

The Fight Against Pancreatic Cancer

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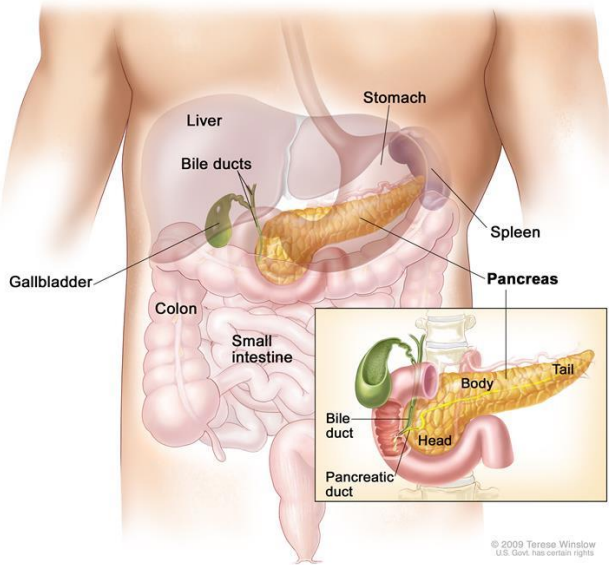
Overview



- Epidemiology/Biology
- Diagnosis
- Early stage disease
 - Surgical treatments
 - Chemotherapy/Radiation treatments
- Advanced stage disease
 - Chemotherapy treatments
- Future Research



Pancreas



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Epidemiology

Estimated New Cases

		Males	Females			
Prostate	180,890	21%		Breast	246,660	29%
Lung & bronchus	117,920	14%		Lung & bronchus	106,470	13%
Colon & rectum	70,820	8%		Colon & rectum	63,670	8%
Urinary bladder	58,950	7%		Uterine corpus	60,050	7%
Melanoma of the skin	46,870	6%		Thyroid	49,350	6%
Non-Hodgkin lymphoma	40,170	5%		Non-Hodgkin lymphoma	32,410	4%
Kidney & renal pelvis	39,650	5%		Melanoma of the skin	29,510	3%
Oral cavity & pharynx	34,780	4%		Leukemia	26,050	3%
Leukemia	34,090	4%		Pancreas	25,400	3%
Liver & intrahepatic bile duct	28,410	3%		Kidney & renal pelvis	23,050	3%
All Sites	841,390	100%	All Sites	843,820	100%	

Estimated Deaths

		Males	Females			
Lung & bronchus	85,920	27%		Lung & bronchus	72,160	26%
Prostate	26,120	8%		Breast	40,450	14%
Colon & rectum	26,020	8%		Colon & rectum	23,170	8%
Pancreas	21,450	7%		Pancreas	20,330	7%
Liver & intrahepatic bile duct	18,280	6%		Ovary	14,240	5%
Leukemia	14,130	4%		Uterine corpus	10,470	4%
Esophagus	12,720	4%		Leukemia	10,270	4%
Urinary bladder	11,820	4%		Liver & intrahepatic bile duct	8,890	3%
Non-Hodgkin lymphoma	11,520	4%		Non-Hodgkin lymphoma	8,630	3%
Brain & other nervous system	9,440	3%		Brain & other nervous system	6,610	2%
All Sites	314,290	100%	All Sites	281,400	100%	

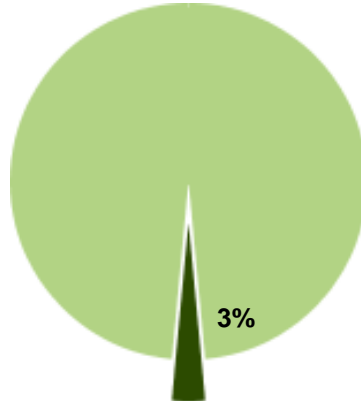
Siegel et al, 2016





Epidemiology

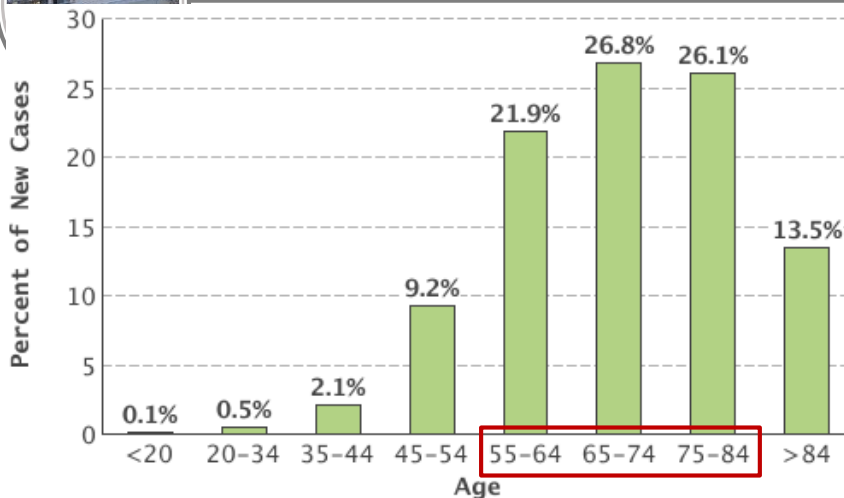
- Estimated 53,000 new cases diagnosed yearly in the US.
 - Males- 27,670
 - Females – 25,400
- Pancreatic Cancer Represent 3% of all new cancer cases in the U.S.



Siegel et al, 2016
SEER Cancer Statistics Review, 1975-2012, National Cancer Institute



Epidemiology



Pancreatic Cancer is most frequently diagnosed among people aged **65-74**

SEER Cancer Statistics Review, 1975-2012, National Cancer Institute





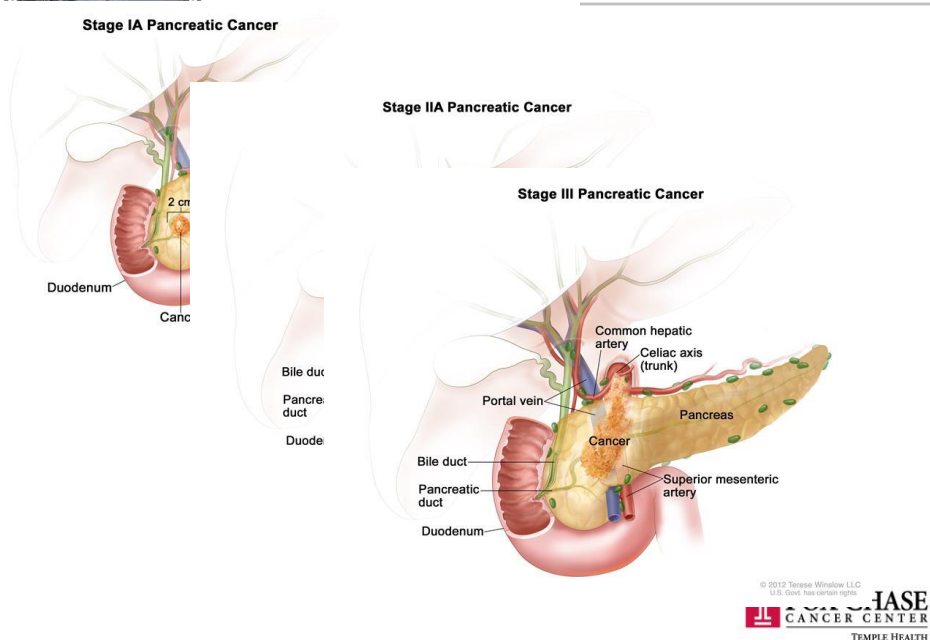
Risk factors

- Smoking
- Overweight
- Personal history of diabetes
- Personal history of chronic pancreatitis – inflammation to the pancreas
- Family history of pancreatic cancer
- Hereditary conditions

SEER Cancer Statistics Review, 1975-2012, National Cancer Institute

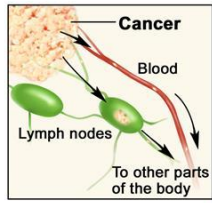


Pancreatic cancer staging

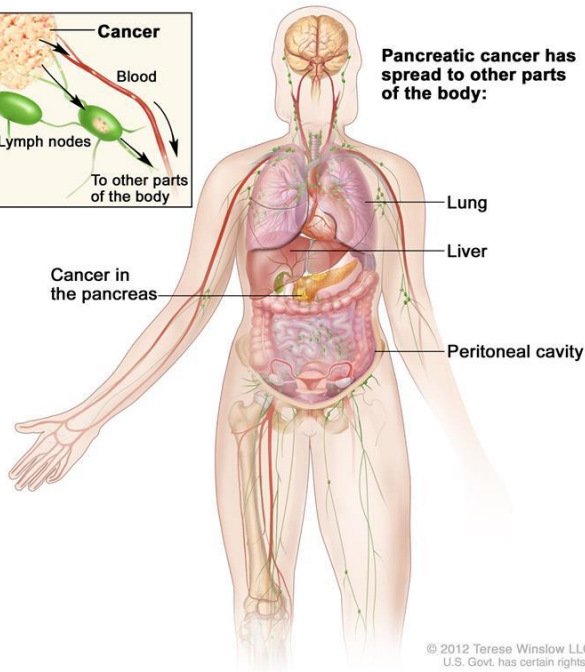




Stage IV Pancreatic Cancer



Pancreatic cancer has spread to other parts of the body:

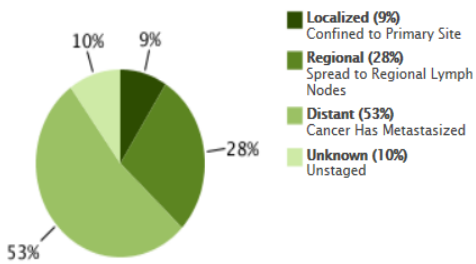


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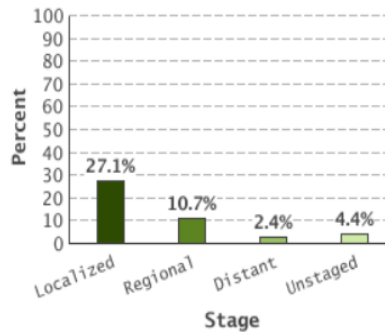


Pancreatic cancer

Percent of Cases by Stage



5-Year Relative Survival



	1975-1977	1987-1989	2005-2011
5 year survival	3%	4%	8%



Siegel et al, 2016



Diagnosis

Challenges in Early Diagnosis:

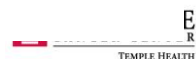
- Usually there are no symptoms or signs in early stages of the disease.
- Many of the signs and symptoms are not specific (weakness, abdominal discomfort, loss of appetite)
- The pancreas is hidden behind other organs and hard to examine.

Siegel et al, 2016



Signs & Symptoms

- Asthenia (weakness) – 86%
- Weight loss and Anorexia (no appetite)– 85%
- Abdominal pain – 79%
- Epigastric pain (stomach) – 71%
- Dark urine – 59%
- Jaundice – 56 %
- Nausea – 51%
- Back pain – 49%
- Diarrhea- 44%
- Vomiting – 33%
- Steatorrhea (fatty stools)– 25%
- Thrombophlebitis – 3%
- Hepatomegaly (large liver) – 39%
- Epigastric mass – 15%
- Ascites (abdominal fluid) – 5%





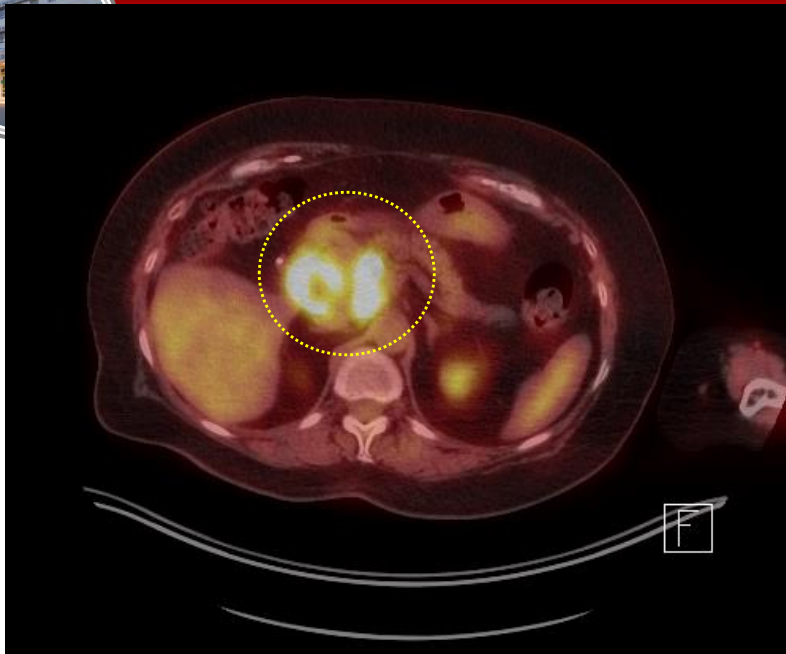
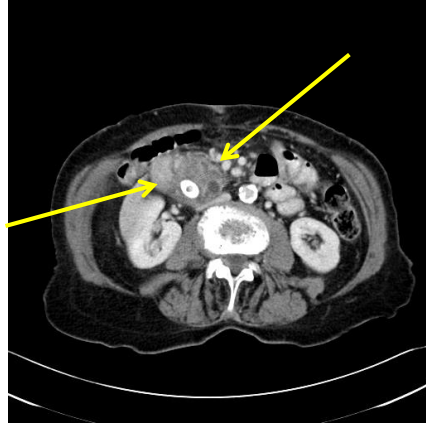
Diagnosis

Blood tests:

- Elevation of liver function tests.
- Elevation of tumor marker – CA19-9

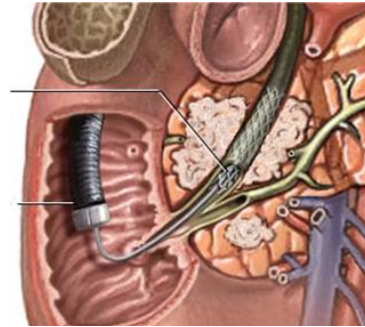
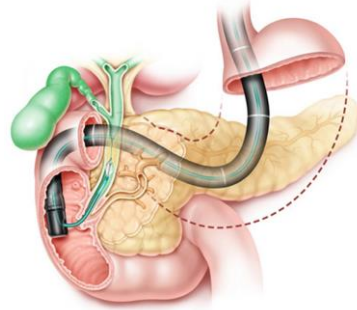
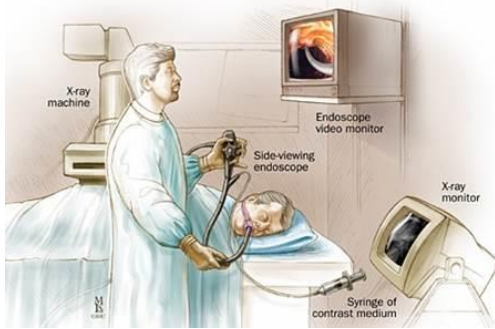
Imaging:

- Ultrasound
- CT Scan
- MRI
- PET-CT



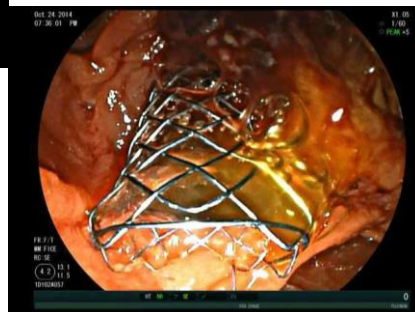
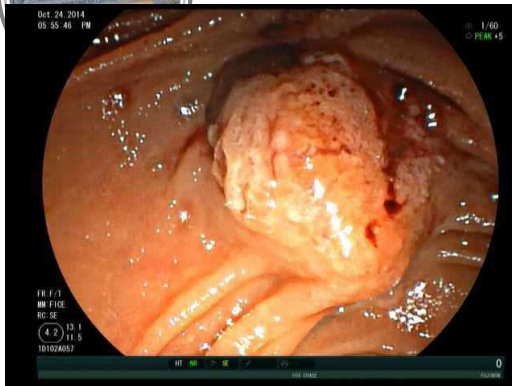


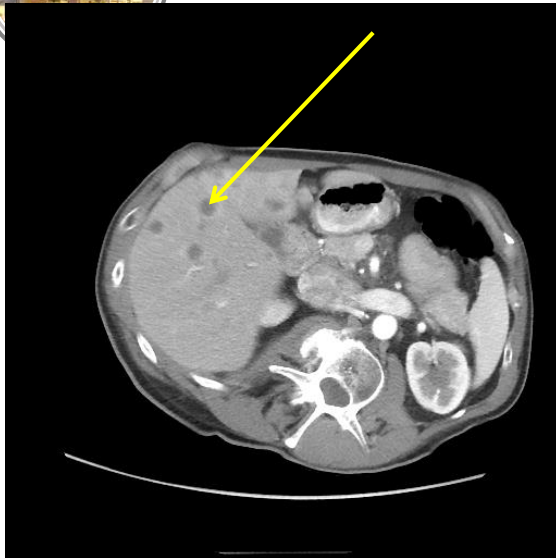
Diagnosis



Invasive tests:

- ERCP
- Endoscopic Ultrasound

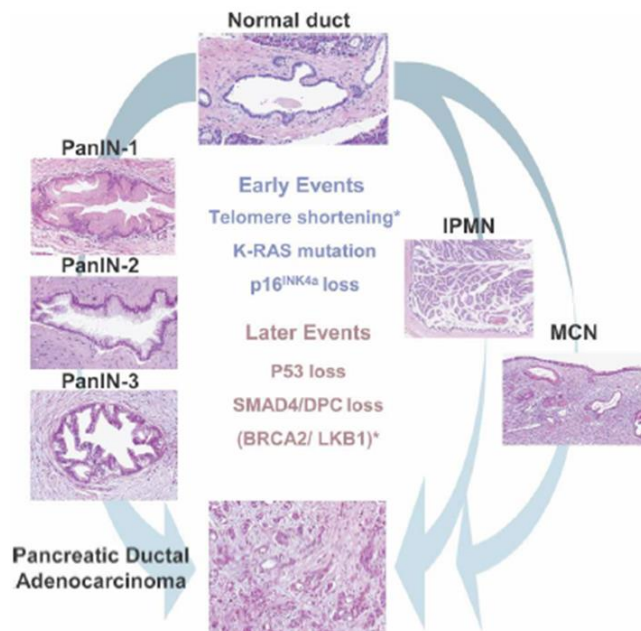




CT guided biopsy for patients with metastatic disease.

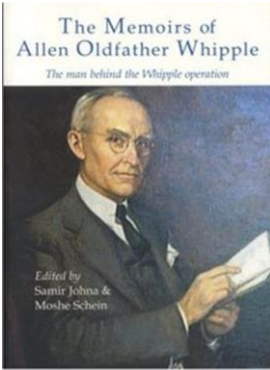


Pathology



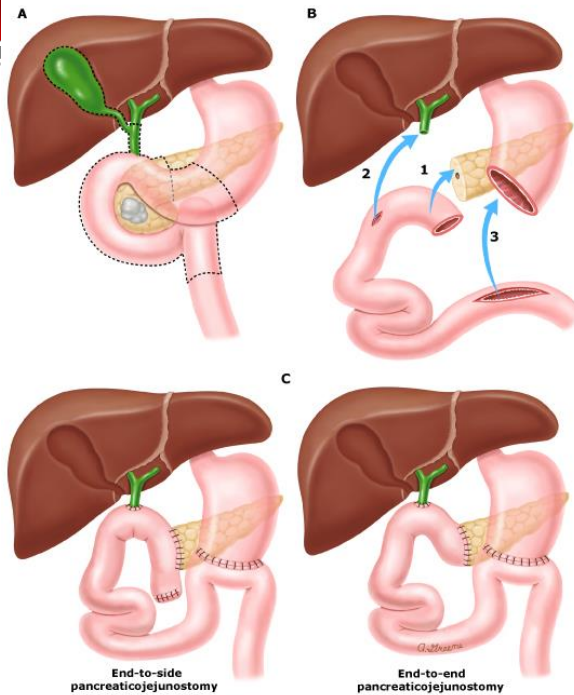


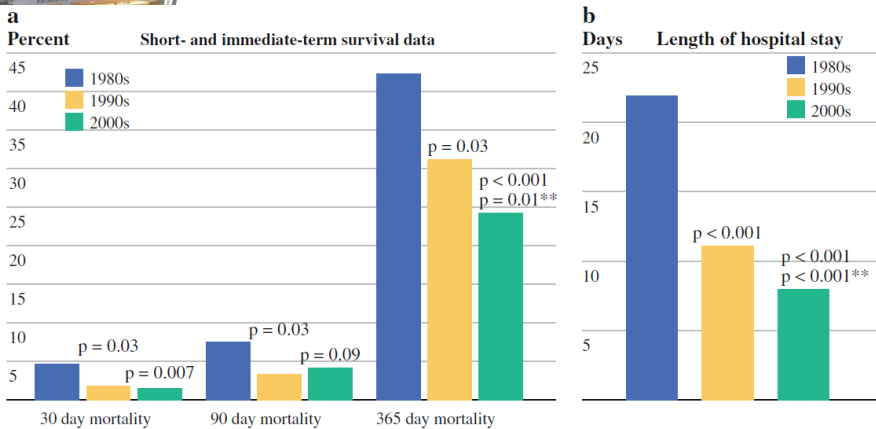
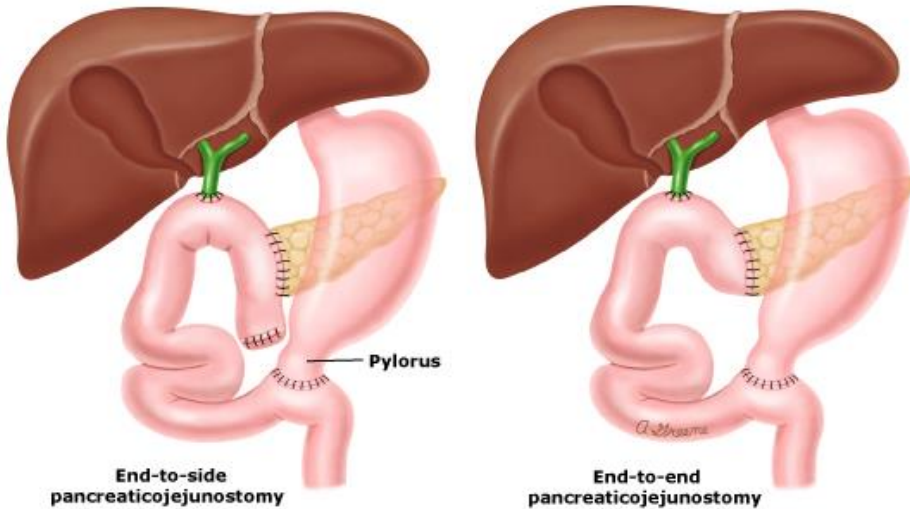
Treatment – Early stage



Allen Oldfather Whipple (1881- 1963)

- Only curative option is surgical resection.
- Removal of the gallbladder, bile ducts, part of the duodenum and head of the pancreas.
- Modification to the surgery have been developed to decrease morbidity.
- Minimally invasive techniques are feasible



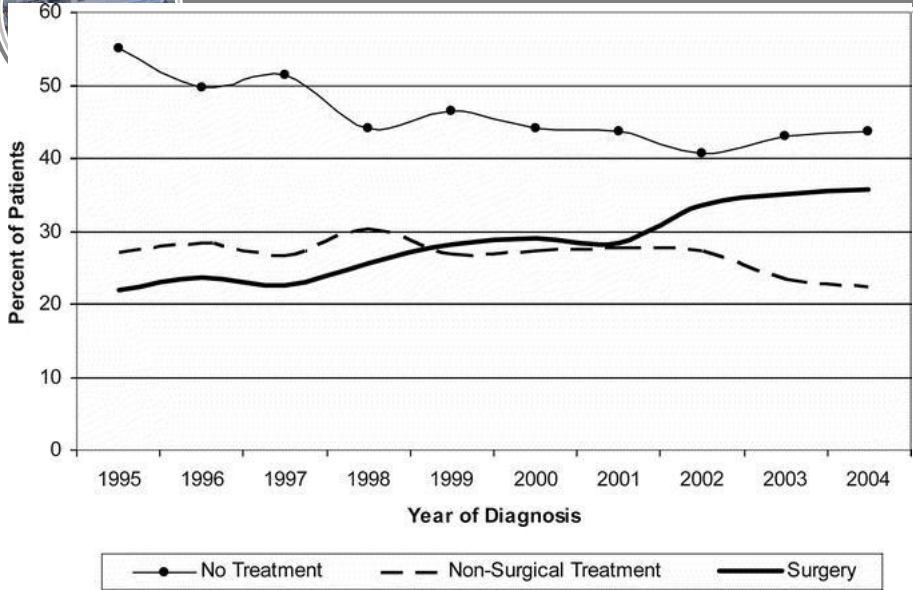


Current peri-operative mortality is approximately 4%.

Winter JM. et al. Annals of surgery 2012



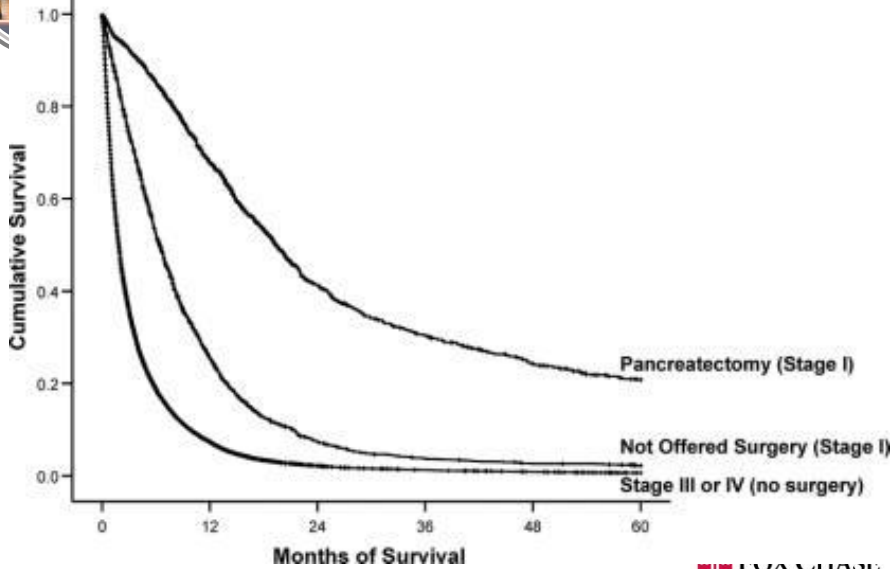
Whipple surgery



Bilimoria K. et al. Annals of surgery 2007



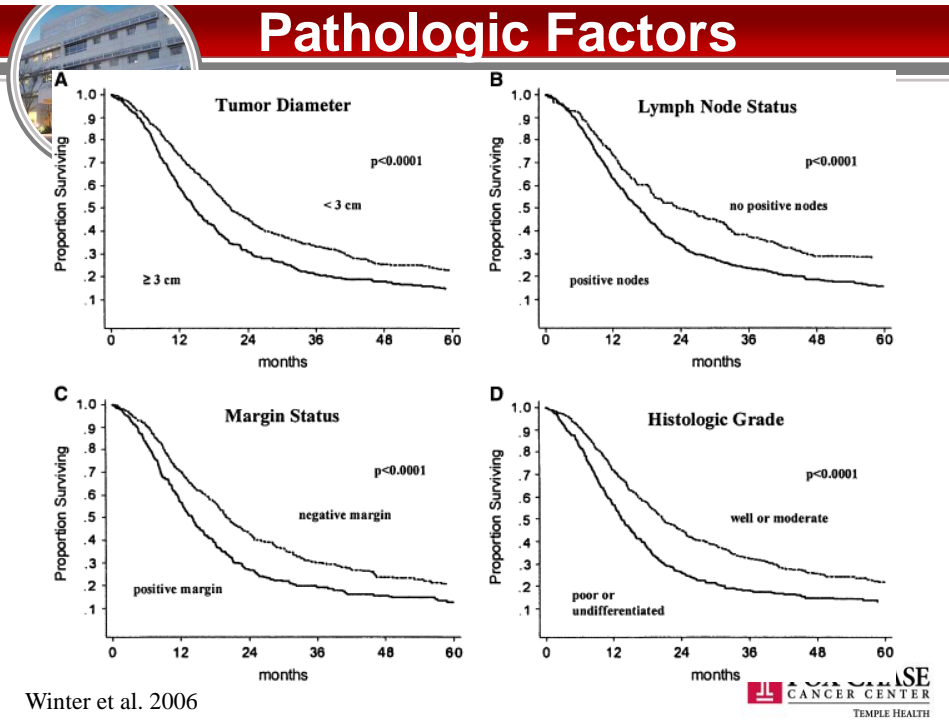
Whipple surgery



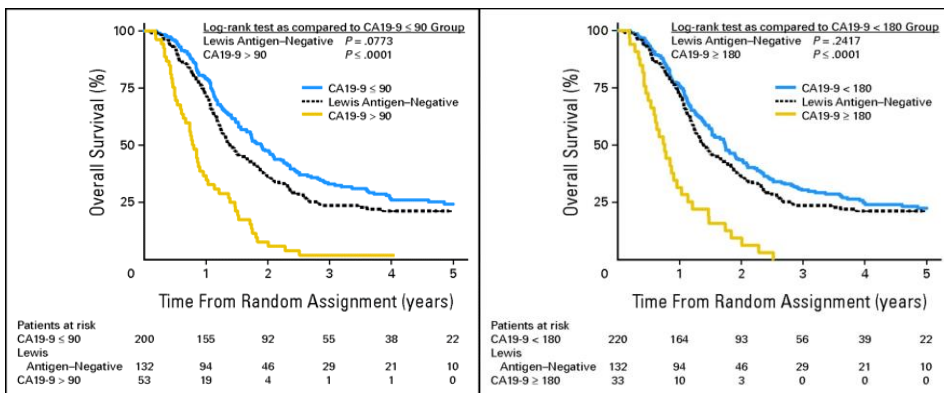
Bilimoria K. et al. Annals of surgery 2007



Pathologic Factors



Postoperative CA 19-9



Berger A. 2008



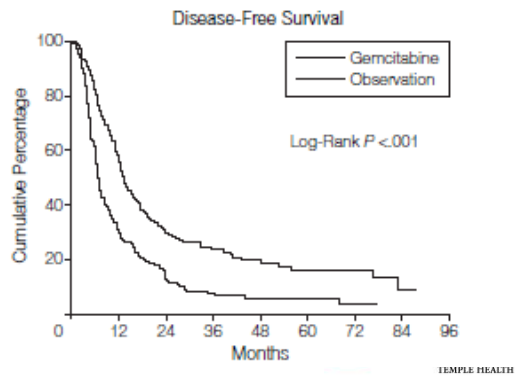
Adjuvant therapy

CONKO study:

Collaborative, multi-institutional, randomized, controlled trial have demonstrated benefit to chemotherapy with gemcitabine for 6 months after surgery.



Oettle et al. JAMA. 2007



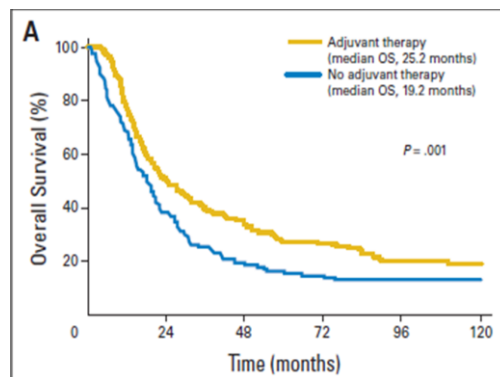
Adjuvant therapy

Chemo-radiation:

Multiple studies have shown some improvement with the addition of chemo/radiation to the post operative therapy.

There is an ongoing debate regarding the benefit.

In the US often used.



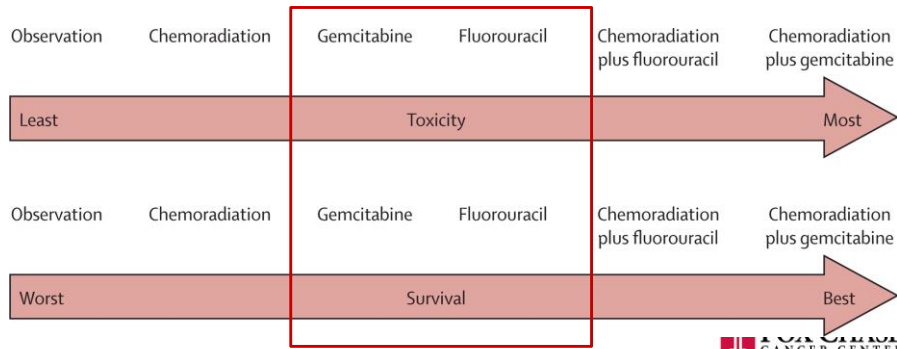
Herman. JM J Clin Oncol. 2008



Adjuvant therapy

Meta-analysis:

- Evaluation of all studies performed with chemotherapy with and without radiation, found chemotherapy with Gemcitabine or Fluorouracil to be the most effective in reducing mortality by about 1/3.



Wei-Chih Liao et al. Lancet Oncology 2013



Adjuvant therapy

Ongoing clinical research:

- 135 studies listed in clinicaltrials.gov for adjuvant therapy for resected pancreatic cancer.
- Large studies in Europe and the US using more aggressive chemotherapy regimens in comparison to single agent gemcitabine.

How does the APACT study work?





Borderline resectable

- Definition varies – mostly in cases with large tumors in close proximity to local blood vessels.
- Tumors encasing the vessel were in the past considered unresectable. However, with vascular re-construction some of these cases can go to surgery.
- Tumor shrinkage with chemotherapy or radiation before surgery used more often – Neoadjuvant therapy.



Neoadjuvant therapy

- About 30-40% of patients are candidates.
- Optimal therapy is controversial.
- Goal – Shrink the tumor and allow for a resection.

Study	# patients	Regimen	# of patients with surgery
Vasile E, 2012	15	FOLFIRINOX+RT	5
Gunturu K, 2013	16	FOLFIRINOX	2
Marthey L, 2015	77	FOLFIRINOX+RT	25
Blazer M, 2015	43	FOLFIRINOX+RT	19
Mellon E, 2015	159	FOLFIRINOX+Gem/ Abraxane+RT	59
Sadot E, 2015	101	FOLFIRINOX+RT	16





Neoadjuvant therapy

Radiation:

- Controversial results regarding the benefit of radiation from clinical trials.
- Often added to the regimen.
- Benefit:
 - Local control
 - Good tolerance
 - Better chance of getting The treatment pre-op.

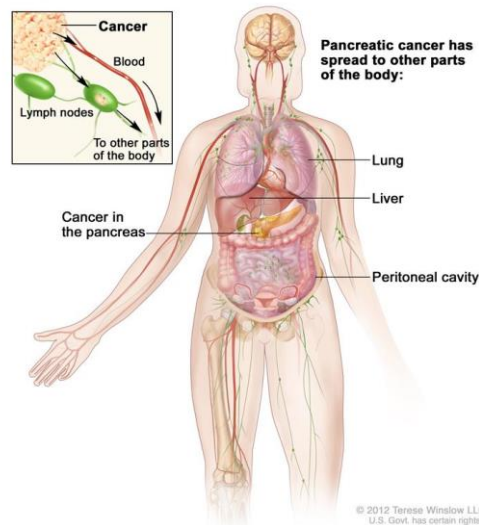


Metastatic disease

Goals:

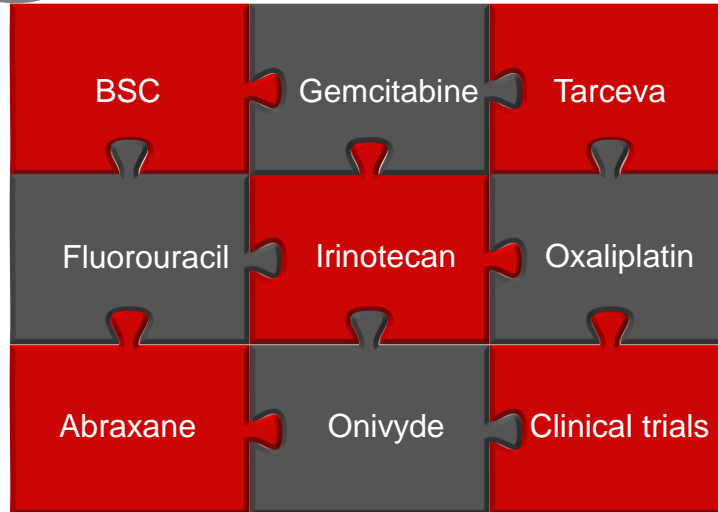
- Drug delivery to all sites.
- Palliative therapy.
- Prolonging survival.
- Improving quality of life.

Stage IV Pancreatic Cancer





Available agents...



FOX CHASE
CANCER CENTER
TEMPLE HEALTH



Advances...

1985

1990

1995

2000

2005

2010

2015

Best supportive care

5-FU

Gemcitabine

Capecitabine

Conclusion from multiple papers (1990s - early 2000s):

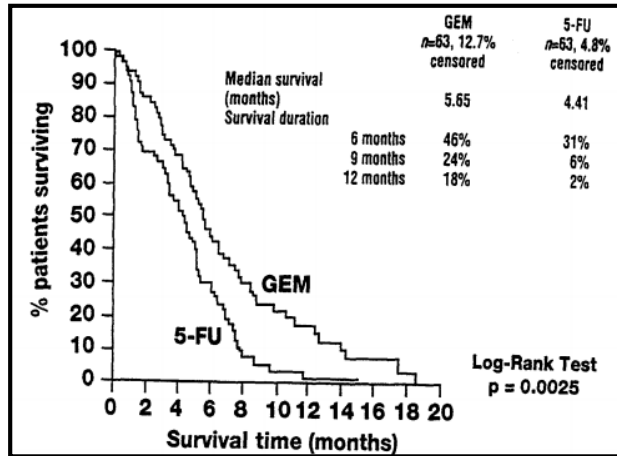
“The only justification for subjecting a patient with advanced pancreatic carcinoma to chemotherapy is the entry of such a patient into a clinical research trial that at least provides the hope that something of value may be accomplished.”

FOX CHASE
CANCER CENTER
TEMPLE HEALTH



Gemcitabine approved in 1997 for first-line therapy of advanced pancreatic cancer

Clinical benefit: 23.8% vs. 4.8%



The next phase....

Phase II

Drugs tested	# patients	Results
Gemcitabine +/- cisplatin	192	No difference
Gemcitabine +/- oxaliplatin	313	No difference
Gemcitabine +/- 5-FU	322	No difference
Gemcitabine +/- capecitabine)	533	No difference
Gemcitabine +/- pemetrexed	565	No difference
Gemcitabine +/- irinotecan	360	No difference
Gemcitabine +/- exatecan	349	No difference

None demonstrated statistically significant improvement in survival

Boeck and Heinemann, 2008.





The next phase....

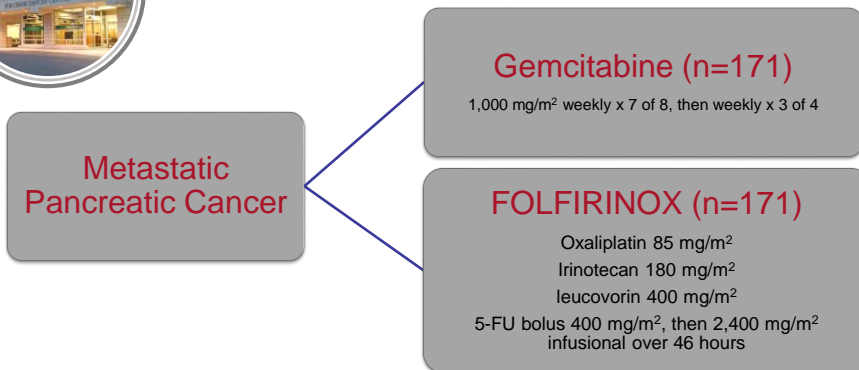
Phase III

Drugs tested	# Patients	Results
Gemcitabine +/- Marimastat	239	No difference
Gemcitabine +/- Tipifarnib	688	No difference
Gemcitabine +/- Erlotinib	569	Minimal improvement with Erlotinib
Gemcitabine +/- Bevacizumab	602	No difference
Gemcitabine +/- Cetuximab	735	No difference
Gemcitabine +/- Axitinib	632	No difference

Bramhall et al, 2002; Van Cutsem et al, 2004; Moore et al, 2007; Kindler et al, 2010; Philip et al, 2010; Kindler et al, 2011.

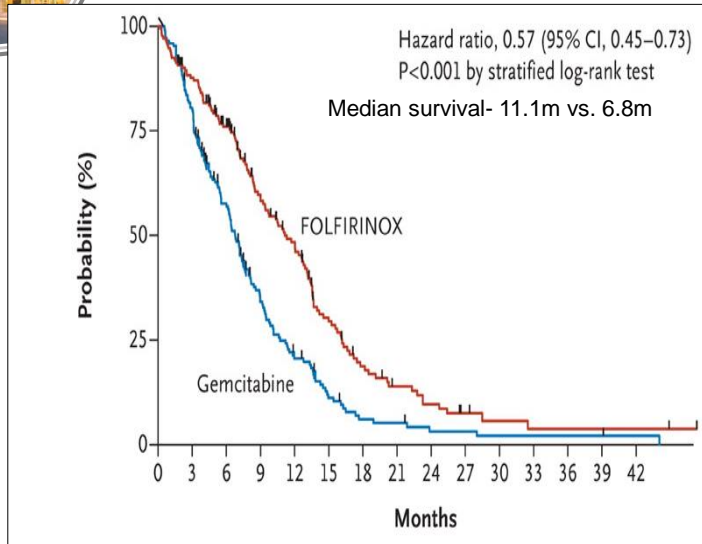


PRODIGE4/ACCORD11



Conroy et al, 2011.

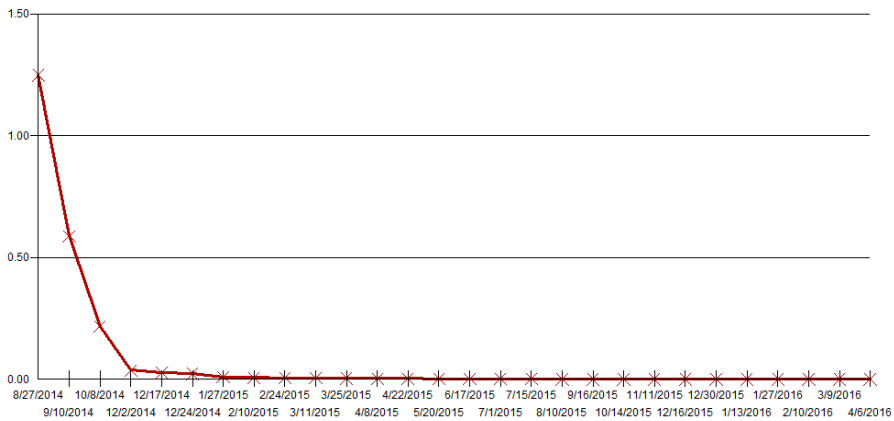




Conroy et al, 2011.



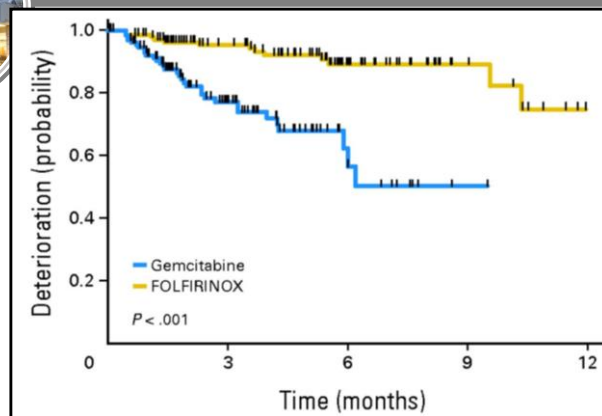
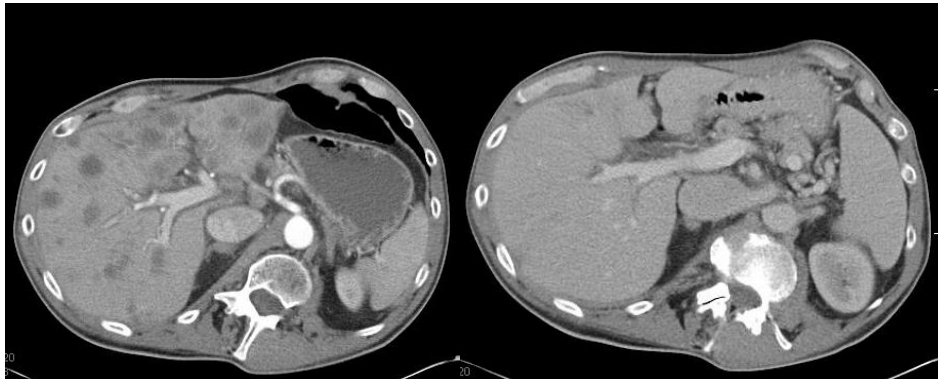
CA 19-9 Trend while on FOLFIRINOX





Pre - treatment

Post - treatment



Improvement in quality of life measures:

- Improvement in symptoms – fatigue, pain, anorexia
- Physical and cognitive function
- Global Health Scores

Gourgou-Bourgade et al, 2013.



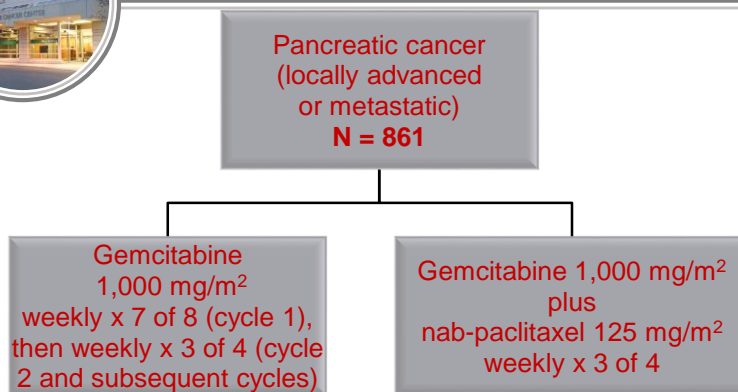


Event	FOLFIRINOX (n=171)	Gemcitabine (n=171)	P value
Hematologic			
Neutropenia	45.7%*	21.0%	< 0.001
Febrile neutropenia	5.4%	1.2%	0.03
Thrombocytopenia	9.1%	3.6%	0.04
Non-hematologic			
Fatigue	23.6%	17.8%	NS
Vomiting	14.5%	8.3%	NS
Diarrhea	12.7%	1.8%	< 0.001
Sensory neuropathy	9.0%	0.0%	<0.001

Conroy et al, 2011.



MPACT study

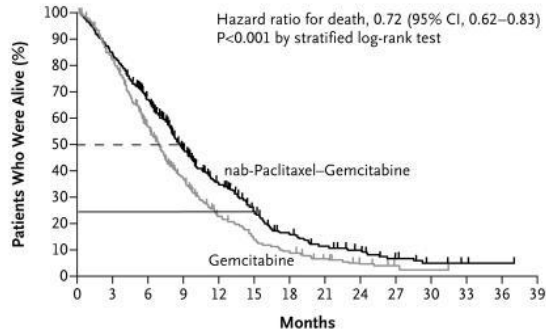


Von Hoff et al, 2013.





A Overall Survival



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39
nab-Paclitaxel-Gemcitabine	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gemcitabine	430	340	220	124	69	40	26	15	7	3	1	0	0	0

Von Hoff et al, 2013.



Safety

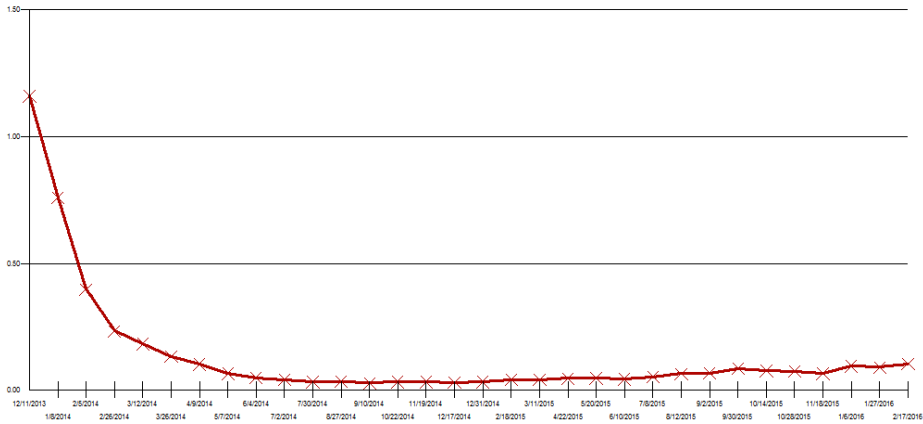
Preferred Term	<i>nab</i> -P + Gem (n = 421)	Gem (n = 402)
Grade ≥3 Hematologic AE, ^a %		
Neutropenia	38	27
Leukopenia	31	16
Thrombocytopenia	13	9
Anemia	13	12
Pts Who Received Growth Factors, %	26	15
Febrile Neutropenia, ^b %	3	1
Grade ≥3 Nonhematologic AE ^b in >5% Pts, %		
Fatigue	17	7
Peripheral 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 <i>nab</i> -P, %	44	--

Von Hoff et al, 2013.





CA 19-9 Trend while on Gemcitabine/Abraxane



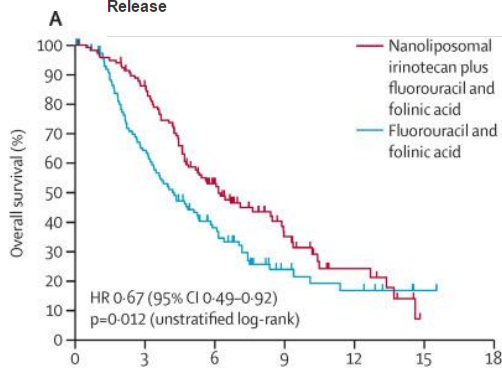
Nanoliposomal Irinotecan

FDA News Release

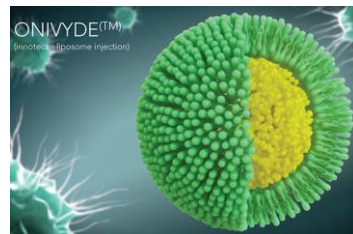
FDA approves new treatment for advanced pancreatic cancer

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For Immediate Release October 22, 2015



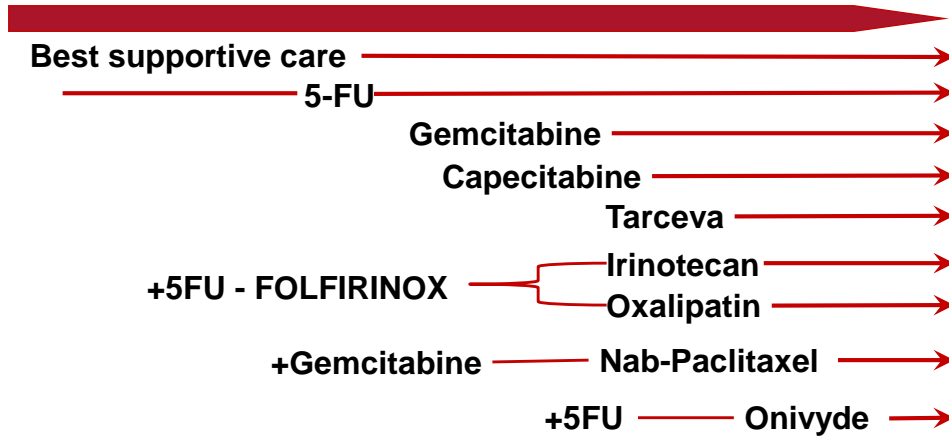
Wang-Gillam A. Lancet, 2015.





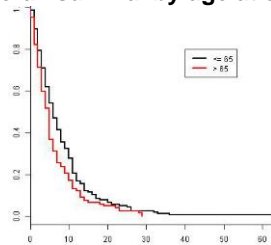
Advances in 2 decades

1985 1990 1995 2000 2005 2010 2015

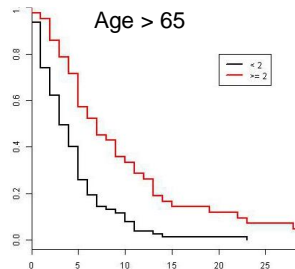
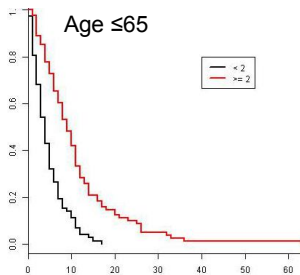


Older patients

Overall survival by age at diagnosis



Overall survival and number of chemotherapy agents



Vijayvergia, N. J Geriatr Oncol, 2015.





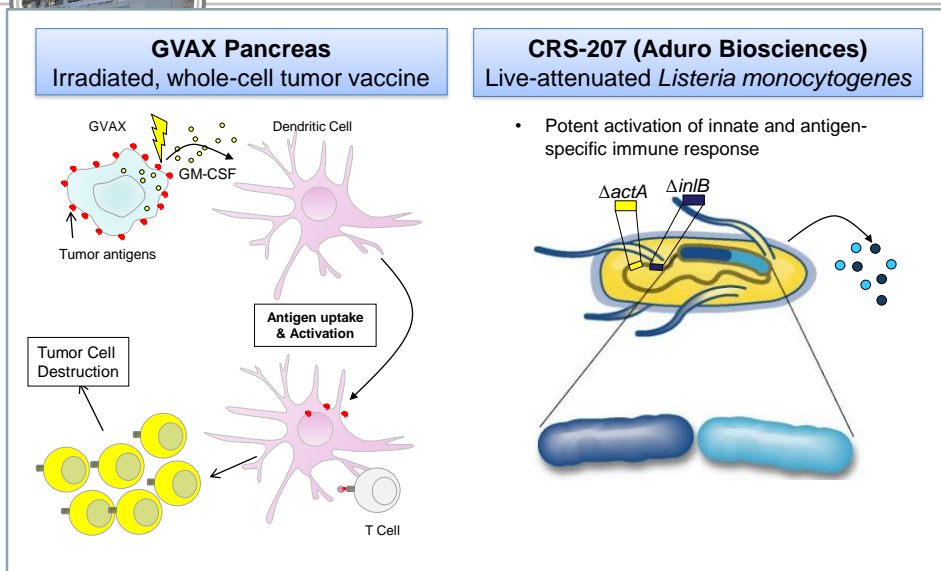
Clinical trials

Ongoing clinical research:

- Over 200 studies listed in clinicaltrials.gov for metastatic pancreatic cancer.
- Most studies involving combination of Gemcitabine/abraxane + Drug X.
- At FCCC – 3 ongoing studies with Gemcitabine +Abraxane +Drug X.
 - Wee Inhibitor → AZ1775
 - Wnt inhibitor → Vantictumab
 - Wnt inhibitor → Ipafricept



Immunotherapy

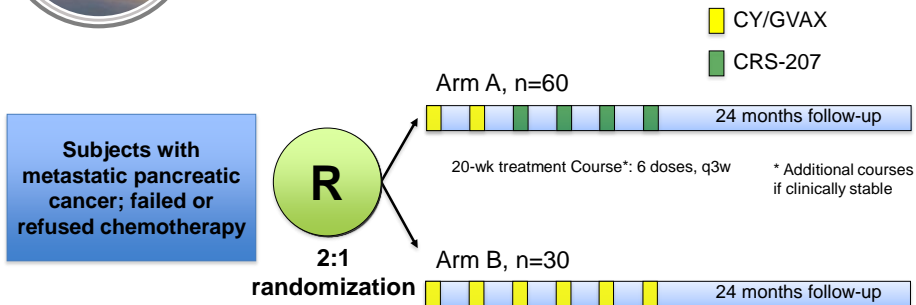


Dung T. Le et al. JCO 2014





Phase 2 Study

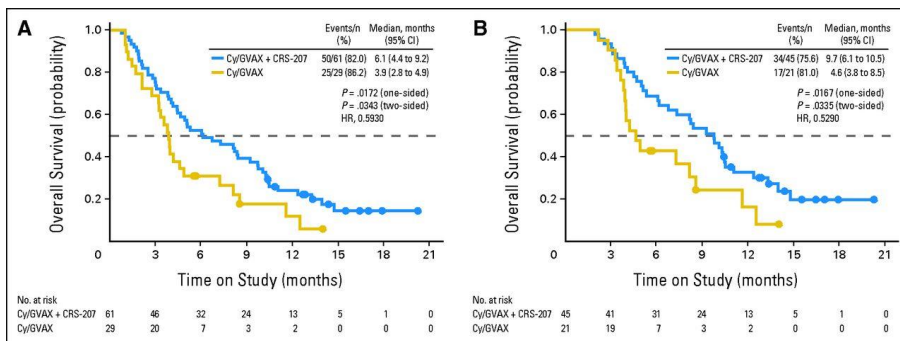


- Prior phase I trial of CRS-207 showed markedly improved survival (17 months) in 3 pancreatic cancer patients who had previously undergone 'boost' with GVAX vaccine.
- Primary objective: overall survival

Dung T. Le et al. JCO 2014



Overall Survival

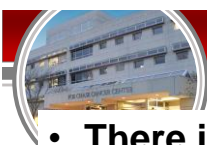
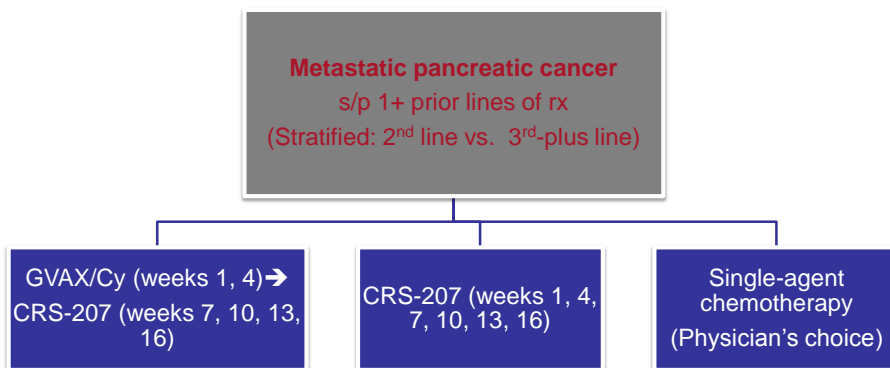


Dung T. Le et al. JCO 2014





Phase II ECLIPSE Trial



Summary

- **There is real optimism in the treatment of this disease!!**
- **Survival has clearly improved for metastatic disease and localized disease.**
- **Renewed interest in drug development has invigorated clinical trials.**
- **Enrollment in clinical trials is highly encouraged!**




**PANCREATIC
CANCER
ACTION
NETWORK**

Patient and Caregiver Support
877-435-8650

Facing Pancreatic Cancer

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**“We must engage an army of heroes in the fight
against pancreatic cancer so that we can know it,
fight it and end it”**

Lisa Niemi Swayze, Chief Ambassador of Hope

Thank you

