Tumor ≤2 cm (T1), confined to pancreas.<br>No spread to lymph nodes (N0). No distant spread (M0). |
| IB | $T_2N_0M_0$ | Tumor >2 cm (T2), confined to pancreas.<br>No spread to lymph nodes (N0). No distant spread (M0). |
| IIA | $T_3N_0M_0$ | Tumor extends outside pancreas (to bile duct, duodenum, peri-pancreatic tissues) but not into major blood vessels (T3).<br>No spread to lymph nodes (N0). No distant spread (M0). |
| IIB | $T_{1\text{-}3}N_1M_0$ | Tumor has spread to lymph nodes (N1).<br>No distant spread (M0). |
| III | $T_4N_{Any}M_0$ | Tumor is growing outside the pancreas into nearby major blood vessels or nerves (T4).<br>Lymph nodes may be involved (Any N).<br>No distant spread (M0). |
| IV | $T_{Any}N_{Any}M_1$ | Distant spread (M1). |

## Real world staging and treatment options

| Stage | Definition | Treatment |
|---|---|---|
| **Resectable** | | |
| Resectable | Can be removed with surgery | Surgery, followed by chemotherapy |
| Borderline resectable | Partly wrapped around blood vessels. Might be removable after chemotherapy and radiation | Chemotherapy + radiation, followed by surgery, if possible |
| **Unresectable** | | |
| Locally advanced | Cannot be removed. Has not spread | Chemotherapy +/- radiation |
| Metastatic | Has spread to other organs | Chemotherapy |

# Resectable PC






No distant spread, does not wrap around key blood vessels

## Standard treatment for resectable pancreas cancer

**Radical pancreaticoduodenectomy (Whipple)**

- Removes: proximal pancreas, lower stomach, bile duct, duodenum, proximal jejunum

**Other surgical options:**

- Head: Whipple with pylorus-preserving procedure
- Body/tail: distal or total pancreatectomy

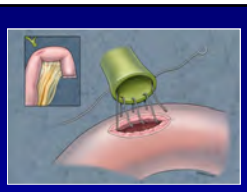
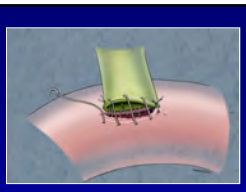
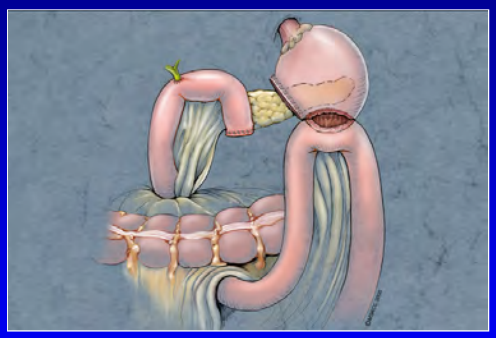
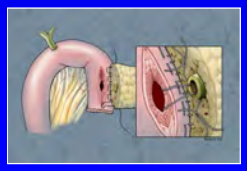
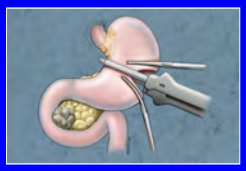
**<15% of PC patients are resectable:**

- Operative mortality 1-5%, major morbidity 20%
- Goals is to remove all of the cancer (R0/R1 resection); if you can't remove it all, you don't operate

**Post-operative (adjuvant) treatment:**

- 6 months of chemotherapy (Gemcitabine or 5-FU)
- Radiation is sometimes given (controversial)

## Pancreatico-duodenectomy
"Whipple procedure"

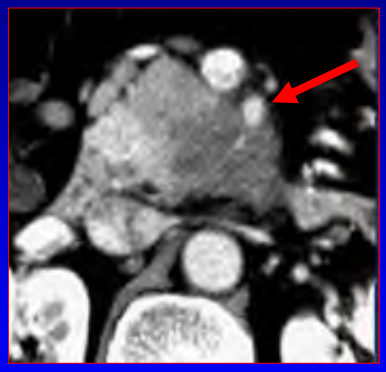
## The surgeon really matters

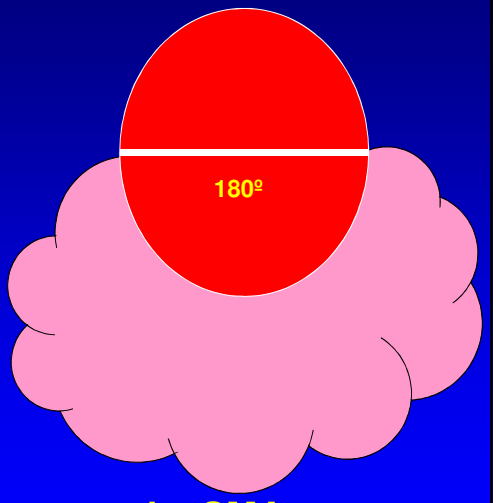
**High volume institutions with high volume surgeons have:**

- Longer survival
- Fewer surgical complications (morbidity) and fewer deaths (mortality)

- **Perioperative mortality:**
  - Low volume MD, low volume hospital: ~15%
  - High volume MD, high volume hospital: <3%

# Borderline resectable






Tumor partially encases the SMA,
an important blood vessel

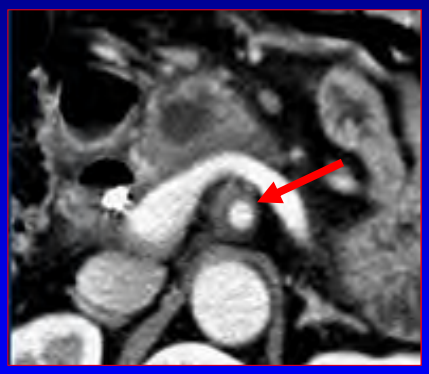
# Borderline resectable PC

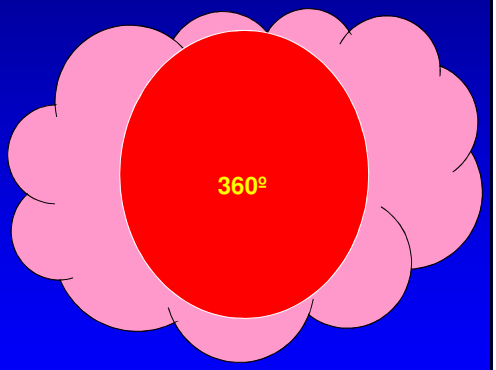
- When the cancer is partly wrapped around a key blood vessel, complete resection is unlikely
- Neo-adjuvant (pre-operative) chemotherapy and radiation is usually given to maximize the chance of completely removing the cancer
- Using the new, more active chemotherapy regimens, FOLFIRINOX and gemcitabine-nab-paclitaxel, may improve the chance of resection

What we still don't know:

- The best chemotherapy regimen for borderline PC, or how long to give it
- The role of radiation

# Unresectable





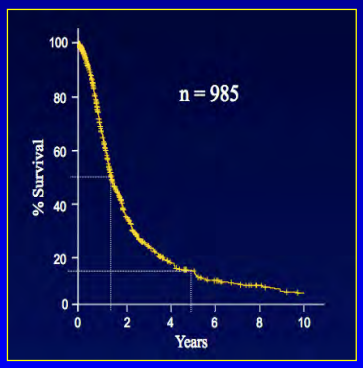

Tumor fully encases SMA

## Unfortunately, about 80% of pancreatic cancers come back after surgery

The goal of post-operative (adjuvant) chemotherapy:

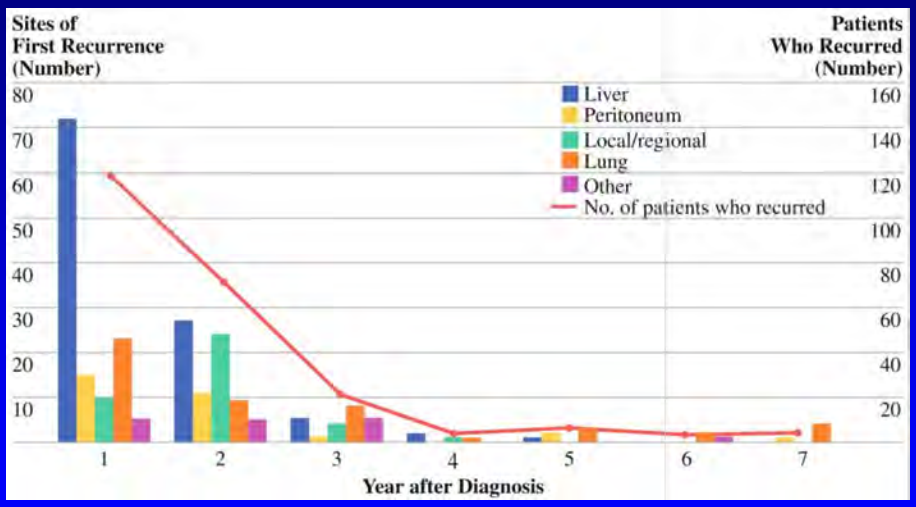
- To prevent the cancer from coming back
- Or to at least delay it from coming back

Once it returns, it is generally no longer considered curable




Survival after surgery

## Patterns of recurrence after resection




Katz, *Ann Surg Oncol* 2009

## Poor prognostic factors that suggest that a cancer is more likely to recur after surgery

- Large tumor size (high T stage)
- Poorly differentiated tumors
- + Lymph node involvement
- Positive resection margins (?)
- CA 19-9:
  - High pre-operative level (>1,000)
  - High post-operative level (>180)
  - No decrease after surgery

## We give 6 months of gemcitabine after surgery because of the results from the CONKO-001 randomized trial

Surgical resection

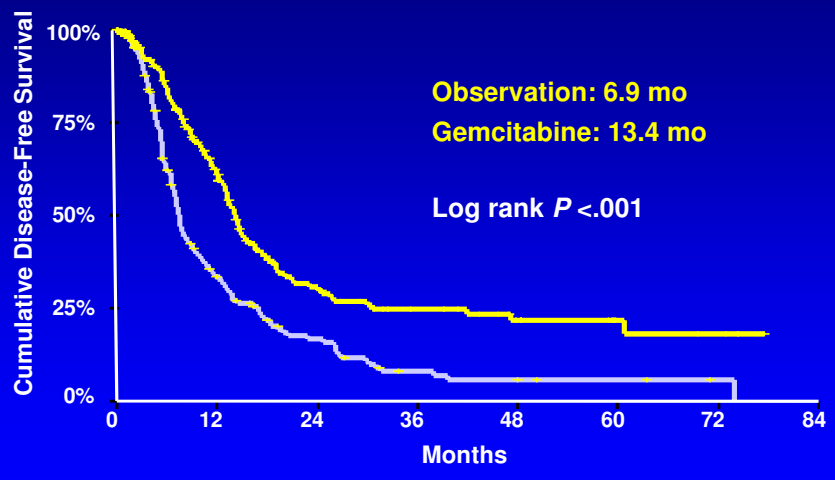
RANDOMIZE

Gemcitabine x 6 months

Observation

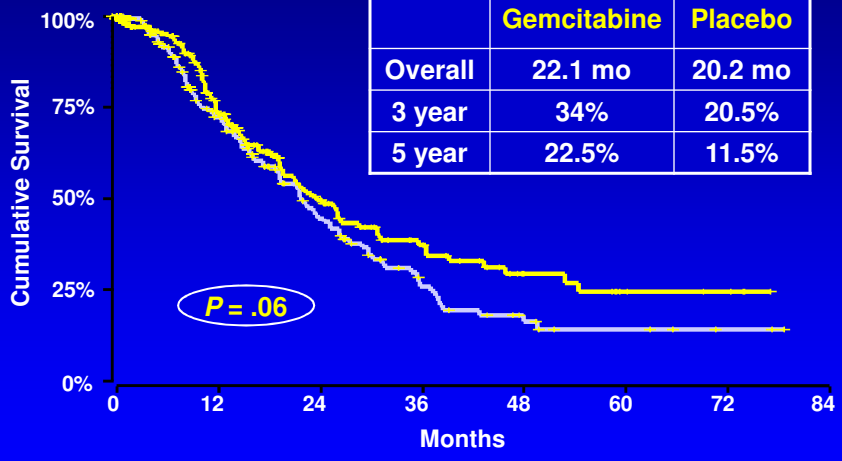
Oettle, *JAMA* 2007

## CONKO-001: Disease-free survival




Oettle H et al. *JAMA.* 2007;297:311-313

# CONKO-001: Overall survival




| | Gemcitabine | Placebo |
|---|---|---|
| Overall | 22.1 mo | 20.2 mo |
| 3 year | 34% | 20.5% |
| 5 year | 22.5% | 11.5% |

Oettle H et al. *JAMA*. 2007;297:311-313

# CONKO-001: Conclusions

- Adjuvant gemcitabine significantly improves both disease-free and overall survival compared to observation
- Adjuvant gemcitabine is associated with more than twice the rate of 5-year survival
- The overall survival benefit from gemcitabine holds for R0 and R1 resections, node +/- disease, and all T stages
- This study supports adjuvant gemcitabine as a community standard
  - Best level 1 evidence: disease-free survival, median and 5 year survival all superior to observation

## Ongoing clinical trials address unanswered questions regarding adjuvant chemotherapy and radiation for resectable PC

**Radiation**

- Is it beneficial? Is it necessary?

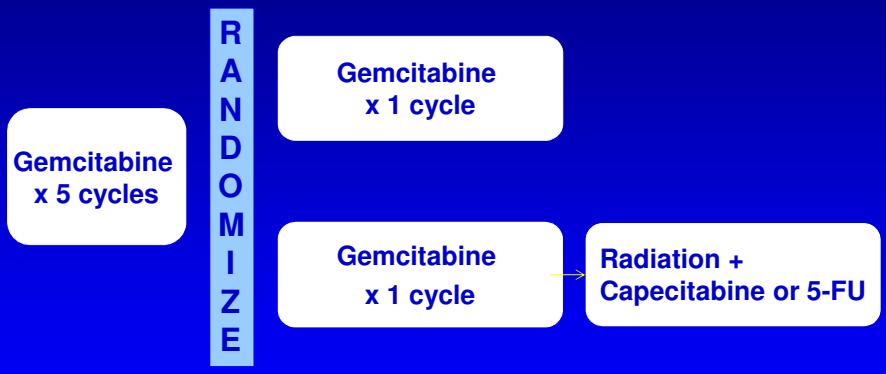
**Chemotherapy**

- Are the newer regimens for advanced disease also better in the post-operative (adjuvant) setting?

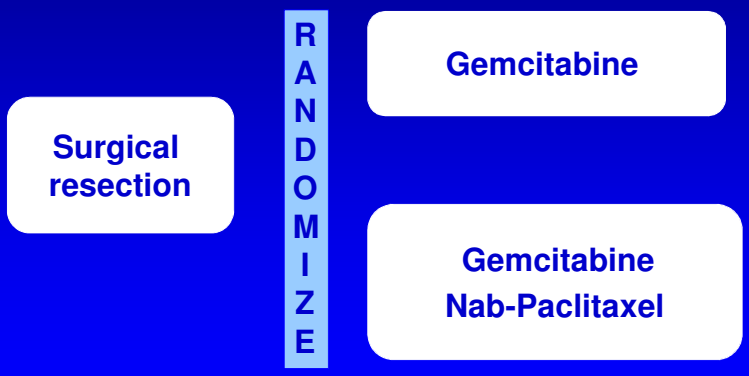
**Timing**

- Is it better to give chemotherapy before surgery?

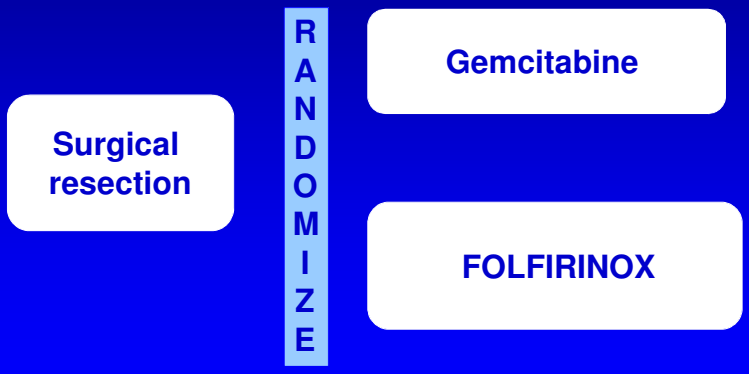
## Evaluating the role of radiation after surgery: RTOG 0848



## Incorporating the newer regimens into post-surgical therapy: Phase III trial of adjuvant gemcitabine + nab-paclitaxel




## Incorporating the newer regimens into post-surgical therapy: Phase III trial of adjuvant FOLFIRINOX vs. Gemcitabine



## Evaluating the role of chemotherapy before and after surgery: FOLFIRINOX


## Summary: Adjuvant therapy for pancreatic cancer

- Adjuvant therapy options increasingly include systemic chemotherapy alone
- Some data supports 5-FU/LV (ESPAC-1, 3)
- Level 1 evidence supports adjuvant gemcitabine (CONKO-001), which improves disease-free and overall survival
- Relative contribution of chemotherapy vs. chemo-radiation unanswered
- The role of newer regimens (FOLFIRINOX, gemcitabine-nab-paclitaxel) is unknown

## Locally advanced PC (LAPC)
## A distinct clinical entity

- Disease has not spread, but cannot be removed, usually due to involvement of blood vessels
  - ~1/3 of PC patients
  - Different biology, outcomes than metastatic PC
- Role of radiation is controversial
  - Controls pain well
  - Can be difficult to tolerate:
    - Side effects include nausea, vomiting, fatigue
  - Recent LAP-07 trial suggests that radiation may not improve survival
  - Optimal timing of radiation also uncertain

## Induction chemotherapy before radiation in LAPC

- Up to ⅓ of LAPC patients develop metastatic disease within the first few months of starting chemotherapy
- Up-front chemotherapy
  - May eradicate occult micro-metastatic disease
  - Spares patients who develop early metastatic progression from toxicities of radiation
  - Limits radiation to patients whose tumors are well-controlled with systemic therapy

## GERCOR retrospective analysis in LAPC

**Impact of CRT after disease control with chemotherapy**

- 181 LAPC pts: chemotherapy for at least 3 months
  - 29% developed metastatic disease during induction chemotherapy
- Investigators choice in the remaining 128 patients
  - Chemo-RT or continue chemotherapy

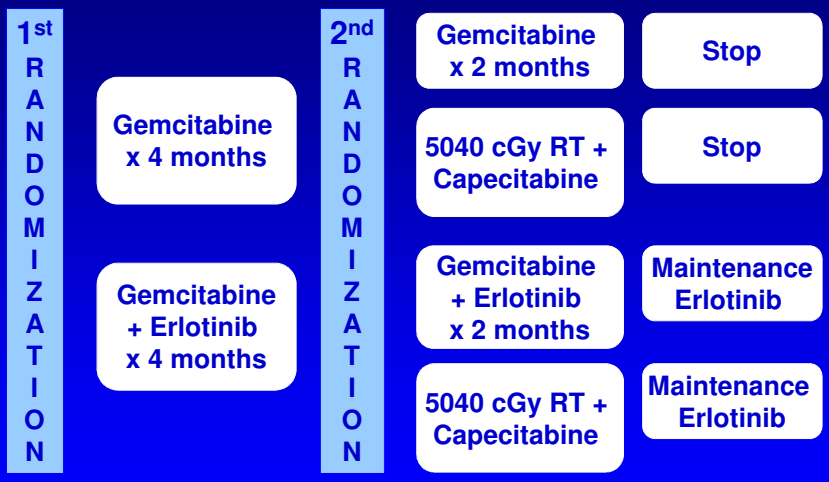
| | Chemo-RT (55%) | Chemo (44%) | P value |
|---|---|---|---|
| PFS | 10.8 mo | 7.4 mo | .005 |
| OS | 15 mo | 11.7 mo | .0009 |

Retrospective study: No definitive conclusions
Hypothesis generating

Huguet, *JCO* 2007

## LAP-07 Trial design

**Does CRT ↑ OS in pts w/tumor control after induction chemo?**




Futility boundary for $1^0$ hypothesis crossed after 442 pts randomized

Hammel, *ASCO* 2013

# LAP-07 Results

| R1+ R2 | Gem-chemo | Gem-CRT | GE-chemo | GE-RT |
|---|---|---|---|---|
| Patients | 68 | 67 | 68 | 66 |
| OS | 18 mo | 16.7 mo | 14.5 mo | 14.7 mo |

| R1 | Gem | Gem-Erlotinib |
|---|---|---|
| Patients | 223 | 219 |
| OS | 13.6 mo | 11.9 mo |
| PFS | 10.7 mo | 9.3 mo |

| R2 | Chemo | Chemo-RT |
|---|---|---|
| Patients | 136 | 133 |
| OS | 16.4 mo | 15.2 mo |
| PFS | 11.8 mo | 12.5 mo |

Hammel, *ASCO* 2013

## LAP-07
# Conclusions

- In LAPC patients with tumor controlled after 4 months of gemcitabine-based chemotherapy
  - CRT is not superior to continuing chemotherapy
  - Author's conclusion: Standard of care in LAPC should remain chemotherapy
    - CRT is an option
- Erlotinib in LAPC
  - Not beneficial
  - Increases toxicity
- Is there a subgroup who might benefit from CRT?
  - Correlative studies pending

## LAP-07
## Potential explanations for these results

- CRT is not superior to continuing chemotherapy
  - Is there *any* role for CRT in LAPC?
- There was inadequate radiation
  - Could we do better with IMRT, SBRT?
- There was inadequate chemotherapy
  - Could we do better with FOLFIRINOX, Gem-*nab*-P?
- There was inadequate chemo during RT
  - SCALOP trial: capecitabine better than gem with RT[1]
  - Are there better agents?
- Only a subset of patients can benefit
  - Can we use biomarkers like *Smad4* to select them?

1. Mukherjee, *Lancet Oncol* 2013

## Chemotherapy for metastatic pancreas cancer

- Metastatic PC has spread, usually to the liver, lungs, or abdominal cavity (peritoneum)

**The goal of chemotherapy treatment for metastatic pancreas cancer is palliative:**

- To shrink or stabilize disease
- To improve or prevent symptoms
- To prolong survival

## The historical perspective: Chemotherapy for metastatic PC

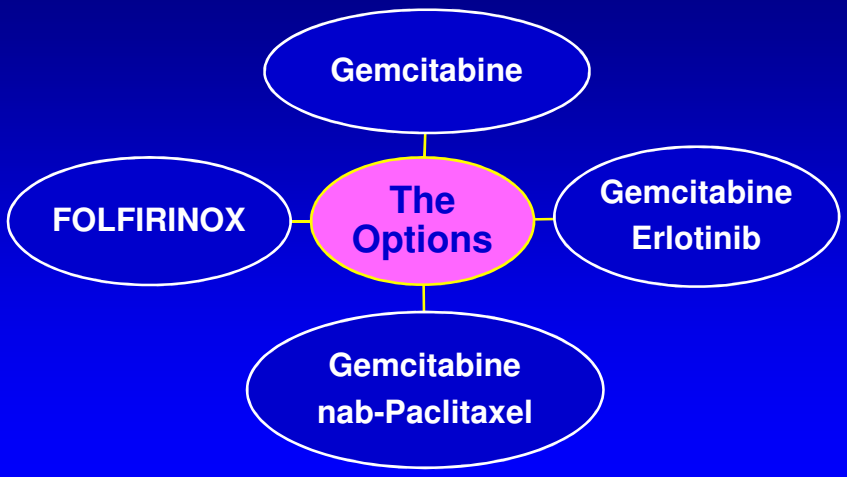
**Long-standing, well-deserved therapeutic nihilism**

- Countless trials over several decades
- Many drugs and combinations tested
- Minimal to no activity observed

## It's 2015

## This dismal outlook has changed

# Now we have choices




## Key milestones in the development of new drugs for pancreatic cancer

| | |
|---|---|
| Pre-1996 | The dark ages. Nothing works |
| 1996 | Gemcitabine improves survival compared with 5-FU. Gemcitabine is approved for PC |
| 1996-2005 | Many agents tested. No drug or drug combination is better than Gemcitabine |
| 2005 | Erlotinib + Gemcitabine modestly improves survival compared with Gemcitabine. Erlotinib is approved for PC |
| 2005-2009 | More drugs tested. Many more negative trials |
| 2010 | FOLFIRINOX improves survival compared with Gemcitabine |
| 2012 | *nab*-Paclitaxel + Gemcitabine improves survival compared with Gemcitabine |

## We've made some progress: Chemotherapy for pancreatic cancer: The dark ages

- Between 1991 and 1994, 25 investigational agents were evaluated in phase II trials for pancreatic cancer
- Median response rate: 0% (range 0-14%)
- Median survival: 3 months

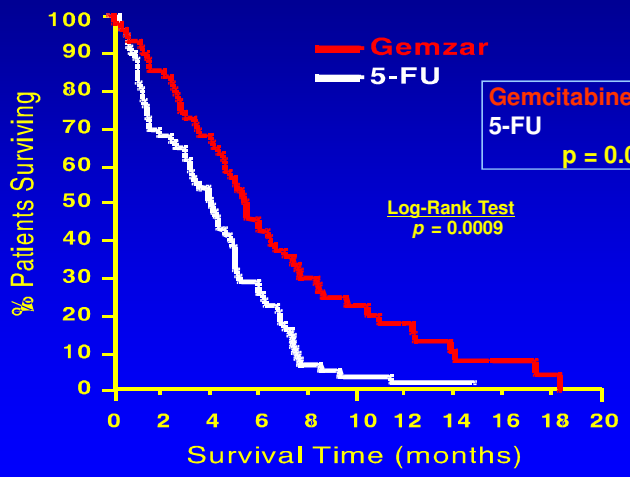
Rothenberg, *Oncology* 1996

## Gemcitabine has a genuine, but modest impact on survival and quality of life

| | Gemcitabine | 5-FU | P value |
|---|---|---|---|
| Patients | 63 | 63 | |
| Tumor Response | 5.4% | 0% | |
| Survival | 5.65 mo | 4.4 mo | 0.0025 |
| 1-year survival | 18% | 2% | 0.0025 |
| TTP | 2.1 mo | 0.9 mo | |
| Clinical Benefit Response | 24% | 5% | 0.0022 |

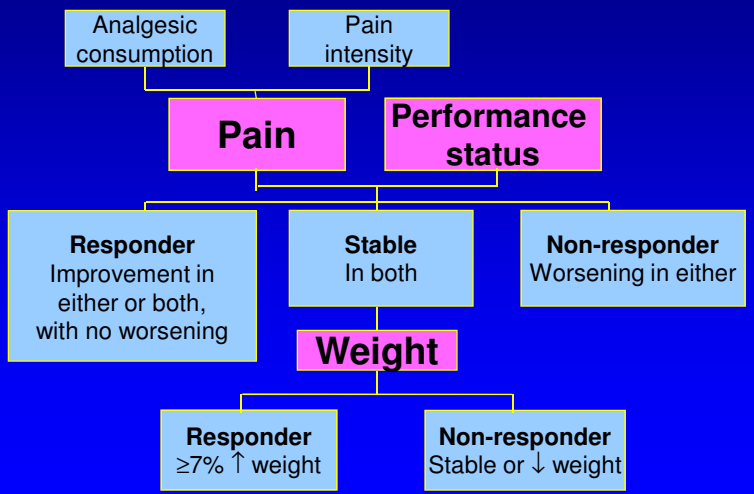
Burris, *JCO* 1997

# Overall survival: Gemcitabine vs. 5-FU




Burris, *JCO* 1997

# We administer gemcitabine principally because it produces "clinical benefit"



## Gemcitabine in context

- The cornerstone of PC therapy for many years

**Gemcitabine:**

- Minimal response rate
- Statistically significant but modest improvement in OS (4.4 vs. 5.6 months)
- Minimal toxicity
- Improves pain and PS and stabilizes weight
- No predictive biomarker
  - hENT1 data to date is negative in advanced disease[1,2]

**The right patient:**

- Elderly patient with a poor PS
- The toxicity averse, symptomatic patient

1. Poplin *JCO* 2013 2. Ormanns, *EJC* 2014

## We should be able to do better than this!

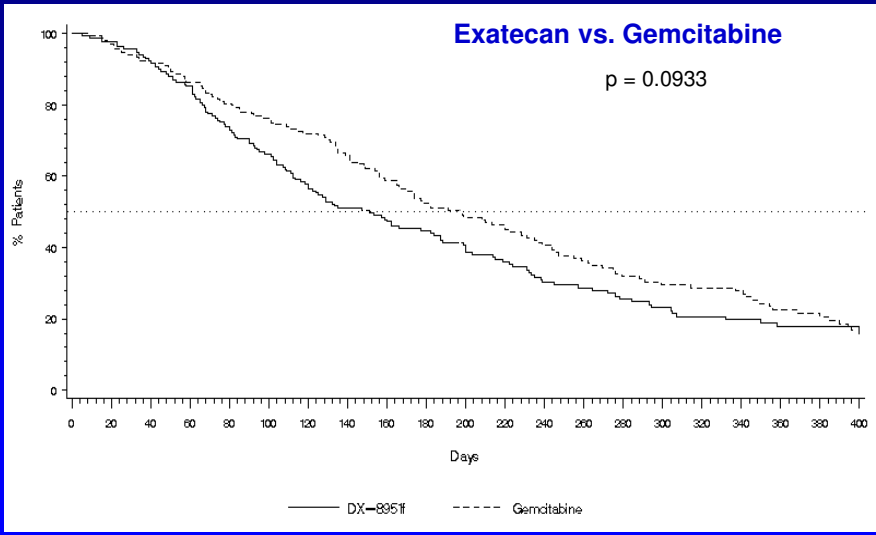
## How do we determine if there are any other drugs that work better than gemcitabine?

**Until recently, the most common designs for randomized trials in pancreatic cancer patients**

- **Drug X**
  **vs. Gemcitabine**
- **Drug X plus Gemcitabine**
  **vs. Gemcitabine**

**Even though gemcitabine doesn't work very well, it still works better than most other drugs**

## In phase III trials of Drug X vs. Gem, Gem usually wins—by ALOT

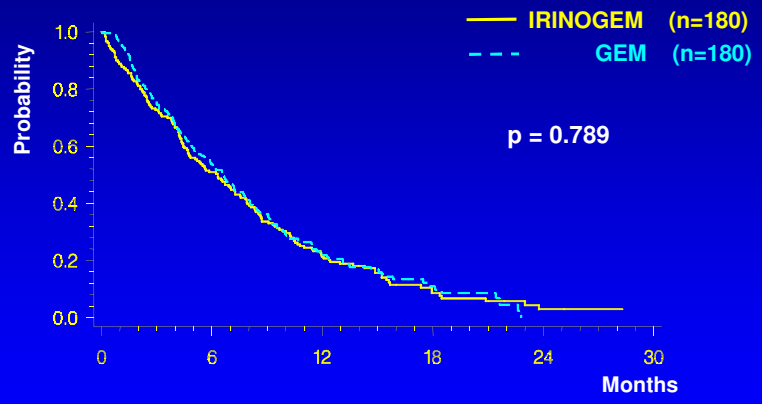



## Gemcitabine also makes sick people feel better, and it is less toxic than most other drugs or drug combinations

## Two drugs should work better than one

## Why not add other drugs to gemcitabine?

## In phase III trials of Drug X + Gem vs. Gem, there is usually greater toxicity with the combination, but no survival difference



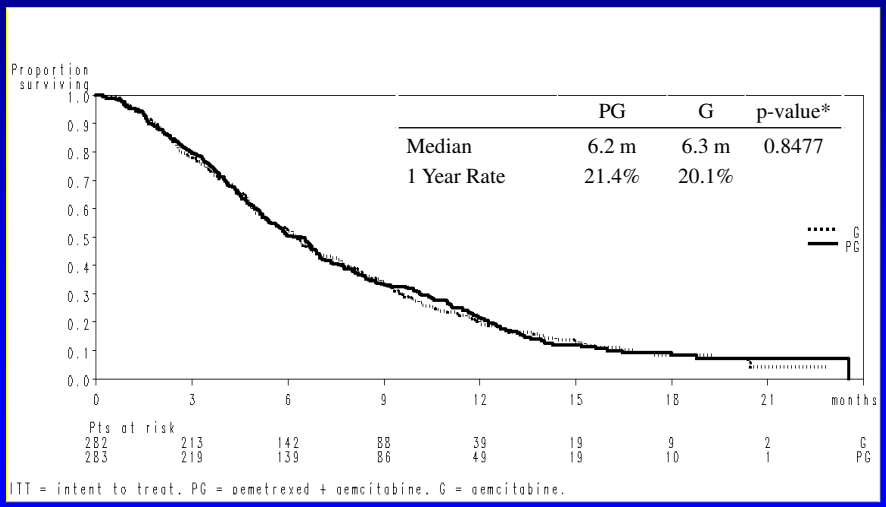

IRINOGEM: median 6.3 months [4.7-7.5] – 1 year OS 21%

GEM: median 6.6 months [5.2-7.8] – 1 year OS 22%

**Unfortunately,**
**most of the time,**
**more is not better**

**Most combination treatments increase side effects, but don't improve survival**

**This pattern of super-imposable survival curves has been the most common outcome of phase III PC trials**



ITT = intent to treat. PG = pemetrexed + gemcitabine. G = gemcitabine.

## Despite "promising activity" of many Gem-doublets in phase II studies, they have not improved survival in phase III trials

| Drug | G + X | G | P value |
|---|---|---|---|
| bolus 5-FU | 6.7 mo | 5.4 mo | 0.11 |
| 24-hr 5-FU | 5.9 mo | 6.2 mo | 0.683 |
| Pemetrexed | 6.2 mo | 6.3 mo | 0.85 |
| Capecitabine | 8.4 mo | 7.3 mo | 0.314 |
| Irinotecan | 6.3 mo | 6.6 mo | 0.789 |
| Exatecan | 6.7 mo | 6.2 mo | 0.52 |
| Cisplatin | 7.6 mo | 6.0 mo | 0.12 |
| Oxaliplatin | 9.0 mo | 7.1 mo | 0.13 |

## This bleak outlook finally changed in 2005 with a Canadian trial

## The NCIC PA3 trial demonstrated a modest improvement in survival for gemcitabine + erlotinib

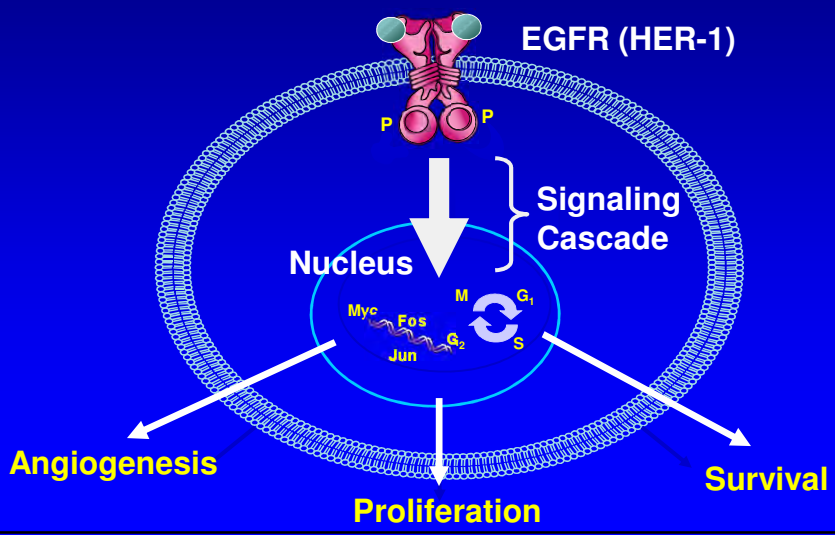
569 pts

- Gemcitabine + Erlotinib — 100 or 150 mg po qd
- Gemcitabine + Placebo

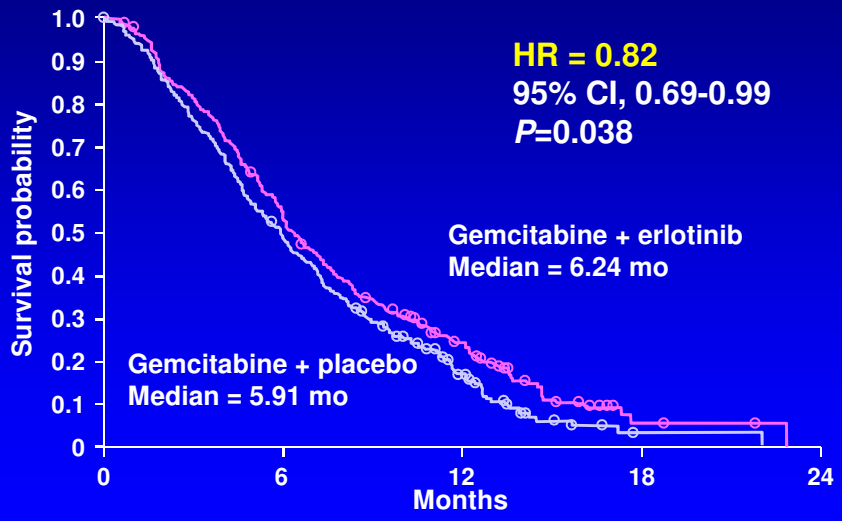
Statistics: 80% power to detect a 33% ↑ survival, $\alpha$=0.05

Moore, *JCO* 2007

## Erlotinib (Tarceva) inhibits the epidermal growth factor receptor (EGFR) tyrosine kinase



# Overall Survival




*Adjusted for PS, pain, and disease extent at randomization.

## Gemcitabine + erlotinib:
## A modest improvement

| | GE | G | HR | P |
|---|---|---|---|---|
| Patients | 285 | 284 | | |
| Response | 8.6% | 8.0% | | |
| Median survival (mo) | 6.24 | 5.91 | 0.82 | 0.038 |
| 1-year survival | 23% | 17% | | 0.023 |
| PFS (mo) | 3.75 | 3.55 | 0.77 | 0.004 |
| QOL (EORTC QLQ-C30) | Better on placebo (↑ diarrhea on GE) | | | |
| GE: Cost/YLG | $500K[1] | | | |
| In 2005, the FDA approved erlotinib in combination with gemcitabine for advanced PC | | | | |

1. Grubbs, *Proc ASCO* 2006

## Can a biomarker predict the activity of erlotinib?

**KRAS mutations**

- Confer resistance to EGFR inhibitors
- Very common in PC (75-90%)
  - The highest incidence of any cancer

**Activating EGFR mutations**

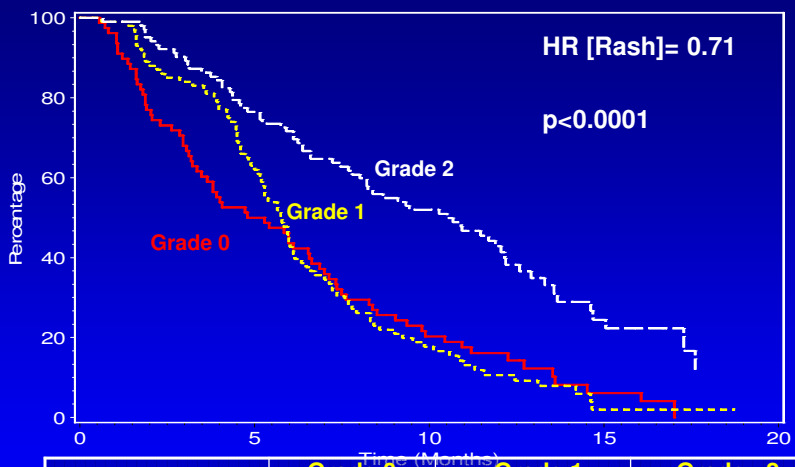
- Rare (<4%)

**Molecular subset analysis of PA3 trial**

  - KRAS status did not predict a survival benefit for gemcitabine + erlotinib

da Cunha Santos, *Cancer* 2010

## Severity of rash correlates with survival




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

## Dose escalation to rash
## The RACHEL study

In patients with grade 0-1 rash after 4 weeks of gemcitabine + erlotinib:

- Does escalating the erlotinib dose to >100 mg improve survival?

| | Standard dose erlotinib (N=75) | Dose-escalated erlotinib (N=70) | p |
|---|---|---|---|
| Rash ≥ Grade 2 | 9% | 41% | <0.0001 |
| OS (mo) | 8.4 | 7.0 | 0.2026 |
| PFS (mo) | 4.5 | 3.5 | 0.6298 |

**Dose-escalating erlotinib increases rash, not survival**

Van Cutsem, 2012

## Gemcitabine + Erlotinib in context

- PA3 is the 1st randomized trial to demonstrate that *any* drug added to Gem prolongs survival in PC

**Erlotinib + gemcitabine produces:**

- A statistically significant improvement in OS (HR 0.82) and PFS (HR 0.77)
- Modest toxicity
- No improvement in QOL
- Substantial cost ($500K/YLG)
- No biomarker to select those most likely to benefit

**Questions:**

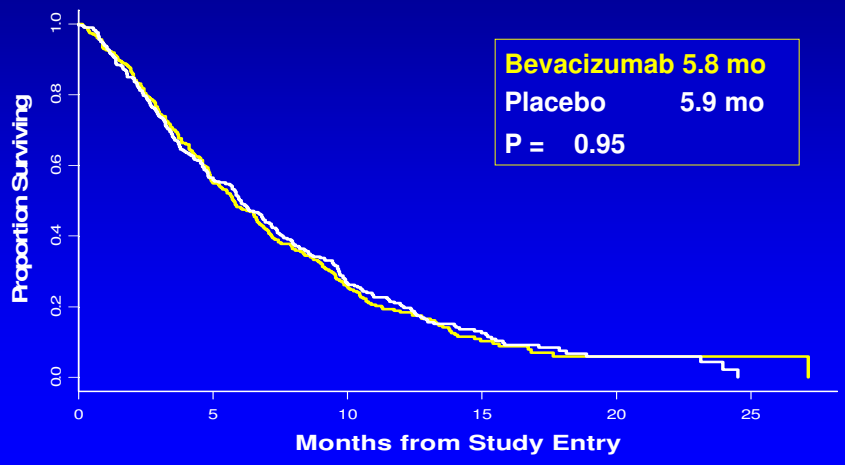
- How clinically meaningful are these results?
- Is the modest benefit worth the expense & toxicity?

**Who is the best patient for this regimen?**

## Over the next 5 years, several more negative phase III trials were reported

| Trial | Drug | N | G + X (mo) | G (mo) | P value |
|---|---|---|---|---|---|
| GEMCAP | Capecitabine | 533 | 7.1 | 6.2 | 0.08 |
| GIP | Cisplatin | 400 | 7.2 | 8.3 | 0.38 |
| E6201 | Oxaliplatin | 832 | 5.7 | 4.9 | 0.22 |
| | FDR Gem | | 6.2 | | 0.04 |
| CALGB 80303 | Bevacizumab | 602 | 5.8 | 5.9 | 0.95 |
| S0205 | Cetuximab | 704 | 6.4 | 5.9 | 0.14 |
| GemAx | Axitinib | 632 | 8.5 | 8.3 | 0.54 |
| AViTA | Bevacizumab (vs. GemErlotinib) | 607 | 7.1 | 6.0 | 0.21 |

## CALGB 80303: Gemcitabine +/- Bevacizumab Once again, no survival difference



## Have we learned anything from these negative trials? A meta-analysis

| | HR survival | P value |
|---|---|---|
| Gem + X | 0.91 | 0.004 |
| Gem + platinum | 0.85 | 0.01 |
| Gem + fluoropyrimidine | 0.90 | 0.03 |
| Gem + other cytotoxic | 0.99 | 0.08 |
| Good PS (≥ 90%) | 0.76 | <0.0001 |
| Poor PS (60-80%) | 1.08 | 0.04 |

- Gem + a platinum or a fluoropyrimidine:
  - Modestly superior to gem alone
- Good PS pts:
  - Survival benefit from combination chemo
- Poor PS pts: No benefit from combination chemo

Heinemann, *BMC Cancer* 2008

## Then came the study that changed the way we think about chemotherapy for pancreatic cancer

# In 2010: A substantial treatment advance
# The PRODIGE 4 - ACCORD 11 trial

342 patients

RANDOMIZE

→ FOLFIRINOX

Primary endpoint: OS

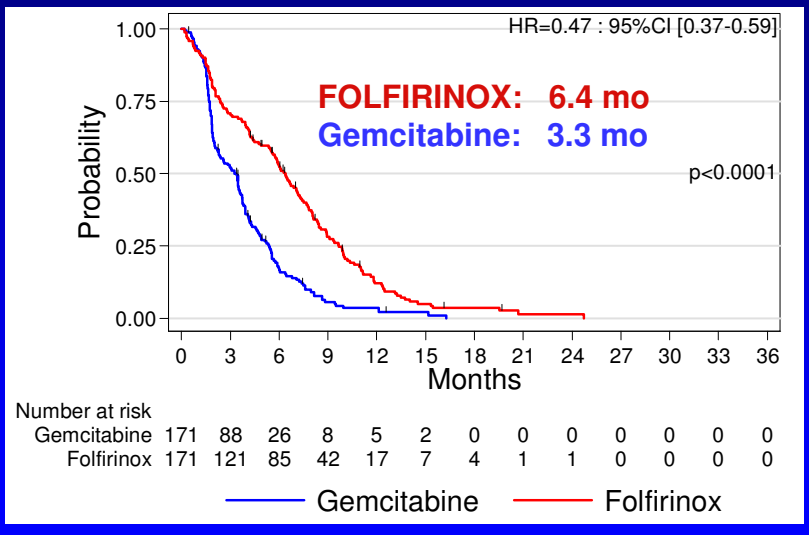
→ Gemcitabine

No prior chemo
PS 0-1
< 76 yrs
Measurable metastatic disease
T. bili < 1.5 x ULN

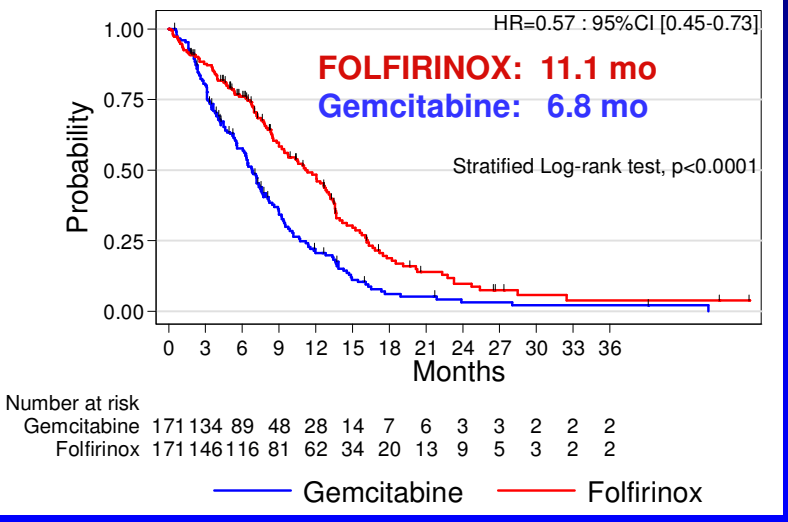
**Stratification:**
- Center
- PS: 0 vs. 1
- $1^0$ tumor location: head vs. other

Conroy, *ASCO* 2010, *NEJM* 2011

# Progression-free survival



# Overall survival




## FOLFIRINOX vs. Gemcitabine

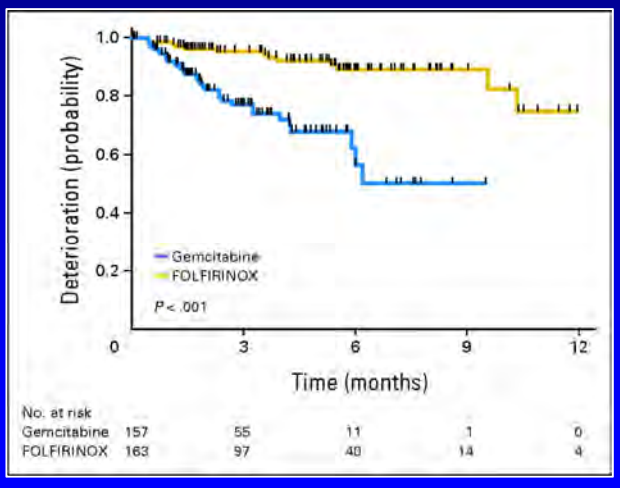
# Efficacy

| | F | G | HR | P |
|---|---|---|---|---|
| Patients | 171 | 171 | | |
| Objective Response | 31.6% | 9.4% | | 0.0001 |
| Stable disease | 38.6% | 41.5% | | |
| Disease control (PR+SD) | 70.2% | 50.9% | | 0.0003 |
| Median survival (mo) | 11.1 | 6.8 | 0.57 | <0.0001 |
| 1-year survival | 48.4% | 20.6% | | |
| 18 month survival | 18.6% | 6% | | |
| PFS (mo) | 6.4 | 3.3 | 0.47 | <0.0001 |

## FOLFIRINOX vs. Gemcitabine
## Selected grade 3 and 4 toxicities

| | F | G | P value |
|---|---|---|---|
| Neutropenia | 45.7% | 21% | <0.001 |
| Febrile neutropenia | 5.4% | 1.2% | 0.03 |
| G-CSF usage | 42.5% | 5.3% | |
| Thrombocytopenia | 9.1% | 3.6% | 0.04 |
| ↑ ALT | 7.3% | 20.8% | <0.001 |
| Diarrhea | 12.7% | 1.8% | <0.001 |
| Fatigue | 23.6% | 17.8% | NS |
| Neuropathy | 9% | 0% | <0.001 |
| Vomiting | 14.5% | 8.3% | NS |
| Alopecia (grade 2) | 32.5% | 3% | 0.0001 |

**Although they had more chemotherapy-related side effects, patients who received FOLFIRINOX felt much better for much longer than patients who received Gemcitabine**




Gourgou-Bourgade, *JCO* 2013

## Finally, a big step forward

**After so many negative trials of gemcitabine doublets, the unprecedented outcomes achieved with FOLFIRINOX are a major treatment advance for good PS pancreatic cancer patients**

No other randomized study has ever:

- Achieved a median survival of nearly a year
- Demonstrated such a high response rate

Despite substantial, but manageable toxicities, FOLFIRINOX also helps patients feel better for longer than if they received gemcitabine (a drug used principally for its impact on symptoms)

- Remarkably, it's even cost-effective

## A paradigm shift

- **This is a true paradigm shift**
  - For the first time, an oncologist can confidently tell a pancreatic cancer patient who has a good performance status that they are very likely to obtain disease control with chemotherapy
- **It has been a very long journey**
  - We are finally beginning to make progress against this devastating disease

## FOLFIRINOX in context

- Significantly improves median OS
  - 11.1 vs. 6.8 mo, HR 0.57, p<0.0001
- Significantly improves PFS
  - 6.4 vs. 3.3 mo HR 0.47, p<0.0001
- Yields a meaningful delay in worsening of QOL
- Is cost-effective
- Is more toxic:
  - 46% gr ¾ neutropenia, 5% febrile neutropenia
  - Vigilant patient selection, education, monitoring are essential
- Impact of routine dose modifications unclear
- No biomarker identified to date
- Who is the optimal patient for FOLFIRINOX?

## Soon afterwards, another study demonstrated that another new combination is more active than gemcitabine

# The MPACT Trial

**861 patients**

- Stage IV
- No prior treatment for metastatic disease
- KPS ≥ 70
- Measurable disease
- Total bilirubin ≤ ULN

***nab*-Paclitaxel**
125 mg/m² IV qw 3/4
+
**Gemcitabine**
1000 mg/m² IV QW 3/4

1:1, stratified by KPS, region, liver metastasis

**Gemcitabine**
1000 mg/m² IV QW 7/8
then QW 3/4

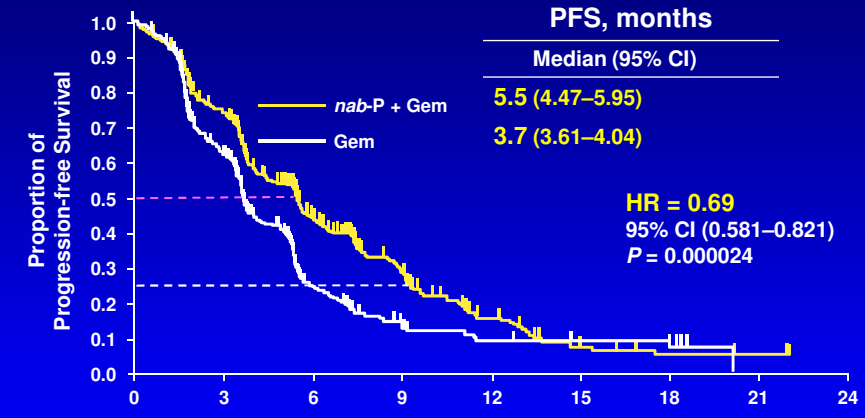
**Primary endpoint: Overall survival**

151 sites
enrolled 861 patients
on 3 continents
over 3 years

- 608 events, 90% power to detect OS; HR = 0.769 (2-sided α = 0.049)
- Treat until progression
- CT scans Q8 wks
- PET scan subset: baseline, wks 8, 16
- CA19-9: at baseline and Q8 wks

von Hoff, ASCO 2013, NEJM 2013

# Progression-free survival




**PFS, months**

| | Median (95% CI) |
|---|---|
| *nab*-P + Gem | 5.5 (4.47–5.95) |
| Gem | 3.7 (3.61–4.04) |

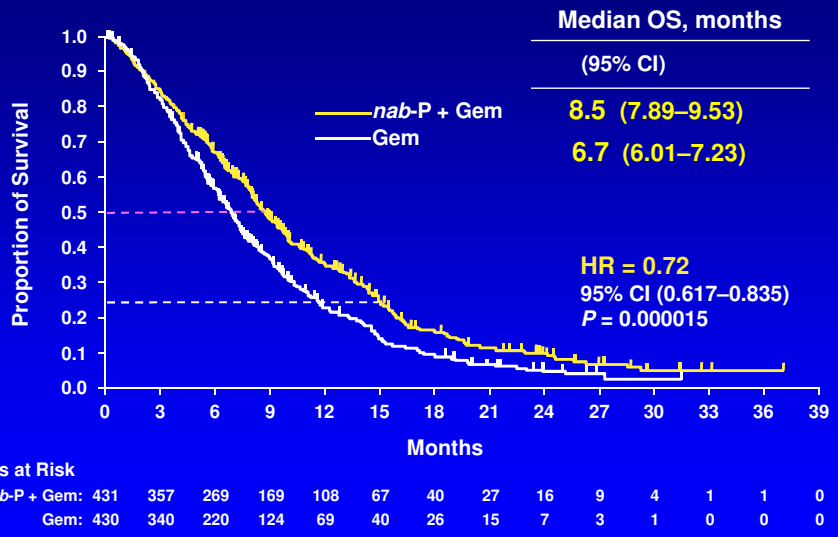
HR = 0.69
95% CI (0.581–0.821)
*P* = 0.000024

**Pts at Risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *nab*-P + Gem: | 431 | 281 | 122 | 62 | 24 | 8 | 4 | 2 | 0 |
| Gem: | 430 | 209 | 51 | 23 | 10 | 6 | 4 | 0 | 0 |

| PFS Rate at | *nab*-P + Gem | Gem | % Increase |
|---|---|---|---|
| 6 months | 44% | 25% | 76% |
| 12 months | 16% | 9% | 78% |

# Overall survival




# Efficacy: *nab*-Paclitaxel-Gemcitabine vs. Gemcitabine

| | *nab*-G | G | HR |
|---|---|---|---|
| Patients | 431 | 430 | |
| Objective Response | 23% | 7% | |
| Stable disease | 25% | 26% | |
| Disease control (PR+SD) | 48% | 33% | |
| Median survival (mo) | 8.5 | 6.7 | 0.72 |
| 1-year survival | 35% | 22% | |
| 18-month survival | 16% | 9% | |
| 24-month survival | 9% | 4% | |
| PFS (mo) | 5.5 | 3.7 | 0.69 |
| Median duration on treatment (mo) | 3.9 | 2.7 | |

## Toxicity: *nab*-Paclitaxel-Gemcitabine vs. Gemcitabine

| | Nab-G | G |
|---|---|---|
| Neutropenia | 38% | 27% |
| Febrile neutropenia | 3% | 1% |
| Thrombocytopenia | 13% | 9% |
| Anemia | 13% | 12% |
| Diarrhea | 6% | 1% |
| Fatigue | 17% | 7% |
| Neuropathy | 17% | <1% |
| G-CSF usage | 26% | 15% |

## The MPACT trial in context

1st randomized trial to demonstrate that a cytotoxic agent added to Gem prolongs survival in PC

*nab*-Paclitaxel + Gemcitabine

- Significantly improves OS
  - 8.5 vs. 6.7 mo, HR 0.72, *P* = 0.000015
- Significantly improves PFS
  - 5.5 vs. 3.7 mo HR 0.69, *P* = 0.000024
- More toxic
  - 38% grade ¾ neutropenia, 17% grade ¾ neuropathy, 17% grade ¾ fatigue
- QOL:
  - Not collected prospectively, Q-TWiST favorable
- Cost effectiveness: Not cost-effective?
- Biomarker: SPARC not predictive

Who is the optimal patient for Gem-nab-Paclitaxel?

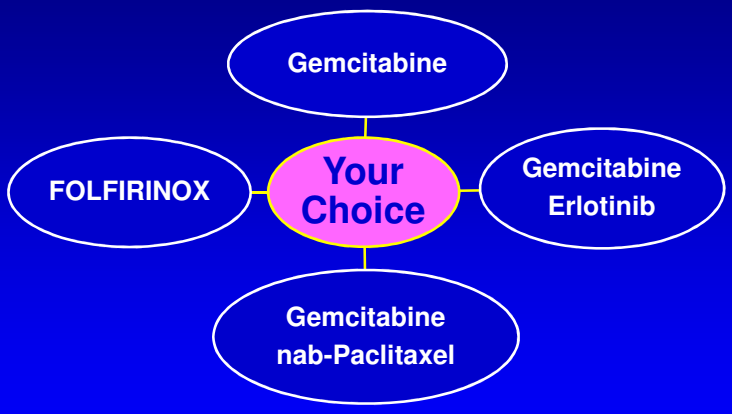
## We're not accustomed to having good treatment choices in PC

**FOLFIRINOX or Gemcitabine-nab-paclitaxel:**

**How do you decide which combination is best for which patient?**

- By understanding the current data
  - And its limitations
- No biomarker can predict which patient will respond to a particular treatment
- No randomized trial compares these 2 regimens
  - Cross-trial comparisons can be problematic

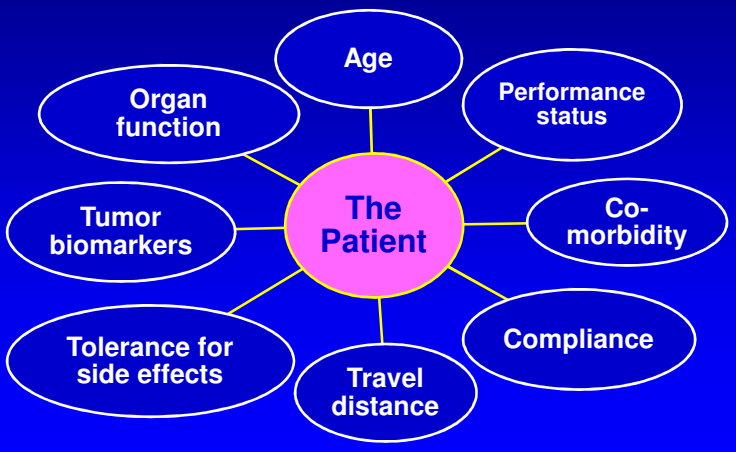
## What factors into our choice of a given regimen?



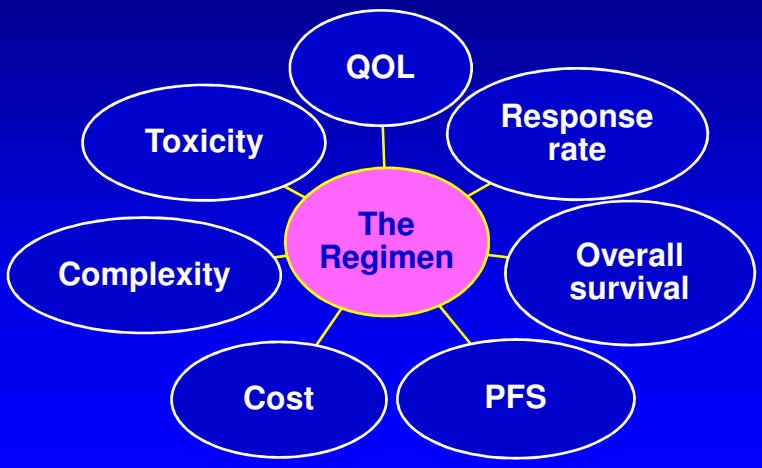

**Understand the data**

**Individualize therapy for each patient**

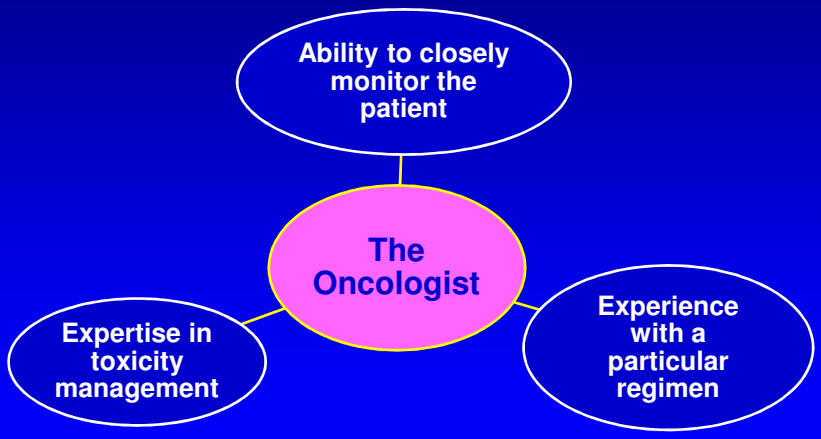
## Patient-related factors that may affect choice of regimen




## Regimen-related factors that may affect choice of treatment



## Physician-related factors that may affect choice of regimen




## Chemotherapy for advanced PC: Where are we now?

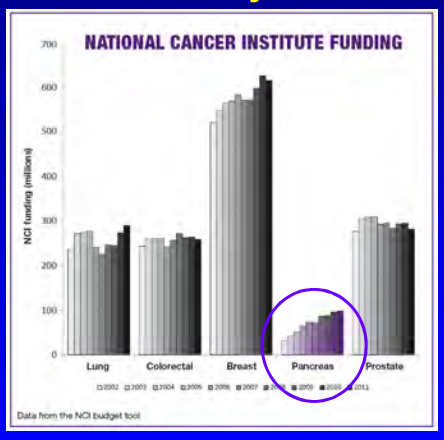
- Gemcitabine
  - Cornerstone of care for many years
  - Improves quality of life, modestly improves survival
- Gemcitabine + erlotinib
  - Marginally improves survival
- Meta-analysis
  - Suggests that good PS pts benefit from Gem + a platinum or a fluoropyrimidine

## Chemotherapy for advanced PC: Where are we now?

- **FOLFIRINOX**
  - Improves RR, PFS, OS in good PS pts
  - More toxic: patient selection and monitoring essential
- **Gemcitabine + *nab*-Paclitaxel**
  - Improves RR, PFS, OS
  - Not as active as FOLFIRINOX, slightly less toxic

**Although we are making incremental progress in the treatment of advanced pancreatic cancer, new drugs and new approaches are still urgently needed!**

## There are fewer research $$ allocated to study pancreas cancer compared with other major cancers




Hopefully this will be changing soon!

## January is National Pancreatic Cancer Clinical Trials Awareness Month

# Fewer than 5% of all pancreatic cancer patients enroll in clinical trials

Hoos et al, JCO 2013

## We need to do better than this

# Types of clinical trials

| Phase | Goal | Patients | Prior treatment | Placebo? |
|---|---|---|---|---|
| I | Dose and side effects | Any cancer | Usually unlimited | No |
| II | Determine effectiveness | All pts must have the same cancer | All pts must the same number of prior treatments, usually 0, 1 or 2 | Not usually |
| III | Compare to a standard regimen | | | Usually |

## How do we select new agents to test in clinical trials for pancreas cancer?

**We look for targets with intriguing data in the laboratory**

**Caveat: Promising preclinical data has led to many disappointing results in patients**

## A core set of 12 signaling pathways are genetically altered in most PC. Some of these pathways, or their downstream mediators, may be potential therapeutic targets


Hidalgo, *Pancreatology* 2014; Jones, *Science* 2008

## How do we select new drugs to test in PC patients?

The choice of drug for a given clinical trial is ultimately based on:

- Availability of agents for clinical testing against a target of interest
- Phase I single-agent and combination safety data
- Willingness of a drug company to test drugs in this disease

## Some types of drugs being evaluated for PC: Chemotherapy

**Cytotoxic chemotherapy:**

- These drugs (such as gemcitabine) affect the DNA of the cancer cell in various ways
  - MM-398: A nano-liposomal irinotecan

**Drugs to enhance the uptake of chemotherapy into the pancreas:**

- These agents target the dense stroma around the tumor that acts as a barrier to protect the cancer cells from chemotherapy
  - Hedgehog pathway inhibitors (worked in the lab, not in patients):
    - GDC-0449, IPI-926
  - Pegylated Hyaluronidase:
    - PEGPH20

## Some types of drugs being evaluated for PC: Targeted therapy

### Targeted therapy:

- These drugs (such as erlotinib) affect signaling pathways that turn cell growth on and off
- Many early trials were unsuccessful, likely because they were offered to unselected patients
- Targeted agents may be more effective in subsets of patients who have the specific abnormalities in their tumors that are targeted by those drugs
  - Targeting abnormal DNA damage repair in patients with BRCA 1 and 2 mutations
    - PARP inhibitors: veliparib, olaparib
  - Targeting Janus kinase (JAK) in patients with high CRP
    - Ruxolitinib

## Some types of drugs being evaluated for PC: Immunotherapy

### Immunotherapy

- Vaccines
  - Stimulate the immune system to attack the cancer
    - GVAX/CRS-207
- Immune checkpoint inhibitors
  - Take off the brakes in the immune system so that it can attack the cancer
    - Several agents in early trials

## Hopefully someday, these headlines will be for pancreatic cancer drugs


WAGE HOPE

## Thank you for your participation.

If you have questions, please contact our Patient and Liaison Services (PALS) program at
(877) 272-6226 or e-mail pals@pancan.org.

**www.pancan.org or wagehope.org**

PANCREATIC CANCER ACTION NETWORK