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Pancreatic cancer – from the past to the future

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Scripps Clinic
Pancreas and Bile Duct Cancer Group

PANCREATIC CANCER ACTION NETWORK
ADVANCE RESEARCH. SUPPORT PATIENTS. CREATE HOPE.

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Objectives

Where is the pancreas and what does it do?

A brief history of the pancreas

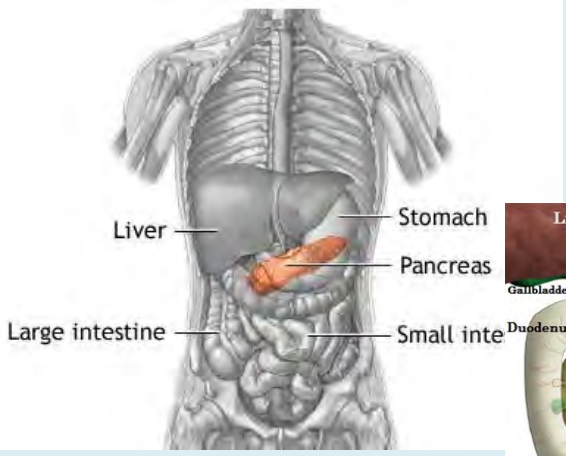
Background

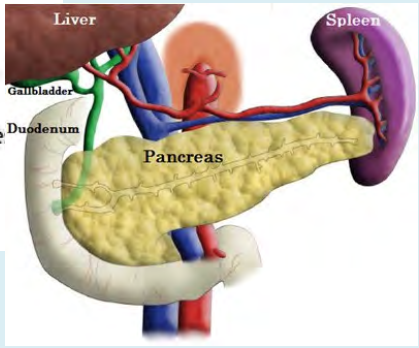
Locally advanced/Borderline resectable

Metastatic

Novel therapies

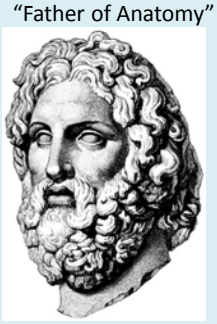
Where is the pancreas and what does it do?





A brief history of the pancreas

"Father of Anatomy"



Herophelus, 4th BC

Pancreas – "all flesh"

Rufus, 1st AD

"Physician to the Gladiators"

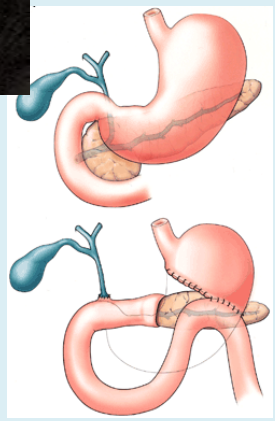
Galen, 2nd AD

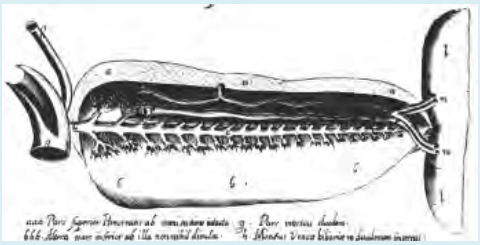
"duct of Wirsung"

Wirsung,Italy (German émigré), 17th AD

"Father of pancreatic surgery"

Whipple, 1881-1963





Background

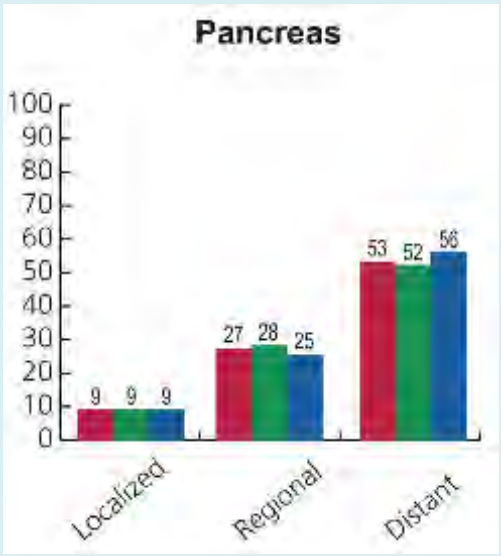
Estimated New Cases[a]

	Males			Females		
Prostate	233,000	27%		Breast	232,670	29%
Lung & bronchus	116,000	14%		Lung & bronchus	106,210	13%
Colorectum	71,850	8%		Colorectum	65,000	8%
Urinary bladder	56,390	7%		Uterine corpus	52,630	6%
Melanoma of the skin	43,890	5%		Thyroid	47,790	6%
Kidney & renal pelvis	39,140	5%		Non-Hodgkin lymphoma	32,530	4%
Non-Hodgkin lymphoma	38,270	4%		Melanoma of the skin	32,210	4%
Oral cavity & pharynx	30,220	4%		Kidney & renal pelvis	24,780	3%
Leukemia	30,100	4%		Pancreas	22,990	3%
Liver & intrahepatic bile duct	24,600	3%		Leukemia	22,280	3%
All Sites	**855,220**	**100%**		**All Sites**	**810,320**	**100%**

Estimated Deaths

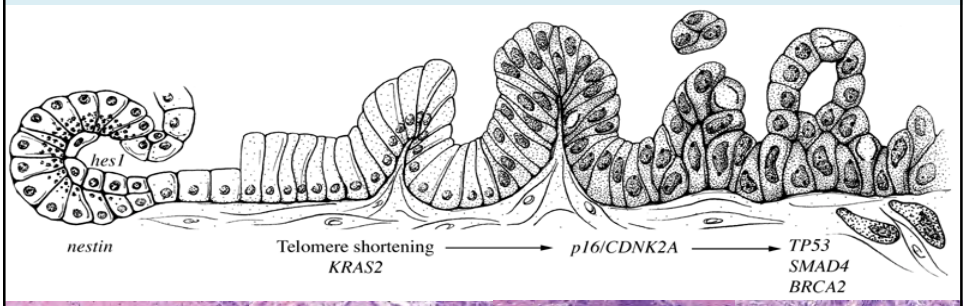
	Males			Females		
Lung & bronchus	86,980	28%		Lung & bronchus	72,330	26%
Prostate	29,480	10%		Breast	40,000	15%
Colorectum	26,270	8%		Colorectum	24,040	9%
Pancreas	20,170	7%		Pancreas	19,420	7%
Liver & intrahepatic bile duct	15,870	5%		Ovary	14,270	5%
Leukemia	14,040	5%		Leukemia	10,050	4%
Esophagus	12,450	4%		Uterine corpus	8,590	3%
Urinary bladder	11,170	4%		Non-Hodgkin lymphoma	8,520	3%
Non-Hodgkin lymphoma	10,470	3%		Liver & intrahepatic bile duct	7,130	3%
Kidney & renal pelvis	8,900	3%		Brain & other nervous system	6,230	2%
All Sites	**310,010**	**100%**		**All Sites**	**275,710**	**100%**

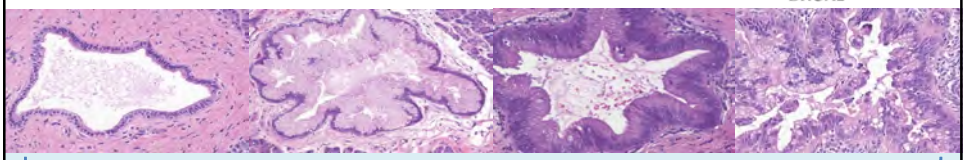
Jemal, CA Cancer Journal, 2014



Jemal, CA Cancer Journal, 2014

The Pathway to Pancreatic Cancer





11.7 ± 3.1 years

Hruban, Int J Clin Exp Pathol, 2008
Yachida, Nature, 2010

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Pancreatic cancer has been a very difficult cancer to treat

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Study	Year	Comparator	Source	No. of patients	Significant survival benefit
Colucci et al.[15]	2002	CDDP+G	Article	107	Yes
Wang et al.[19]	2002	CDDP+G	Abstract	34	No
Li and Chao[18]	2004	CDDP+G	Abstract	46	No
Reni et al.[17]	2005	CDDP-Epi-5-FU+G	Article	104	No
Louvet et al.[3]	2005	Oxaliplatin+G	Article	313	No
Heinemann et al.[16]	2006	CDDP+G	Article	198	No
Poplin et al.[38]	2006	Oxaliplatin+G	Abstract	555	No
Berlin et al.[20]	2002	5-FU+G	Article	322	No
Riess et al.[23]	2005	5-FU-FA+G	Abstract	466	No
Hermann et al.[21]	2005	Capecitabine+G	Abstract	319	No
Ohkawa[22]	2004	UFT+G	Abstract	19	No
Cunningham et al.[4]	2005	Capecitabine+G	Abstract	533	Yes
Rocha Lima et al.[27]	2004	Irinotecan+G	Article	360	No
Oettle et al.[24]	2005	Pemetrexed+G	Article	565	No
Abou-Alfa et al.[26]	2006	Exatecan+G	Article	349	No
Stathopoulos et al.[25]	2006	Irinotecan+G	Article	130	No
Bramhall et al.[7]	2002	Marimastat+G	Article	239	No
Van Cutsem et al.[5]	2004	Tipifarnib+G	Article	688	No
Shapiro et al.[9]	2005	G17DT+G	Abstract	383	No
Moore et al.[28]	2007	Erlotinib+G	Abstract	569	Yes

Di Marco, Onc Rep, 2010

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If all you have is a hammer . . .

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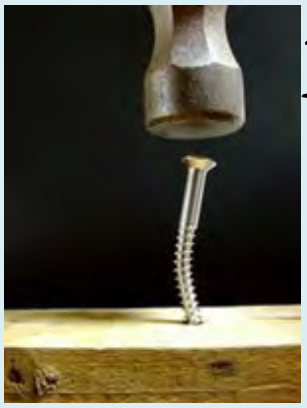
5-Fluorouracil



Gemcitabine

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Locally advanced disease

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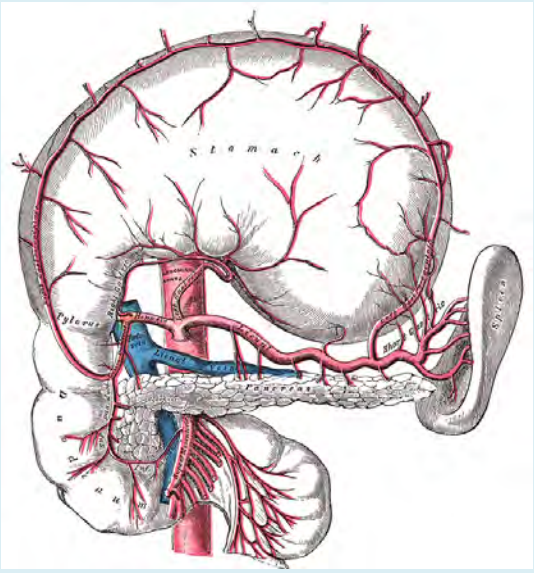

- About 30% of patients present with locally advanced pancreatic cancer
- Tumors that are not metastatic, but cannot be removed surgically
- T4 lesions – tumors that involve the SMA or celiac trunk

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Treatment considerations

- What type of radiation?
- What type of chemotherapy?
- What about concurrent chemo-radiotherapy?
- What happens when concurrent chemo-radiotherapy has been completed?

Annals of Oncology

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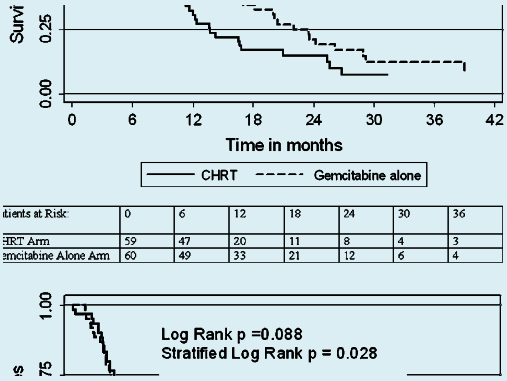
Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000–01 FFCD/SFRO study



Chauffert, Ann Oncol, 2008

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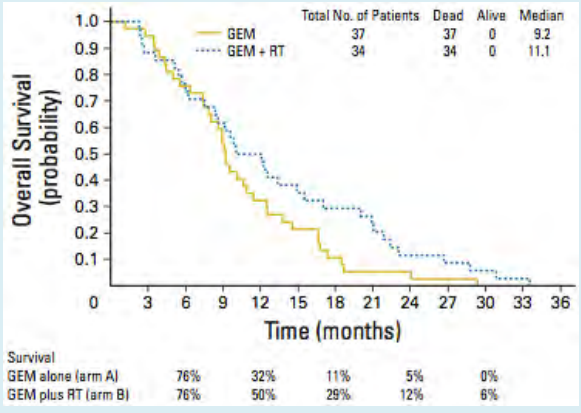
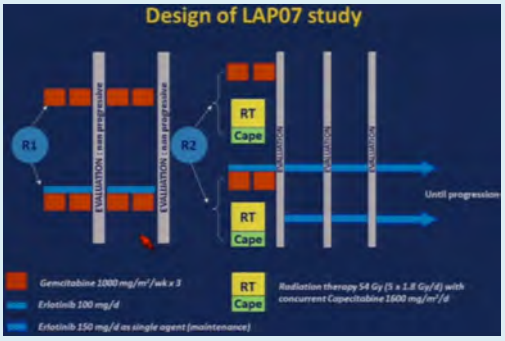
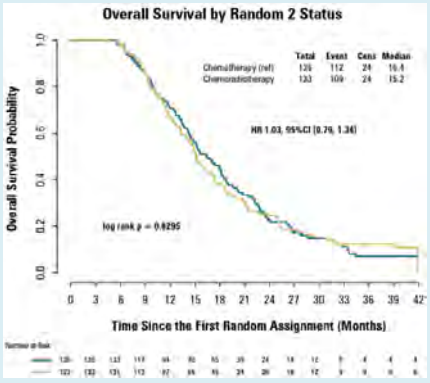
Gemcitabine Alone Versus Gemcitabine Plus Radiotherapy in Patients With Locally Advanced Pancreatic Cancer: An Eastern Cooperative Oncology Group Trial



Loehrer, J Clin Oncol, 2011

Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study





Huguet, ASCO 2014, #4001

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- CLINICAL STUDY ALWAYS FIRST OPTION
- Concurrent chemo-radiotherapy with gemcitabine, then an additional 5 cycles of single-agent gemcitabine
- Other options:
  - Single agent gemcitabine
  - Combination chemotherapy of gemcitabine/nab-paclitaxel or FOLFIRINOX

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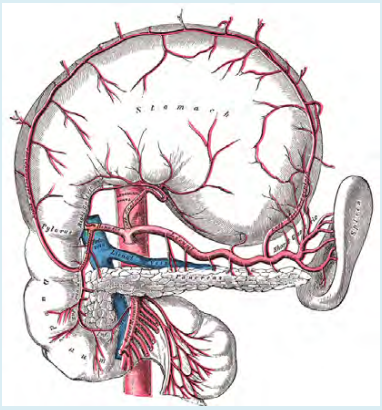
Borderline Resectable

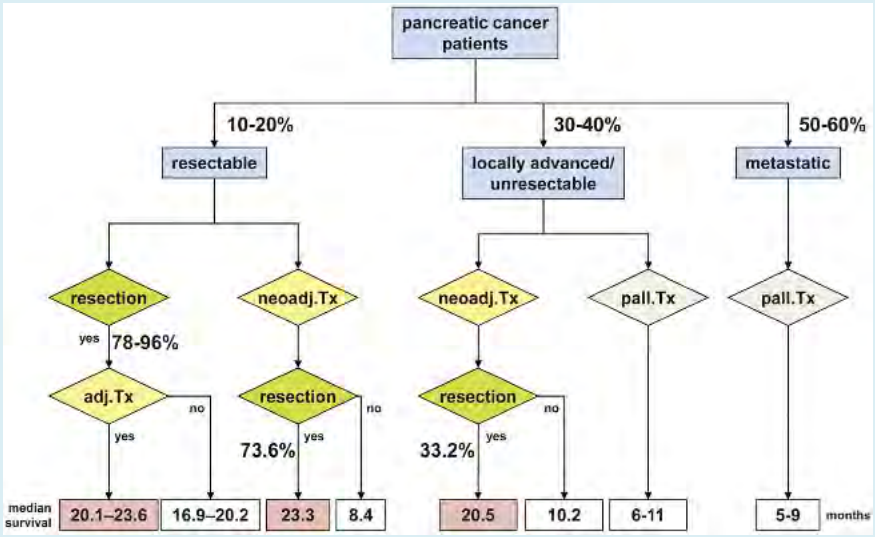
TABLE 1. Intergroup Criteria for the Clinical Staging of Localized PDAC

	Potentially Resectable	Borderline Resectable	Locally Advanced
SMV-PV	TVI < 180	TVI ≥ 180 and/or reconstructable* occlusion	Unreconstructable occlusion
SMA	No TVI	TVI < 180	TVI ≥ 180
CHA	No TVI	Reconstructable*, short-segment TVI of any degree	Unreconstructable TVI
Celiac Trunk	No TVI	TVI < 180	TVI ≥ 180

Abbreviations: PDAC, pancreatic ductal adenocarcinoma; SMV-PV, superior mesenteric or portal vein; SMA, superior mesenteric artery; CHA, common hepatic artery; TVI; tumor-vessel interface.
* Normal vein or artery proximal and distal to the site of suggested tumor-vessel involvement suitable for vascular reconstruction.



Katz, ASCO Ed Book, 2014



Gillen, PLoS Med, 2010

Table 4. Disease Stage Before and After the Administration of Neoadjuvant Therapy

			No. of Patients (%)						
			Post-Treatment Stage[a]						
				PR		BL		LA	
Pretreatment Stage	No. of Patients	Metastatic Disease	Total	No. Resected	Total	No. Resected	Total	No. Resected	Total No. Resected
AHPBA/SSO/SSAT classification									
BL	115	20 (17)	1 (1)	1 (100)	92 (80)	77 (84)	2 (2)	2 (100)	80
LA	7	1 (14)	0 (0)	0 (0)	0 (0)	0 (0)	6 (86)	5 (83)	5
MD Anderson classification									
PR	50	8 (16)	37 (74)	36 (97)	5 (10)	3 (60)	0 (0)	0 (0)	39
BL	72	13 (18)	1 (1)	1 (100)	58 (81)	45 (78)	0 (0)	0 (0)	46

Abbreviations: AHPBA/SSO/SSAT, Hepatopancreaticobiliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract; BL, borderline resectable; LA, locally advanced; MD Anderson, The University of Texas M. D. Anderson Cancer Center; PR, potentially resectable.
[a] According to corresponding staging classification from AHPBA/SSO/SSAT or MD Anderson.

Median OS
- all comers: 22 months
- resected: 33 months
- not resected: 12 months

RECIST response was not associated with longer median OS (p=0.78)

Table 3. Clinicopathologic Profile of 85 Patients Who Underwent Resection of Borderline Resectable Pancreatic Ductal Adenocarcinoma

Characteristic	No. of Patients (%)
No. of patients	85 (100)
Neoadjuvant therapy	
Chemotherapy	65 (76)
Gemcitabine-platinum	56 (86)
Gemcitabine with or without other	9 (14)
Chemoradiation	81 (95)
Chemosensitizer	
Gemcitabine	40 (49)
5-FU	41 (51)
EBRT dose	
30 Gy	13 (16)
Standard[a]	68 (84)

Katz, Cancer, 2012

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Borderline resectable disease

- Several therapeutic approaches:
  - CLINICAL STUDY ALWAYS FIRST OPTION
  - Combination chemotherapy first, then consider
  - Concurrent chemoradiotherapy

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Metastatic disease

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Study	Year	Comparator	Source	No. of patients	Significant survival benefit
Colucci et al.[15]	2002	CDDP+G	Article	107	Yes
Wang et al.[19]	2002	CDDP+G	Abstract	34	No
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Moore et al.[28]	2007	Erlotinib+G	Abstract	569	Yes

Di Marco, Onc Rep, 2010

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Randomized Phase II Study of Gemcitabine Administered at a Fixed Dose Rate or in Combination With Cisplatin, Docetaxel, or Irinotecan in Patients With Metastatic Pancreatic Cancer: CALGB 89904

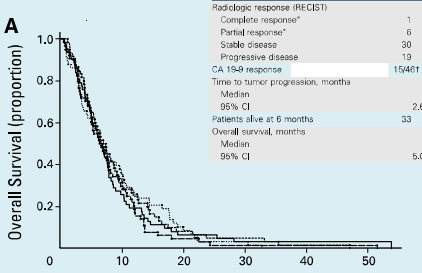

Table 4. Efficacy Results According to Treatment Arm

Efficacy	Arm A: Gemcitabine/ Cisplatin (n = 56) No. of Patients	%	Arm B: FDR Gemcitabine (n = 43) No. of Patients	%	Arm C: Gemcitabine/ Docetaxel (n = 57) No. of Patients	%	Arm D: Gemcitabine/ Irinotecan (n = 51) No. of Patients	%
Radiologic response (RECIST)								
Complete response*	1	2	0		0		1	2
Partial response*	6	11	6	14	7	12	6	12
Stable disease	30	54	25	58	30	53	28	55
Progressive disease	19	34	12	28	20	35	16	31
CA 19-9 response	15/461	33	16/38	42	19/48	42	16/48	33
Time to tumor progression, months								
Median	4.5		3.3		4.1		4.0	
95% CI	2.6 to 5.5		2.7 to 4.6		2.4 to 4.9		2.5 to 5.2	
Patients alive at 6 months	33	53	33	57	35	54	34	57
Overall survival, months								
Median	6.7		6.4		6.4		7.1	
95% CI	5.0 to 7.8		4.4 to 9.9		5.1 to 7.9		5.4 to 8.8	

Kulke, J Clin Oncol, 2009

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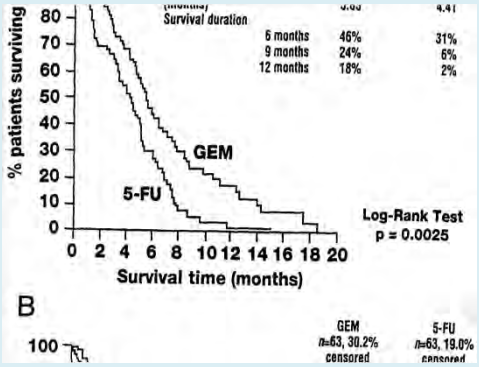
iels.[19] The drug requires intracellular phosphorylation results in the accumulation of difluorodeoxycytidine nosphate (dFdCTP).[20] The dFdCTP competes with xycytidine triphosphate (dCTP) for incorporation into

IN.

Address reprint requests to Daniel D. Von Hoff, MD, FA Institute for Drug Development, Cancer Therapy and Research ter, 14960 Omicron Dr, San Antonio, TX 78245; Email dan_von



Burris, J Clin Oncol, 1997

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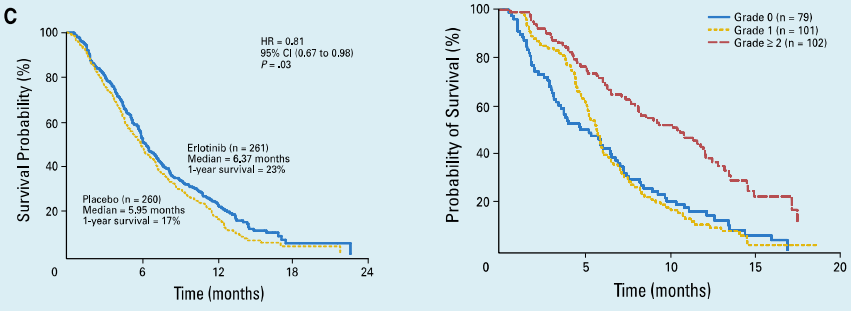
Erlotinib Plus Gemcitabine Compared With Gemcitabine Alone in Patients With Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group



Moore, J Clin Oncol, 2007

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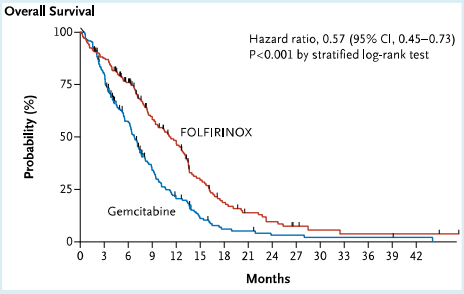
The NEW ENGLAND JOURNAL *of* MEDICINE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer



Variable	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
Response — no. (%)			
Complete response	1 (0.6)	0	
Partial response	53 (31.0)	16 (9.4)	
Stable disease	66 (38.6)	71 (41.5)	
Progressive disease	26 (15.2)	59 (34.5)	
Could not be evaluated	25 (14.6)	25 (14.6)	
Rate of objective response†			<0.001
No. (%)	54 (31.6)	16 (9.4)	
95% CI	24.7–39.1	5.4–14.7	
Rate of disease control‡			<0.001
No. (%)	120 (70.2)	87 (50.9)	
95% CI	62.7–76.9	43.1–58.6	
Response duration — mo			0.57
Median	5.9	3.9	
95% CI	4.9–7.1	3.1–7.1	

Conroy, N Engl J Med, 2011

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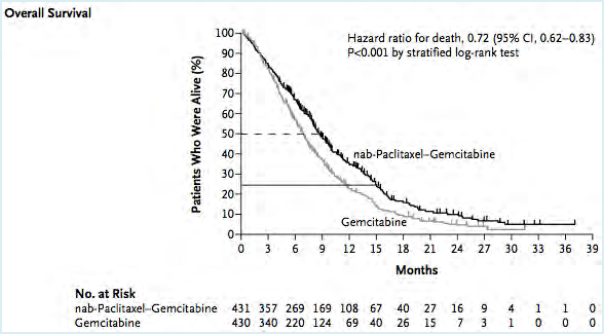
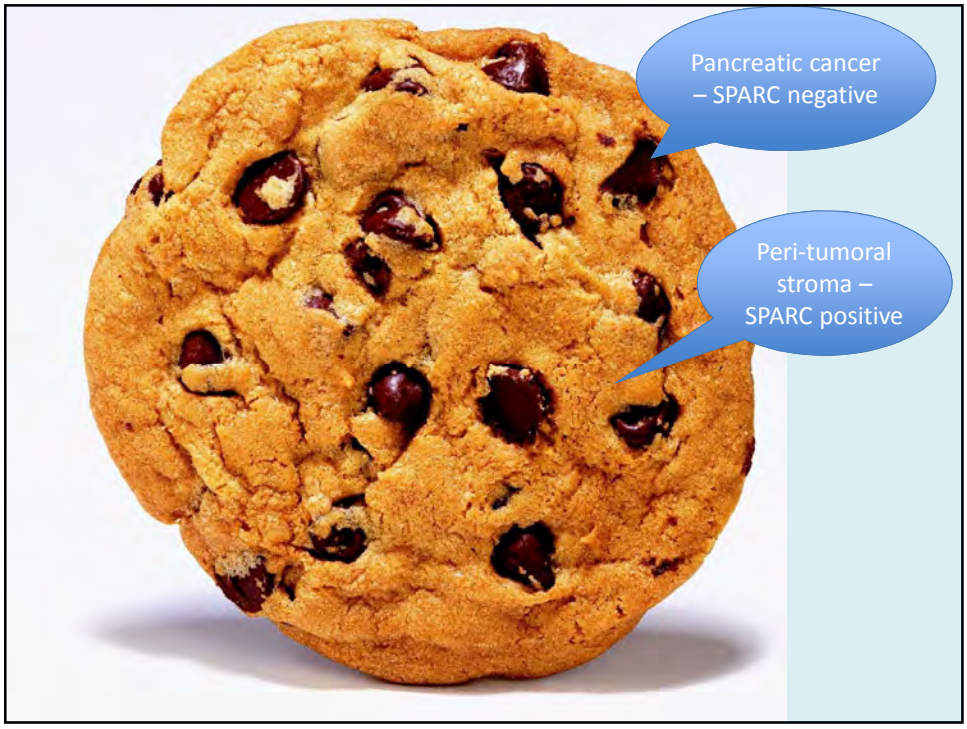
The NEW ENGLAND JOURNAL *of* MEDICINE

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine



Von Hoff, N Engl J Med, 2013

Efficacy Variable	nab-Paclitaxel plus Gemcitabine (N=431)	Gemcitabine Alone (N=430)	Hazard Ratio or Response-Rate Ratio (95% CI)*	P Value
Overall survival				
Median overall survival — mo (95% CI)	8.5 (7.9–9.5)	6.7 (6.0–7.2)	0.72 (0.62–0.83)	<0.001
Survival rate — % (95% CI)				
6 mo	67 (62–71)	55 (50–60)		<0.001
12 mo	35 (30–39)	22 (18–27)		<0.001
18 mo	16 (12–20)	9 (6–12)		0.008
24 mo	9 (6–13)	4 (2–7)		0.02
Progression-free survival				
Median progression-free survival — mo (95% CI)	5.5 (4.5–5.9)	3.7 (3.6–4.0)	0.69 (0.58–0.82)	<0.001
Rate of progression-free survival — % (95% CI)				
6 mo	44 (39–50)	25 (20–30)		
12 mo	16 (12–21)	9 (5–14)		
Response				
Rate of objective response				
Independent review				
No. of patients with a response	99	31	3.19 (2.18–4.66)	<0.001
% (95% CI)	23 (19–27)	7 (5–10)		
Investigator review				
No. of patients with a response	126	33	3.81 (2.66–5.46)	<0.001
% (95% CI)	29 (25–34)	8 (5–11)		
Rate of disease control†				
No. of patients	206	141	1.46 (1.23–1.72)	<0.001
% (95% CI)	48 (43–53)	33 (28–37)		
Best response according to independent review — no. (%)				
Complete response	1 (<1)	0		
Partial response	98 (23)	31 (7)		
Stable disease	118 (27)	122 (28)		
Progressive disease	86 (20)	110 (26)		
Could not be evaluated‡	128 (30)	167 (39)		



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Finally . . .
substantial survival benefits

1 year survival:

- Gemcitabine alone – 18% (1997)
- Gemcitabine plus erlotinib – 23% (2007)
- FOLFIRINOX – 48% (2011)
- Gem plus nab-paclitaxel – > 35%
  (app 50% in phase II trial, 2011)

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CLINICAL STUDY ALWAYS FIRST OPTION

BUT, IF NOT POSSIBLE:

- Poor performance status:
  - Gemcitabine alone or with erlotinib
- Good performance status:
  - Front-line – gemcitabine plus nab-paclitaxel
  - Second line – FOLFIRINOX if possible, or an oxaliplatin-based regimen

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Novel Therapies

Novel Therapies at Scripps Clinic

Scripps Clinic
Pancreas and Bile Duct Cancer
Group

PANCREATIC CANCER ACTION NETWORK
ADVANCE RESEARCH. SUPPORT PATIENTS. CREATE HOPE.

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THRESHOLD PHARMACEUTICALS

TH-CR-404 Study

A Randomized Cross-over Phase 2 Study of the Safety and Efficacy of Two Dose Levels of TH-302 in Combination with Gemcitabine Compared with Gemcitabine Alone in Previously Untreated Patients with Locally Advanced Unresectable or Metastatic Pancreatic Adenocarcinoma

TH-302: An Optimized Hypoxia-Activated Prodrug

Preclinical summary

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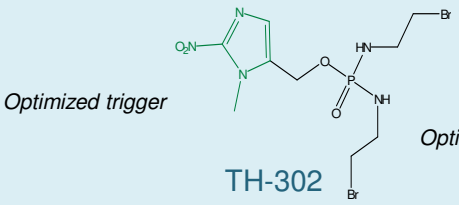
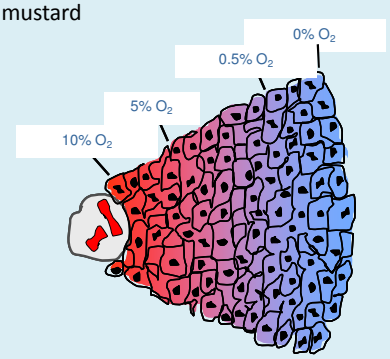


TH-302

2-nitromidazole hypoxia trigger covalently linked to a brominated version of isophosphoramide mustard



Study TH-CR-404

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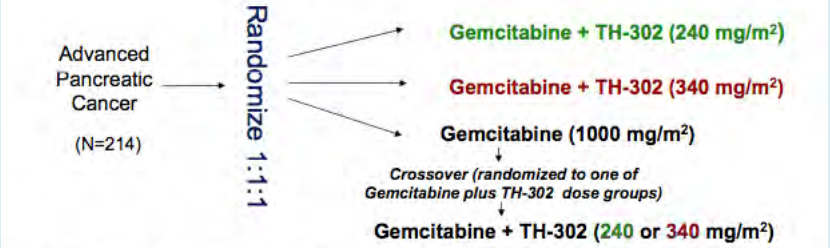
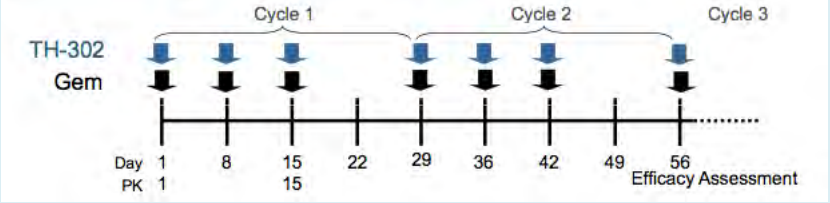
Randomized Phase 2 Study Design (June 2010- June 2011; 45 sites)



Stratification: Stage (Unresectable Locally Advanced vs. Distant Metastases)



Borad, ESMO, 2012

Study TH-CR-404

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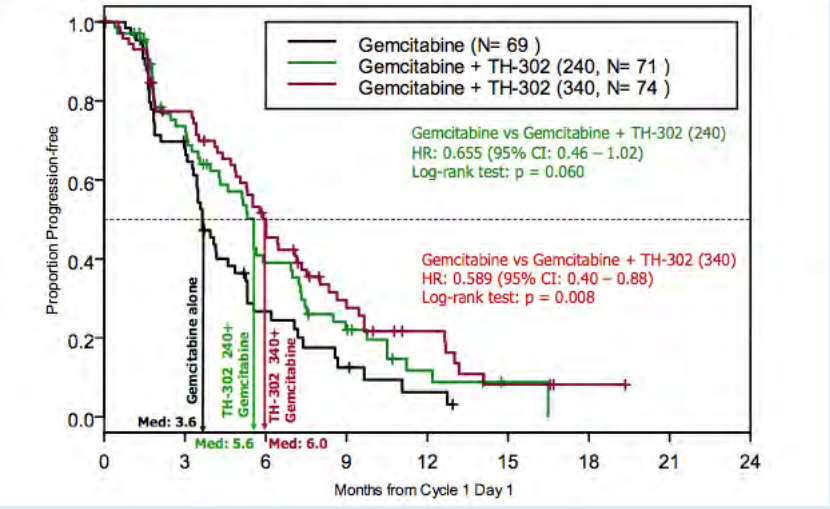
Progression-free Survival by Treatment Arm



Study TH-CR-404

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RECIST Best Response

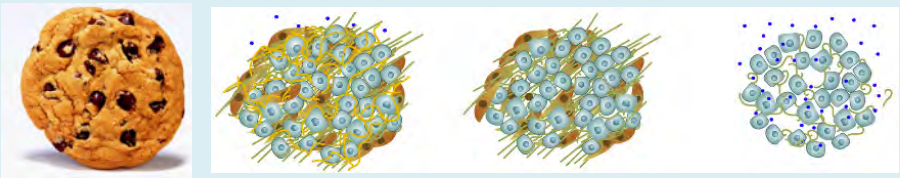
	Gemcitabine (N=69)	Gemcitabine + TH-302 (240 mg/m²) (N=71)	Gemcitabine + TH-302 (340 mg/m²) (N=74)
Response			
CR	0 (0%)	0 (0%)	2 (3%)
PR	7 (10%)	12 (17%)	17 (23%)
SD	39 (57%)	41 (58%)	37 (50%)
PD	12 (17%)	13 (18%)	12 (16%)
NA*	11 (16%)	5 (7%)	6 (8%)
Response	7 (10%)	12 (17%)	19 (26%)
P-value** vs. Gemcitabine		0.220	0.021

* No Response assessment on study. Unless specified, subject is classified as PD for analysis.

** Cochran-Mantel-Haenzel test stratifying for extent of disease.

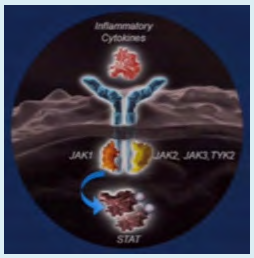
Halozyme THERAPEUTICS

PEG-PH20 plus nab-paclitaxel plus gemcitabine compared with nab-paclitaxel plus gemcitabine in subjects with stage IV untreated pancreatic cancer (HALO-102-202)



Incyte

A randomized double-blind phase 2 study of ruxolitinib (RUX) or placebo (PBO) with capecitabine (CAPE) as second-line therapy in patients (pts) with metastatic pancreatic cancer (mPC)



Study Design

Patient Eligibility
- Histologically confirmed metastatic PDAC
- Karnofsky PS ≥60
- Failed gemcitabine

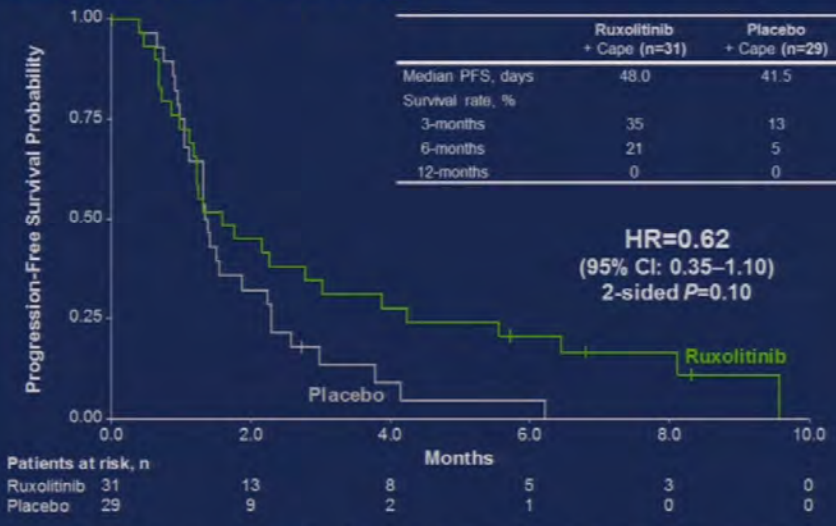
RANDOMIZED 1:1

n=64: **Ruxolitinib** (15 mg BID, days 1–21) + **Capecitabine** (1000 mg/m² BID, days 1–14)

n=63: **Placebo** (BID, days 1–21) + **Capecitabine** (1000 mg/m² BID, days 1–14)

Endpoints

Progression-Free Survival in Patients with CRP > 13 mg/L



	Ruxolitinib + Cape (n=31)	Placebo + Cape (n=29)
Median PFS, days	48.0	41.5
Survival rate, %		
3-months	35	13
6-months	21	5
12-months	0	0

HR=0.62
(95% CI: 0.35–1.10)
2-sided *P*=0.10

Patients at risk, n						
Ruxolitinib	31	13	8	5	3	0
Placebo	29	9	2	1	0	0

- PFS in patients with CRP ≤ 13 mg/L: 0.82 (95% CI: 0.47–1.41); *P*=0.47

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A Randomized Phase II Open Label Study to Assess the Efficacy and Safety of Gemcitabine + Nab-Paclitaxel (Abraxane®) With or Without ODSH (2-0, 3-0 Desulfated Heparin) as First Line Treatment of Metastatic Pancreatic Cancer

ODSH is a modified heparin molecule with low anticoagulant activity that may interfere with pancreatic cancer growth, metastasis, and chemotherapy resistance

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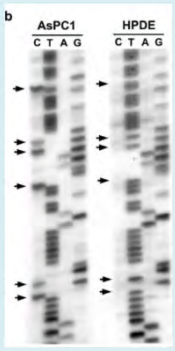
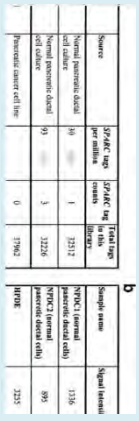
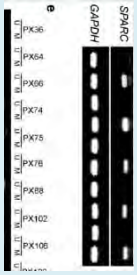
A Randomized Phase II Study of Gemcitabine and Nab-Paclitaxel in Combination with 5-Azacitidine







- Novel investigator-initiated study
- SPARC expression is absent in the pancreatic cancer due to DNA methylation
- 5-azacitidine is a hypomethylating agent that can re-express SPARC
- This could enhance activity of gemcitabine-nab-paclitaxel therapy

Sato, Oncogene, 2003

Any questions?