What's New in the Treatment of Pancreatic Cancer?

Lots!

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Fox Chase Cancer Center
September 17, 2013

Overview

- Staging and Workup
- Resectable Disease
  - Surgery
  - Adjuvant therapy
- Locally Advanced
  - Borderline resectable
  - Unresectable
- Metastatic Disease

Epidemiology

- ~43,140 new cases
- ~36,800 deaths
- 4th leading cause of cancer death
- Median age = 69 years
- Males 1.5 X risk of females

How do patients usually present?

- Jaundice
  - Obstructive
  - Often relieved with stent placement by GI
- Abdominal/back pain
  - Direct tumor effect
- Weight loss
  - malabsorption

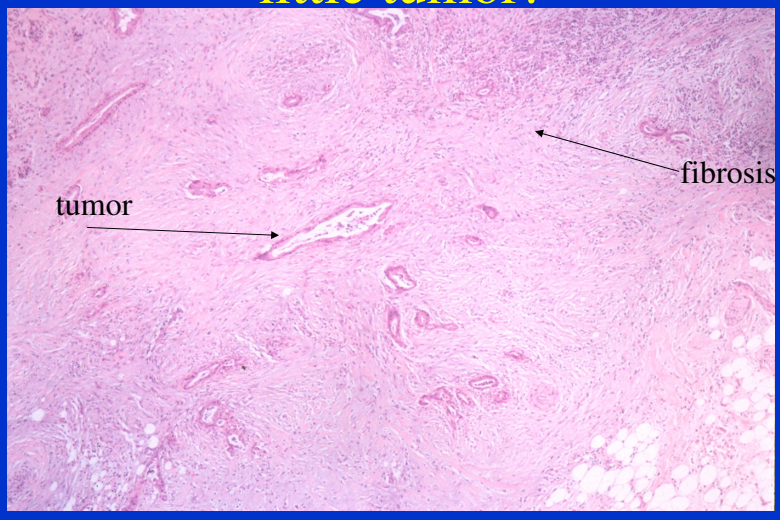
Usual workup

- Ultrasound (often for jaundice)
- CT scan (can help with diagnosis and staging)
- Endoscopic ultrasound
- PET – not usually required
- If clear pancreatic mass and/or metastatic lesions
  - Biopsy

Pathology

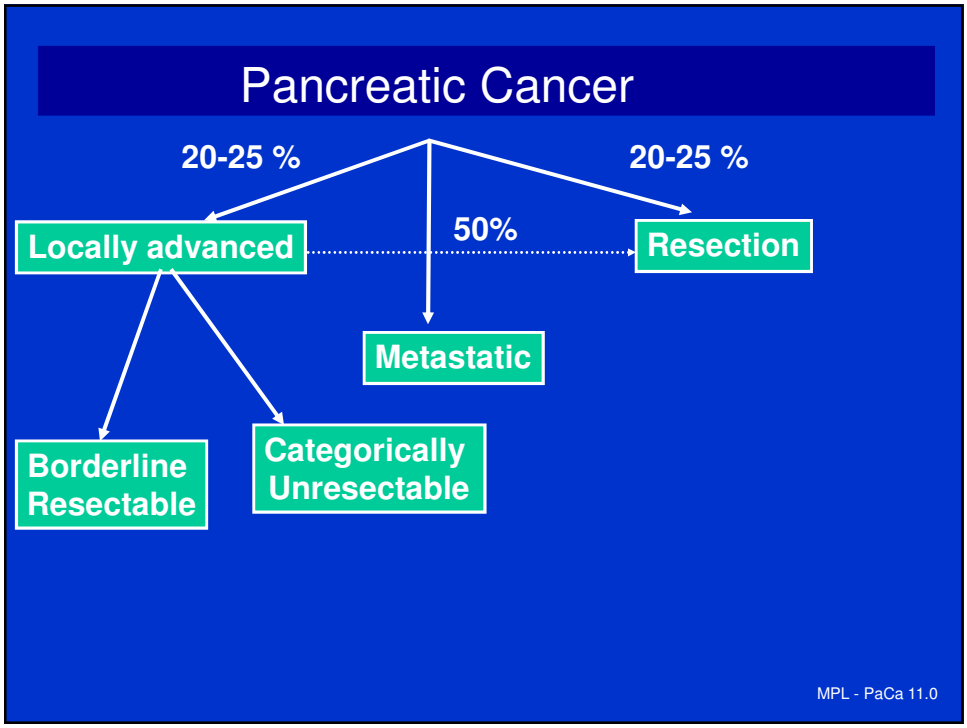
- Adenocarcinoma most common
- There are rarer pancreatic tumor types:
  - Islet cell tumors
  - Acinar cell
  - Squamous cell

There can be a lot of scar and a little tumor!



Once we have a diagnosis and stage…

Clinical categories to guide therapy



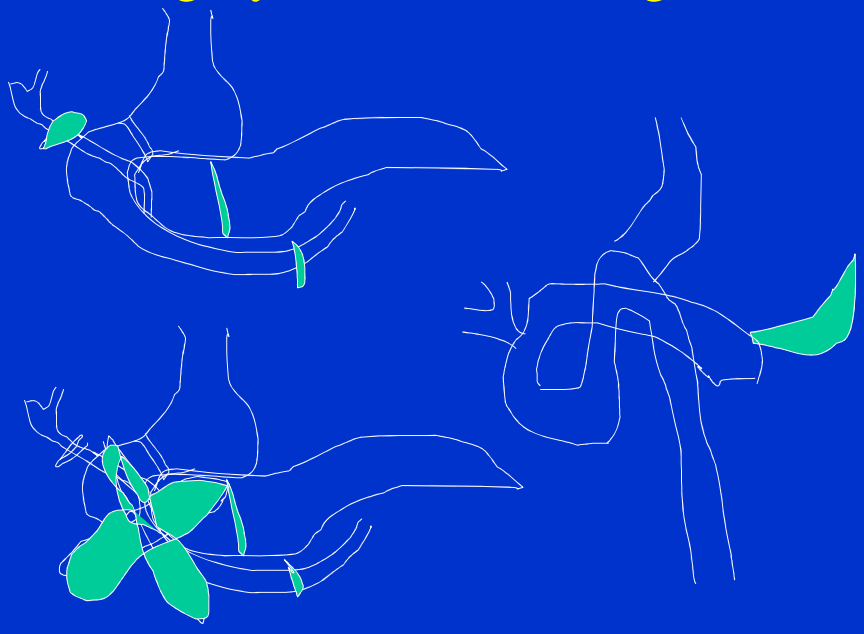
Practical Categories and Treatment

• Resectable	• Surgery
• Locally Advanced - borderline resectable	• Chemo or Chemo/XRT
• Locally advanced unresectable	• Chemo or chemo/XRT
• Metastatic	• Chemotherapy

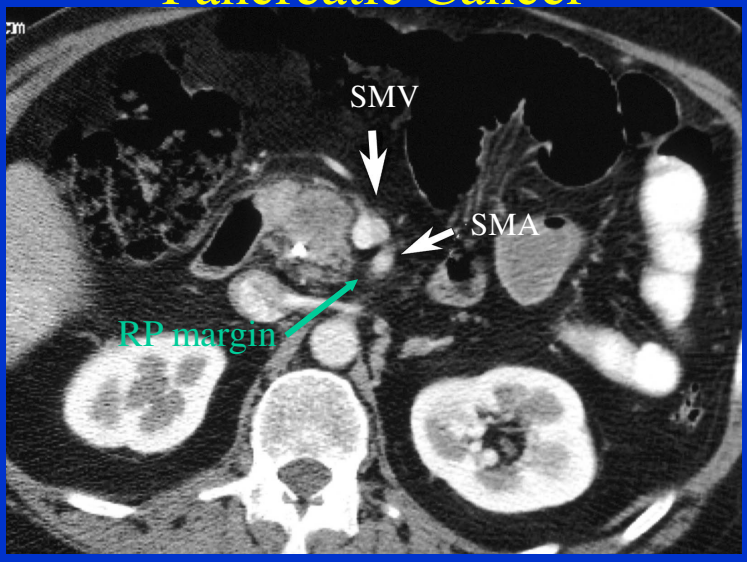
What makes a tumor resectable?

- No metastatic disease
- No significant vessel involvement
- Patient can tolerate a major operation

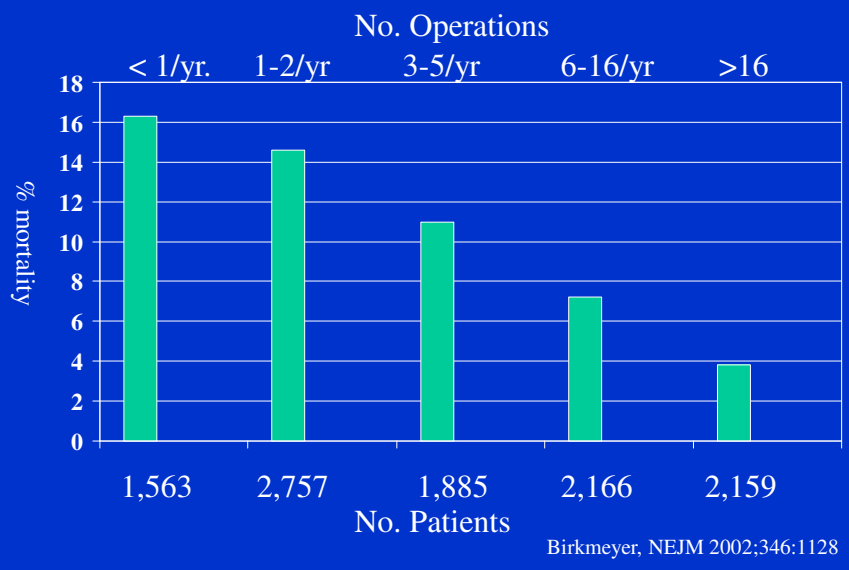
Surgery for the non-surgeon!



A Particular Challenge in Pancreatic Cancer



It matters where surgery is done!



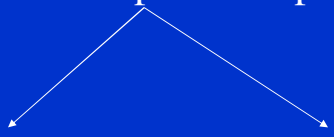
Birkmeyer, NEJM 2002;346:1128

Postoperative (Adjuvant) Therapy - Rationale

- Many patients are at risk for recurrence
  - Due to microscopic disease
- Chemotherapy has benefit in advanced disease
- Local recurrence may be an issue
  - Role of radiation therapy

GITSG Adjuvant Trial (Kalser *et al*, Arch Surg 120:899, 1985)

- Randomized **43** patients **over 8 years** who underwent curative resection (- margins) of adenocarcinoma of pancreas postoperatively to



•Split course XRT (20 Gy over 2 weeks X 2)

•5-FU 500 mg/m² by bolus for 3 days each XRT cycle, then weekly for up to 2 years

Observation

Results

	Adjuvant Therapy (n=21)	No adjuvant therapy (n=22)
Median Survival (months)	20	11 (p=.03)
2-year survival (%)	42	15 (p=.03)
5-year survival (%)	19	5 (p=.03)

ESPAC-1

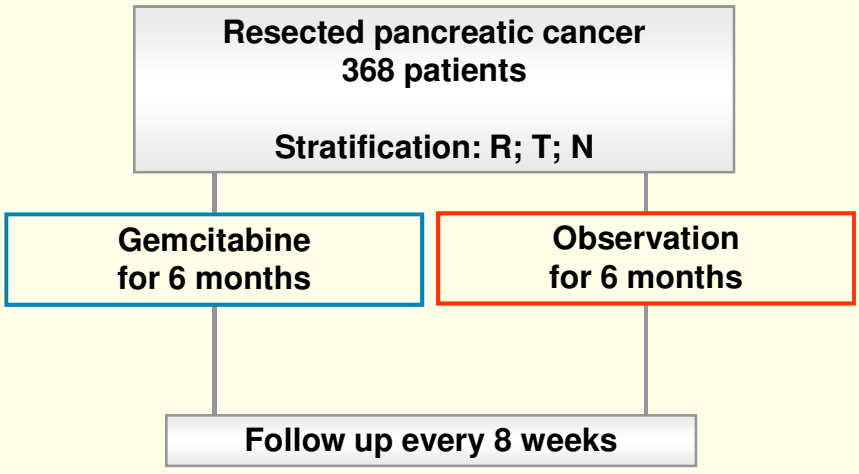
	Chemotherapy N=147	No chemotherapy N=142	P-value
Median survival (m)	20.1	15.5	0.009
2-year survival (%)	40	30	
5-year survival (%)	21	8	

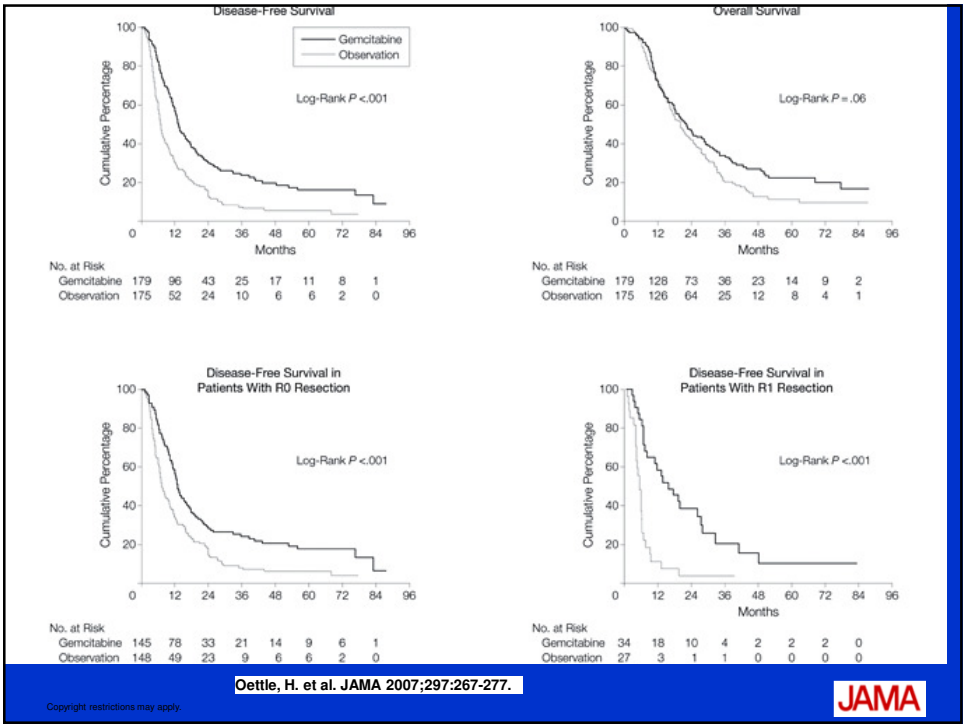
ESPAC-1

	Chemoradiotherapy N=145	No chemoradiotherapy N=144	P-value
Median survival (m)	15.9	17.9	0.05
2-year survival (%)	29	41	
5-year survival (%)	10	20	

CONKO-001 Study Design

Charité - Universitätsmedizin Berlin - Campus Virchow Klinikum



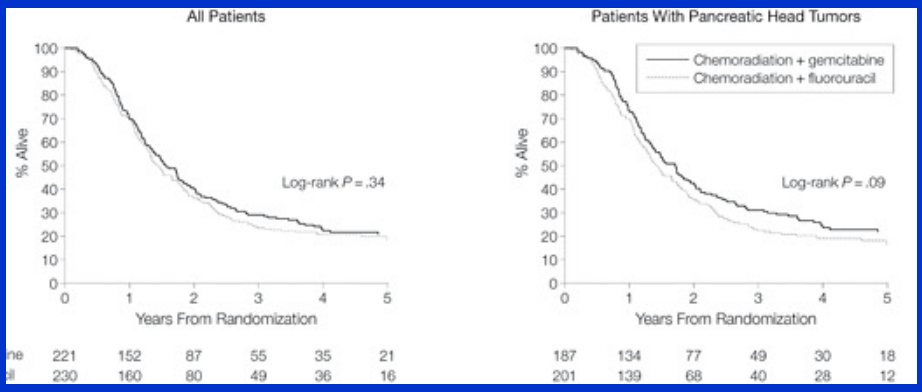


Oettle, H. et al. JAMA 2007;297:267-277.

Copyright restrictions may apply.

JAMA

RTOG 9704



Regine, W. F. et al. JAMA 2008;299:1019-1026.

Copyright restrictions may apply.

JAMA

ESPAC-3 Study Design

Charité - Universitätsmedizin Berlin - Campus Virchow Klinikum

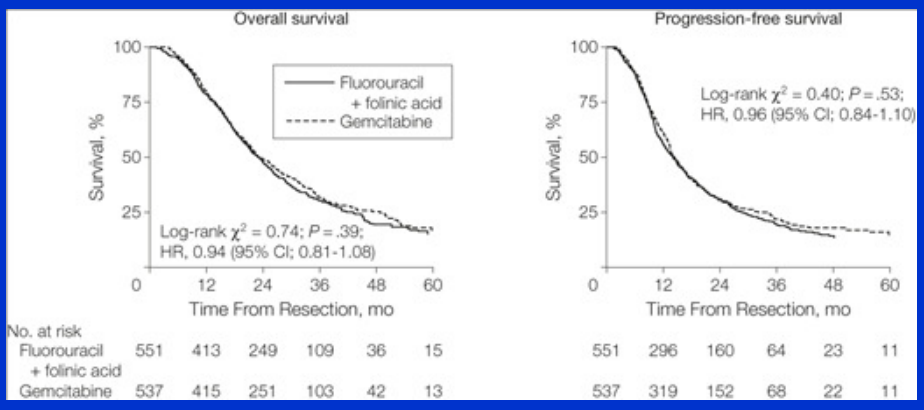
Resected pancreatic cancer
1,088 patients
R0 or R1 resection
Stratification: margin, country

Gemcitabine for 6 months

5-FU/FA for 6 months

Primary endpoint overall survival

ESPAC-3 Results



Adjuvant Therapy Overview

- Chemotherapy with modest benefit
  - Gemcitabine or 5-FU
- Radiation therapy still debated
  - Often used if local recurrence a concern
- We use these older studies as a building block to incorporate new advances

Ongoing Adjuvant Studies

- US Cooperative Group
  - Radiation therapy or not
- Outside-US Cooperative Group
  - Gemcitabine vs. FOLFIRINOX
    - Taking recent advance from metastatic disease
- Industry
  - HyperAcute® vaccine – NewLink Genetics

Borderline Resectable
Versus
Locally Advanced Unresectable

WARNING!

Only surgeons understand this!!

Don’t feel bad if you are confused!

- On a recent pancreas cancer call, half of the two hour time slot was spent by the surgeons debating the definition of borderline resectable.
- Involves analysis of degree of blood vessel involvement
  - Abutting vessels – borderline
  - Encasing vessels – categorically unresectable

Controversy!

The locally advanced debate..

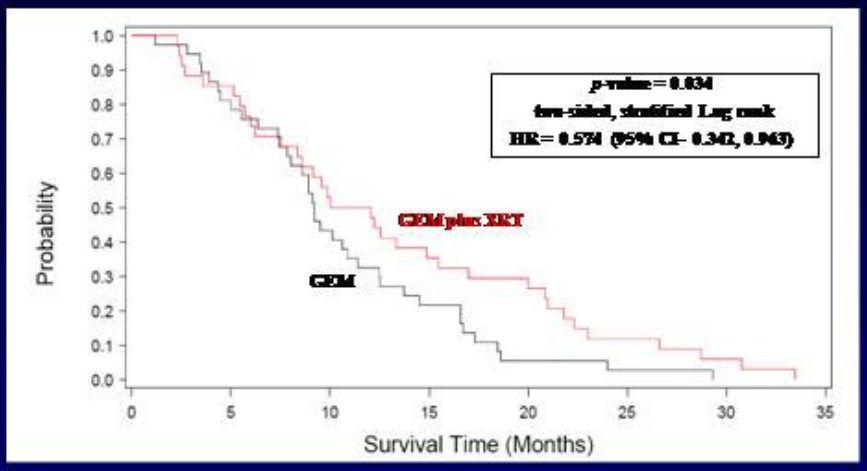
Is radiation therapy helpful?

A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized unresectable pancreatic cancer: E4201

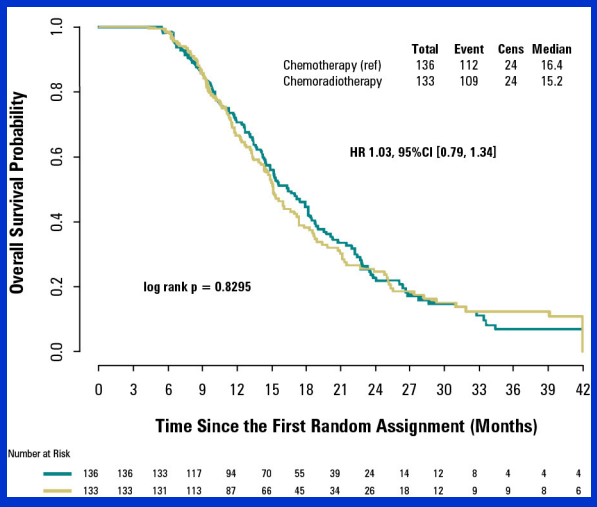
P. J. Loehrer Sr., M. Powell, H. Cardenes,
L.Wagner, J. Brell, R. Ramanathan,
C. Crane, S. Alberts, A. B. Benson

On behalf of
The Eastern Cooperative Oncology Group

Overall Survival



Recent large study- LAP-07



Hammel et al. ASCO, 2013

Recap of Locally Advanced

- Chemotherapy is an important therapy
- Radiation therapy is commonly used
  - For borderline resectable, commonly
  - For categorically unresectable, sometimes

Remember that our treatment of earlier stage disease utilizes only gemcitabine or 5-FU

Let's move to some advances in metastatic disease

What about metastatic disease?

So how did we get here?

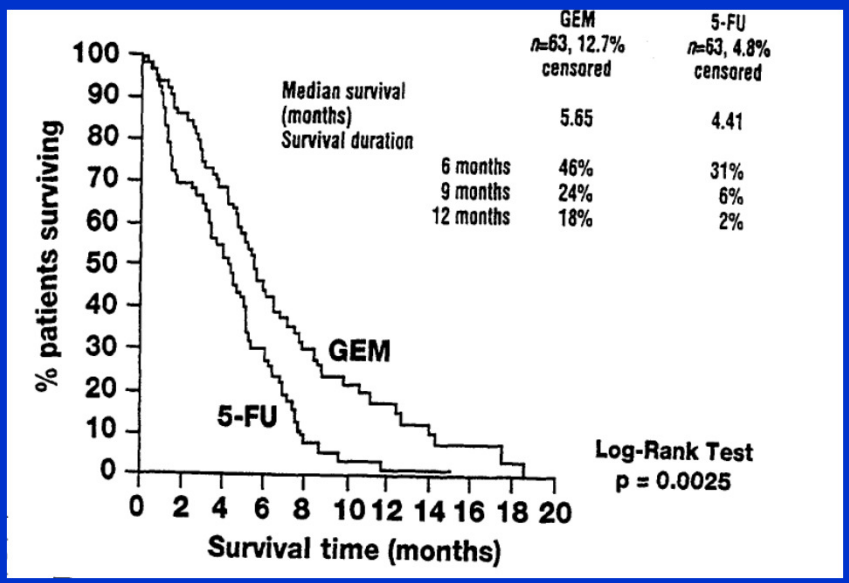
Available Systemic Agents

- Gemcitabine – "old" standard
- Nab-pacliataxel – just approved with gemcitabine
- 5-Fluorouracil ("5-FU")
- Oxaliplatin
- Irinotecan

FOLFIRINOX

- Erlotinib – oral targeted therapy

The gemcitabine approval study



PA.3 Study Schema

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

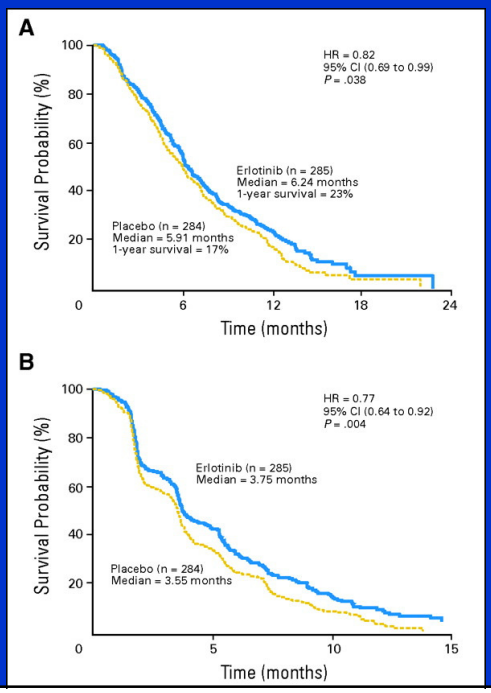
Stratification
- Center
- PS (0/1 vs 2)
- Stage of disease

RANDOMIZE

Gemcitabine + Erlotinib

Gemcitabine + Placebo

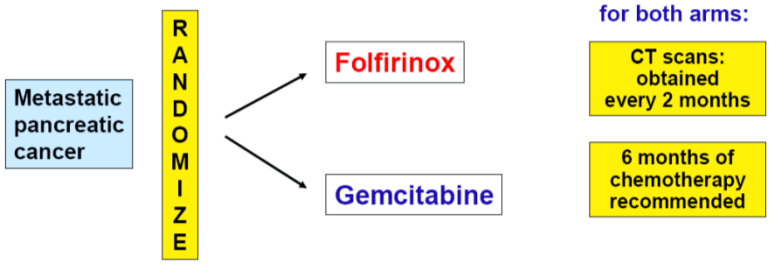
Moore et al. J Clin Oncol. 2007 May 20;25(15):1960-6. Epub 2007 Apr 23.



ASCO, 2010

FOLFIRINOX

Prodige 4 - ACCORD 11 trial design



Stratification :

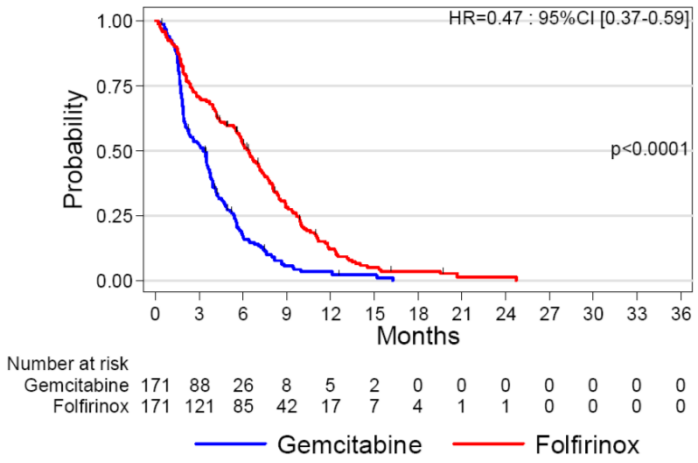
- center
- performance status: 0 versus 1
- location of the tumor: head versus other location of the primary

Objective Response Rate

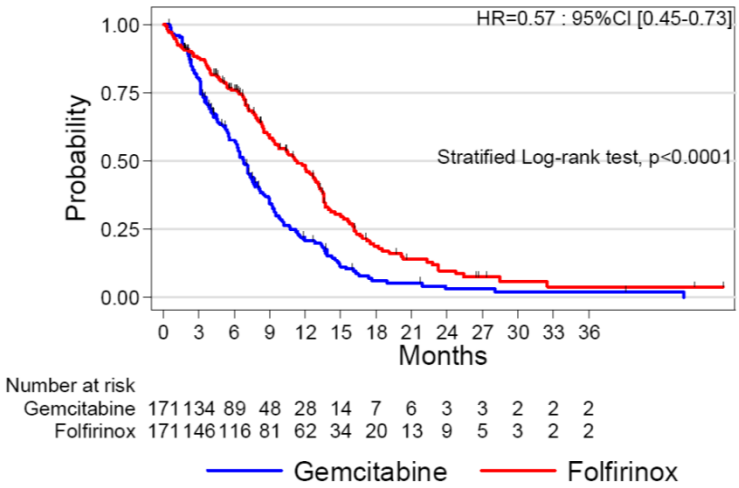
	Folfirinox N=171	Gemcitabine N=171	p
Complete response	0.6%	0%	
Partial response	31%	9.4%	0.0001
CR/PR 95% CI	[24.7-39.1]	[5.9-15.4]	
Stable disease	38.6%	41.5%	
Disease control CR+PR+SD	70.2%	50.9%	0.0003
Progression	15.2%	34.5%	
Not assessed	14.6%	14.6%	
Median duration of response	5.9 mo.	4 mo.	ns

Progression-Free Survival

Median PFS Folfirinox: 6.4 mo. **Median PFS Gemcitabine: 3.3 mo**



Overall Survival



Safety: hematological AEs

AE, % per patient	Folfirinox N=167		Gemcitabine N=169		p
	All	Grade 3/4	All	Grade 3/4	Grade 3/4
Neutropenia	79.9	45.7	54.8	18.7	0.0001
Febrile Neutropenia	7.2	5.4	2.4	0.6	0.009
Anemia	90.4	7.8	94.6	5.4	NS
Thrombocytopenia	75.2	9.1	54.8	2.4	0.008

42.5 % of the pts received G-CSF in the F arm *vs* 5.3% in the G arm
One toxic death occurred in each arm
AE, adverse event

FOLFIRINOX conclusions

- One standard of care for fit patients
- Caution with biliary stents/infection
- FOLFOX/FOLFIRI also reasonable options

Gemcitabine + Nab-paclitaxel

- Phase 1/2 study
- 63 patients
- Weekly gem
- Weekly nab-paclitaxel 100-150 mg/m2
- RPTD – gem 1000, nab, 125
- 26% PR
- Randomized phase 3 ongoing

Von Hoff et al. ASCO, 2009. Abst 4525

Study Design

Planned N = 842

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

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

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

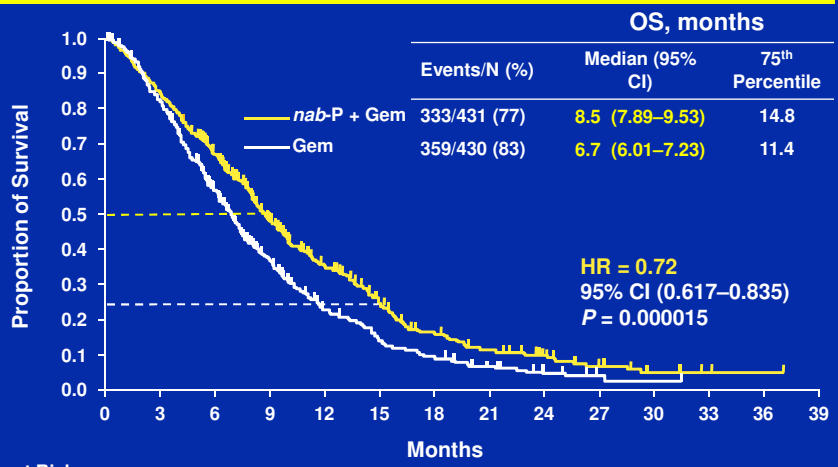
Gemcitabine
1000 mg/m² IV qw for 7/8 weeks
then qw 3/4 weeks

- **Primary Endpoint:**
  - OS
- **Secondary Endpoints:**
  - PFS and ORR by Independent Review (RECIST)
- **Safety and Tolerability**
  - by NCI CTCAE v3.0

- With 608 events, 90% power to detect OS HR = 0.769 (2–sided α = 0.049)
- 1 interim analysis for futility
- Treat until progression
- CT scans every 8 weeks

Von Hoff et al., ASCO GI 2013 LBA148 5

Overall Survival



	OS, months		
	Events/N (%)	Median (95% CI)	75th Percentile
nab-P + Gem	333/431 (77)	8.5 (7.89–9.53)	14.8
Gem	359/430 (83)	6.7 (6.01–7.23)	11.4

HR = 0.72
95% CI (0.617–0.835)
P = 0.000015

Pts at Risk

nab-P + Gem:	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gem:	430	340	220	124	69	40	26	15	7	3	1	0	0	0

Von Hoff et al., ASCO GI 2013 LBA148 51

Safety

Preferred Term	*nab*-P + Gem (n = 421)	Gem (n = 402)
Pt with at least 1 AE Leading to Death, %	4	4
Grade ≥3 Hematologic AE, [a] **%**		
Neutropenia	38	27
Leukopenia	31	16
Thrombocytopenia	13	9
Anemia	13	12
Pts Who Received Growth Factors, %	26	15
Febrile Neutropenia, [b] **%**	3	1
Grade ≥3 Nonhematologic AE [b] **in >5% Pts, %**		
Fatigue	17	7
Peripheral Neuropathy [c]	17	<1
Diarrhea	6	1
Grade ≥3 Neuropathy		
Time to Onset, median days	140	113
Time to Improvement by 1 Grade, median days	21	29
Time to Improvement to Grade ≤1, median days	29	--
Pts Who Resumed *nab*-P, %	44	--

[a] Based on lab values; [b] Based on investigator assessment of treatment-related events; [c] grouped term

Von Hoff et al., ASCO GI 2013 LBA148 52

Take-homes from firstline metastatic therapy

- For patients with good performance status combination therapy improves outcome
  - FOLFIRINOX
  - Gemcitabine + nab-paclitaxel
- For patients with borderline performance status single agent therapy may be more appropriate
- For patients with compromised performance status chemotherapy may not be an option
- Ultimate goal to incorporate in locally advanced and resectable states

Second-line therapy for metastatic disease

A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO-003 study.

- CONKO*-003 -

U. Pelzer

Kubica K[1], Stieler J[1], Schwaner I[2], Heil G[3], Gömer M[4], Mölle M[5], Hilbig A[1], Dörken B[1], Riess H[1], Oettle H[1]

[1]Universitätsmedizin Berlin - Charité Centrum für Tumormedizin; Berlin Germany; [2]Outpatient Department Berlin; [3]Klinikum Lüdenscheid; [4]Klinikum Bielefeld; [5]Outpatient Department Dresden; AIO; Deutsche Krebsgesellschaft e.V.

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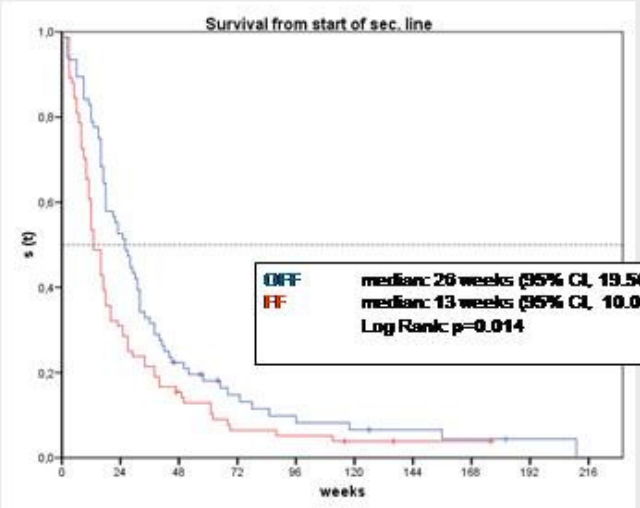
CONKO-003 Results – 2nd line OS



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Second-line therapy

- Some data but fewer studies
- In general, we tend to treat with the "other" type of chemotherapy
- If initial FOLFIRINOX …
  - then gem-based
- If initial gem + nab-paclitaxel…
  - then 5-FU-based

So how do we move forward with our new regimens?

1. Incorporate them earlier
   a. Locally advanced
   b. Adjuvant

2 Add promising new drugs

Incorporating earlier…

- Borderline resectable – US coop study
  - FOLFIRINOX then chemoradiotherapy

And earlier!....

- European postoperative study
  - FOLFIRINOX vs. gemcitabine

Considerations for new drugs

- Generally develop in metastatic disease
- Options:
  - Combine with frontline chemotherapy
    - Generally gemcitabine + nab-paclitaxel
  - As single agent in refractory disease

Examples of ongoing and planned frontline studies

- Gemcitabine/nab-paclitaxel plus
  - ODSH – novel anticoagulant
  - JAK1/2 inhibitor
  - Wnt pathway inhibitor
  - WEE1 inhibitor – US coop group
  - And on and on!!!

Third-line studies ongoing or planned

- Y90-hPAM4
  - Radiolabeled antibody
- MM398
  - Liposomal encapsulated irinotecan

Summary

- There is real optimism about the treatment of pancreatic cancer
- We still have a lot of work to do!
- Key themes in research
  - Developing new drugs
  - Incorporating new regimens earlier in the disease

Thank You!

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