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KENTUCKY
MARKEY CANCER CENTER
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A Cancer Center Designated by the
National Cancer Institute

Pancreatic cancer treatment approaches

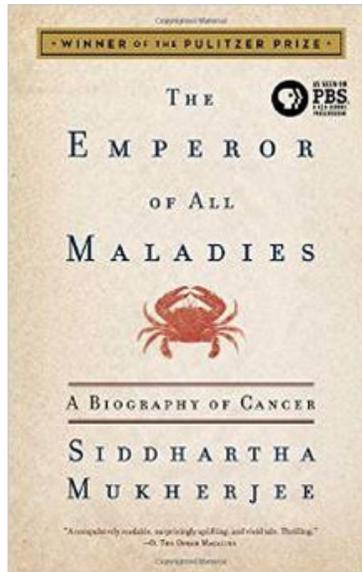
WAGE HOPE **PANCREATIC CANCER ACTION NETWORK**

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September 17th, 2015

Outline

- General principles of cancer
- Pancreatic cancer overview
- Advances in systemic therapy
- Management of locally advanced disease
- New approaches: Immunotherapy
- Case presentations
- Conclusion

Introduction to Oncology



Introduction to Oncology

- Treatment options fall into two main categories
 - **Local therapy:**
 - Surgery
 - Radiation
 - **Systemic therapy:**
 - Chemotherapy
 - Immune therapy
- Most cancers are treated with a combination approach e.g. surgery followed by chemotherapy and radiation

Introduction to Oncology

- **Goals of treatment should be clear from the start**

- **Cure the cancer**

- In general this applies to early stage cancers
- Treatment is usually intensive and patients can get very sick from the treatment itself in an attempt to eradicate the cancer

- **Improve length of life and quality of life**

- Generally applies to advanced cancers or patients who are not in good shape for intensive treatment
- Treatment is less intensive and may involve symptom control only

Introduction to Oncology

- **Cancer is a systemic disease**

- Initial lesson from William Halsted and the radical mastectomy for breast cancer
- After curative-intent resection, early and late metastases are frequent in most solid tumors

- Usual paradigm:

- Localized disease → **Curative intent treatment**

Surgery ± radiation (prevent local relapse)

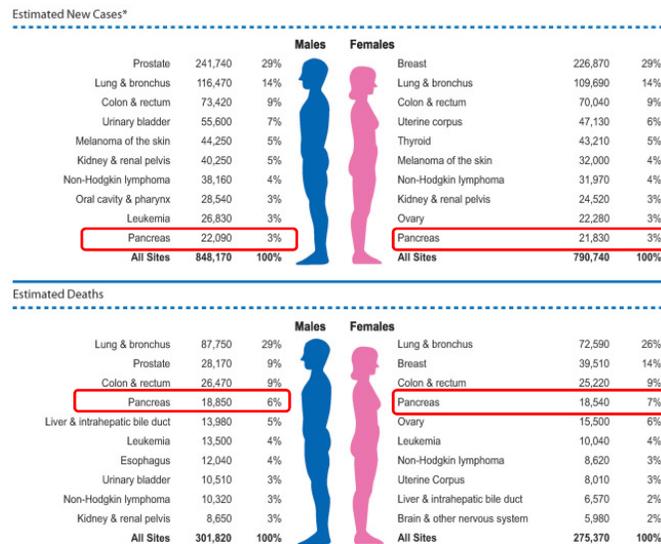
± chemotherapy (prevent distant relapse)

- Metastatic disease → **Palliative-intent treatment** (usually chemotherapy)

Pancreatic Cancer: Challenges

- Stage for stage, pancreatic cancer is associated with the lowest survival rates of any major cancer type
- The vast majority of patients are inoperable at the time of diagnosis
- Pancreatic cancer is inherently resistant to most currently available therapies
- Many patients suffer from rapidly declining performance status, cachexia, pain and depression
- Compared with other cancer types, research funding for pancreatic cancer is disproportionately low given its mortality rate (fourth for cancer-related deaths in the US population)

Pancreatic Cancer Incidence and Mortality

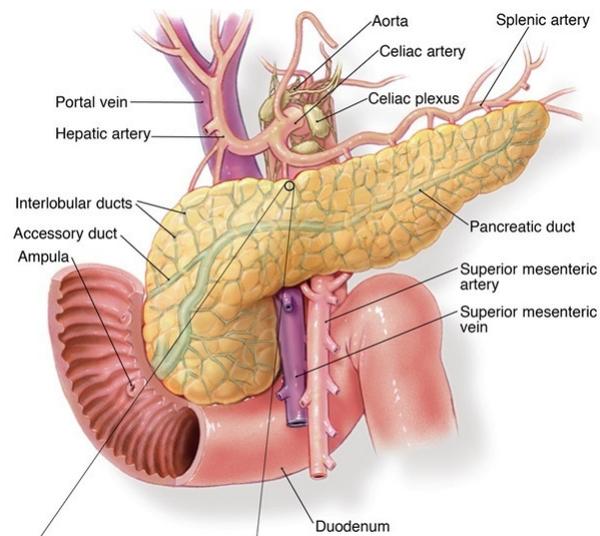


Siegel R, et al. CA Cancer J Clin. 2012;62:10-29.

Patients Often Staged Clinically, Not by TNM

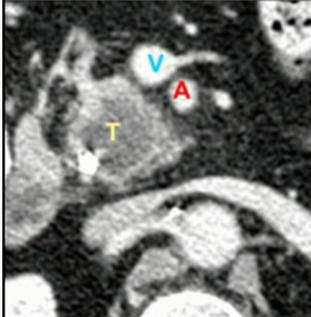
- Resectable (or operable)
 - No vascular involvement
- Borderline resectable
 - Moderate vascular involvement
- Locally advanced - Unresectable
 - Significant vascular involvement
- Metastatic

The Pancreas



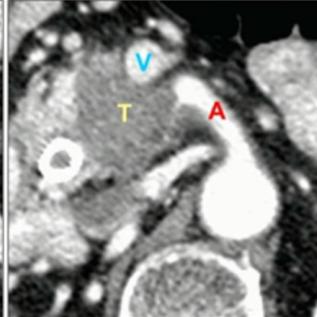
Definition of tumor-vessel interface

No/minor interface



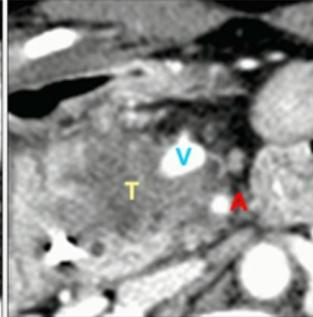
R0 resection likely
Surgery/adjuvant tx standard
Resectable

Moderate interface



R1 resection likely
Surgical results suboptimal
Borderline resectable

Major interface



R2 resection likely
Surgery not indicated
Unresectable

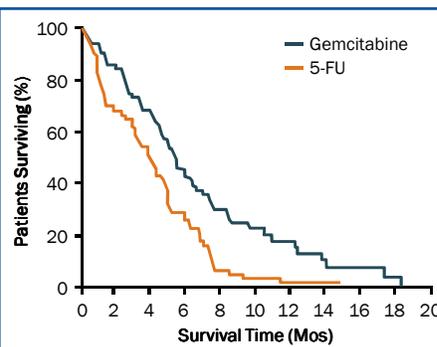
Chemotherapy for advanced/metastatic pancreatic cancer

Gemcitabine for Metastatic Pancreatic Cancer

- Pivotal study defining role for gemcitabine as first-line treatment for patients with advanced pancreatic cancer

	Gem	5-FU	P-value
Median Survival	5.6 m	4.4 m	0.0025
1-year Survival	18%	2%	0.0025
Clinical Benefit*	24%	5%	0.0022
Response Rate	5%	0%	NS

*A composite of pain (analgesic consumption and pain intensity), performance status, and weight. Clinical benefit required a sustained (≥ 4 weeks) improvement in at least 1 parameter without worsening in any others.



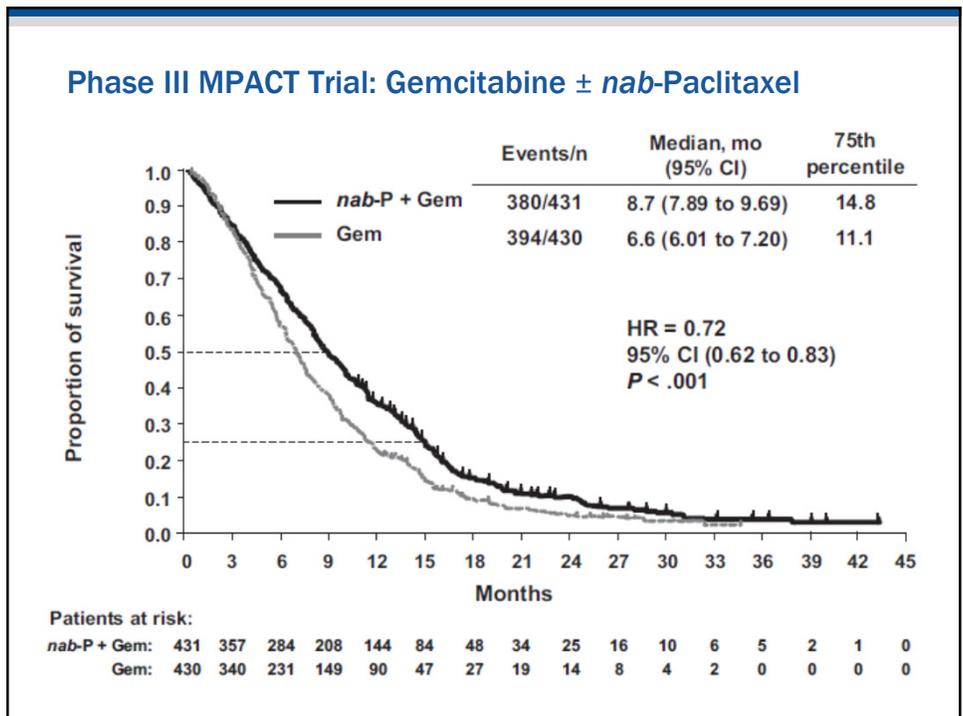
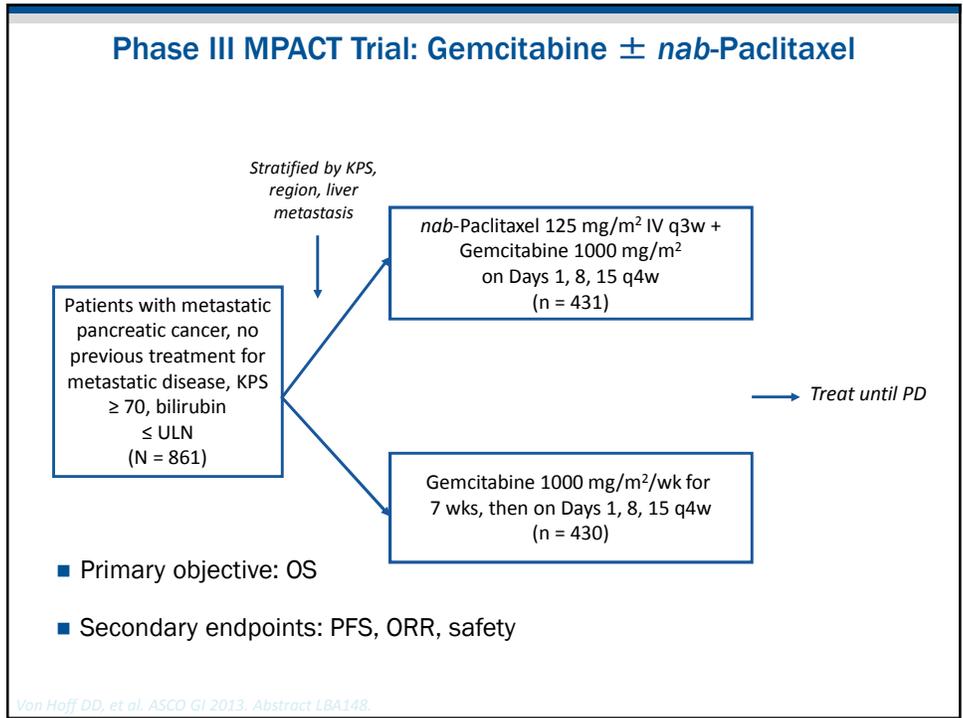
Burris HA, et al. *J Clin Oncol*. 1997;15:2403-2413

Phase III trials: Gemcitabine doublets vs Monotherapy

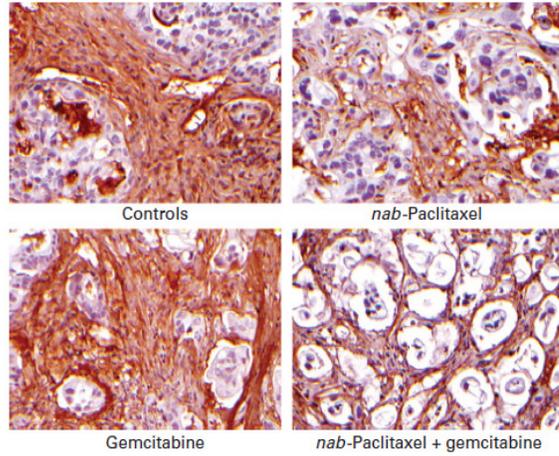
Regimen	N	Control Arm, Months	Study Arm, Months
Gem vs Gem + cisplatin	192	6.0	7.6
Gem vs Gem + oxaliplatin	313	7.1	9.0
Gem vs Gem + 5-FU	322	5.4	6.7
Gem vs Gem + capecitabine	533	6.2	7.1
Gem vs Gem + pemetrexed	565	6.2	6.3
Gem vs Gem + irinotecan	360	6.6	6.3
Gem vs Gem + exatecan	349	6.2	6.7

All negative trials

Heinemann V, et al. *BMC Cancer*. 2008;8:82



Pancreatic cancer resistance: the stroma

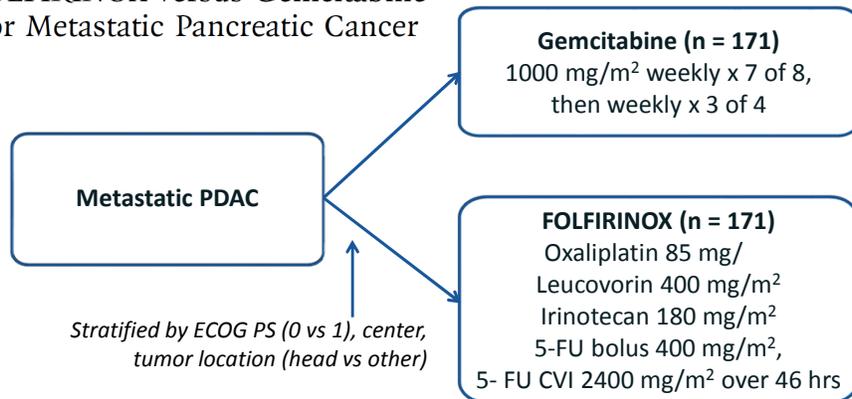


Immunohistochemical assay for collagen type 1 fibers in a gemcitabine-resistant human pancreatic cancer xenograft treated with *nab*-paclitaxel, gemcitabine, or gemcitabine plus *nab*-paclitaxel.

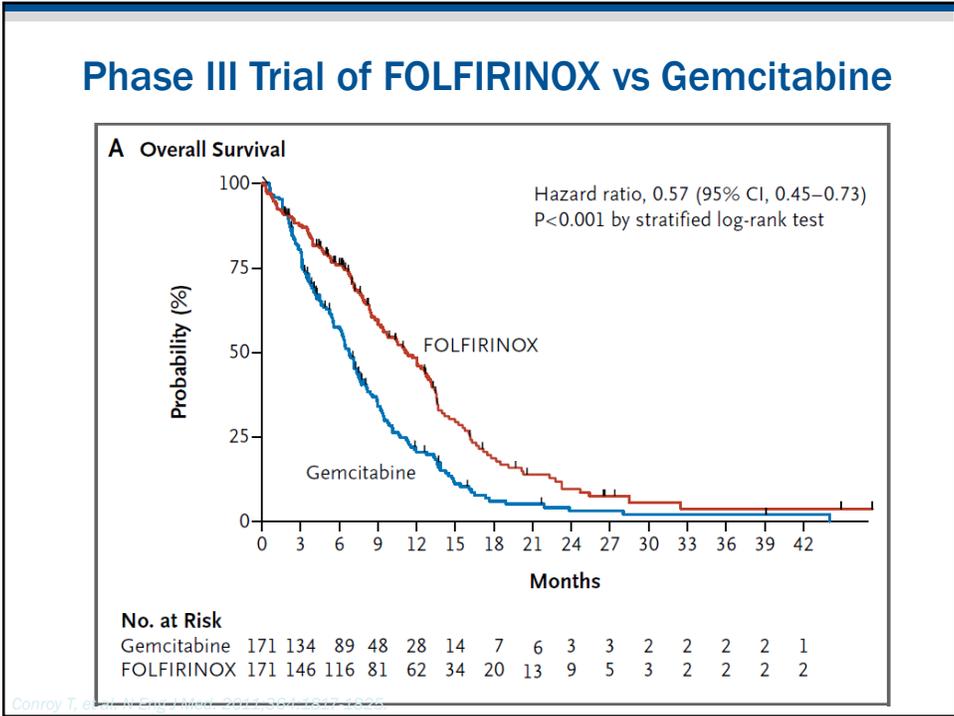
Phase III Trial of FOLFIRINOX vs Gemcitabine

The NEW ENGLAND JOURNAL of MEDICINE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer



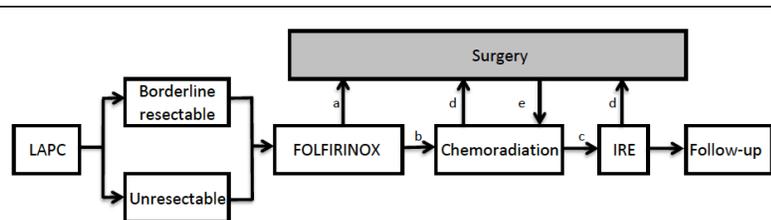
Conroy T, et al. *N Engl J Med*. 2011;364:1817-1825



- ### Summary of chemotherapy
- There are two standard chemotherapy options for advanced pancreatic cancer:
 - FOLFIRINOX – usually used in younger patients who are in very good shape
 - Gemcitabine/*nab*-paclitaxel – well tolerated and effective even in frail patients

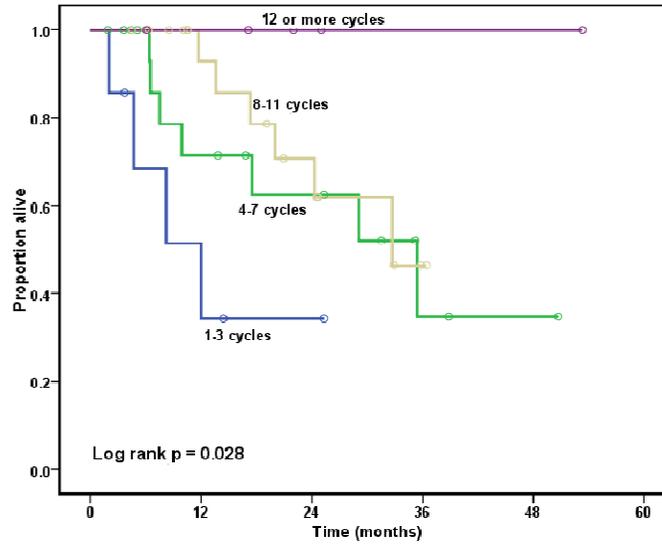
Approach to patients with locally advanced pancreatic cancer

Current algorithm for LAPC



- a Patients with resectable disease after chemotherapy will be offered surgery
- b Patients with unresectable but localized disease after chemotherapy will be offered chemoradiation
- c Patients with unresectable but localized disease after chemoradiation will be offered IRE
- d Patients with resectable disease after chemoradiation or IRE will be offered surgery
- e Patients who undergo surgery will be offered adjuvant chemoradiation if radiation was not given before

FOLFIRINOX for LAPC – Dose intensity



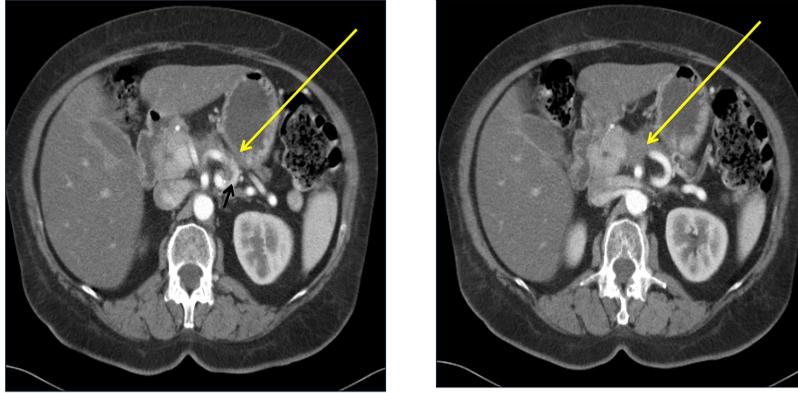
Relationship between the number of full-dose cycles of neoadjuvant FOLFIRINOX and Survival

Ablation of LAPC with the Nanoknife™

Percutaneous Irreversible Electroporation for Downstaging and Control of Unresectable Pancreatic Adenocarcinoma

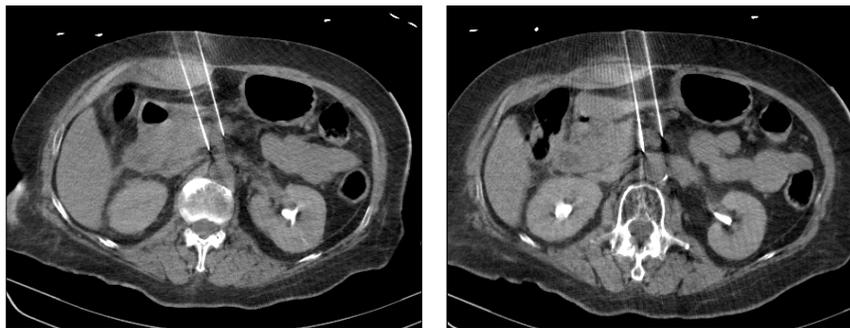
Govindarajan Narayanan, MD, Peter J. Hosein, MD, Geetika Arora, MD, Katuzka J. Barbery, MD, Tatiana Froud, MD, Alan S. Livingstone, MD, Dido Franceschi, MD, Caio M. Rocha Lima, MD, and Jose Yrizarry, MD

IRE (Nanoknife) example



62 year-old female with pancreatic adenocarcinoma and celiac axis encasement

IRE (Nanoknife) example



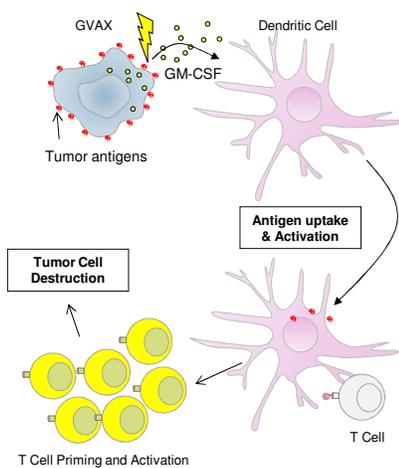
Percutaneous placement of 4 probes around the tumor followed by delivery of an electric current between pairs or probes, leading to irreversible electroporation

Immune therapies for pancreatic cancer

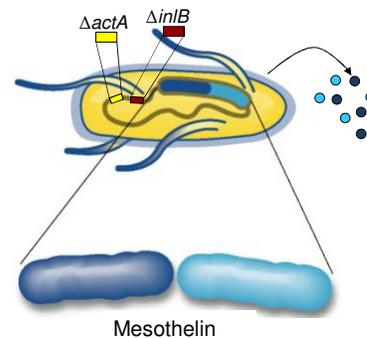
- GVAX Pancreas + CRS-207 vaccines
- Algenpantucel-L vaccine
- Immune checkpoint inhibitors
 - Ipilimumab and Nivolumab
 - IDO inhibitors

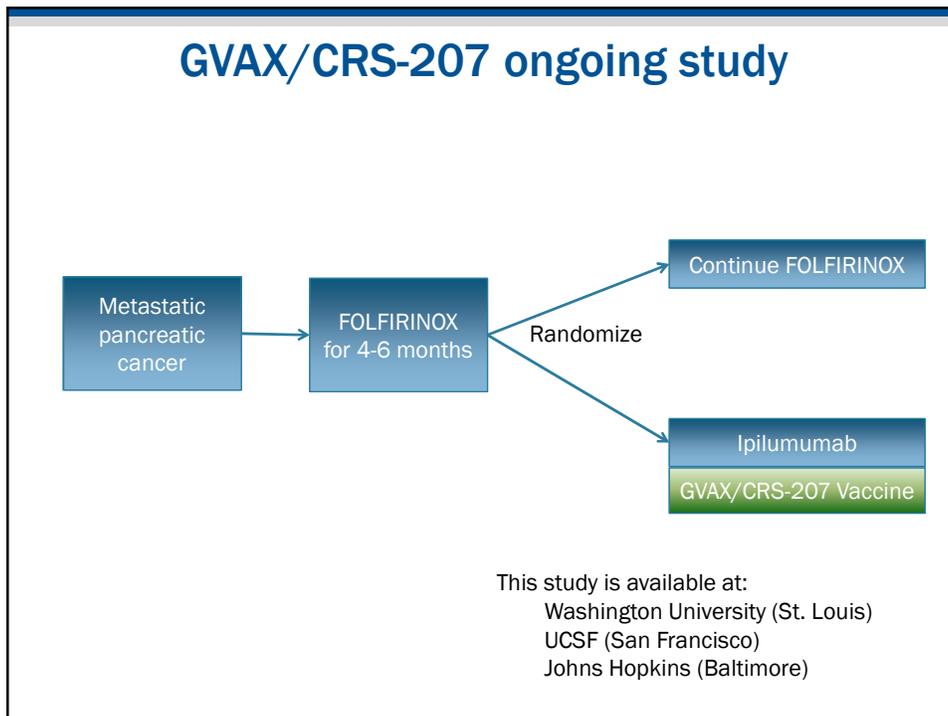
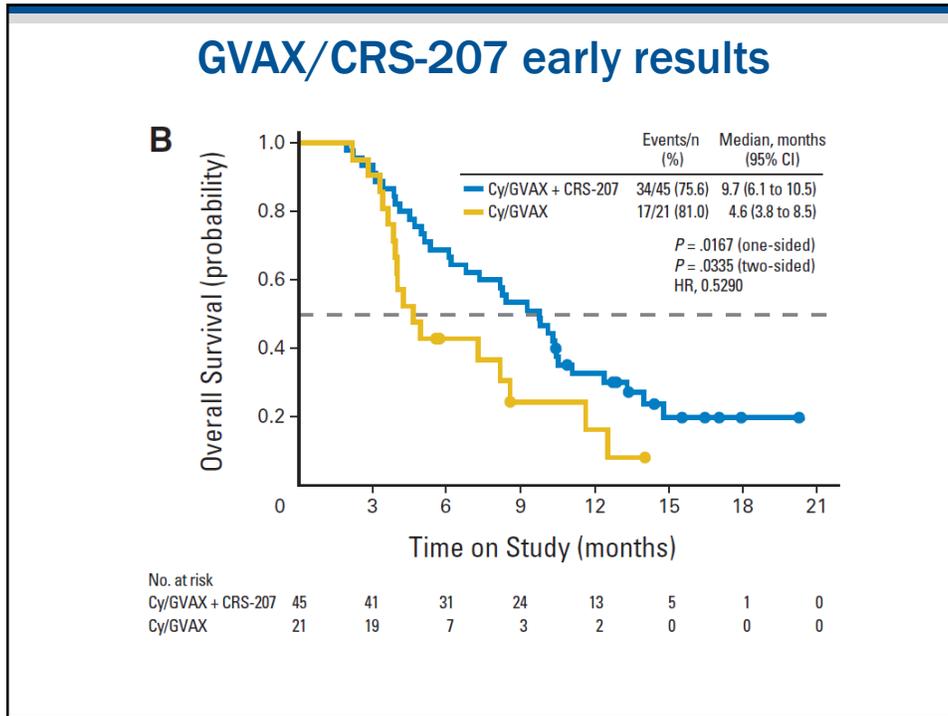
GVAX/CRS-207 vaccine

GVAX Pancreas Irradiated, whole-cell tumor vaccine

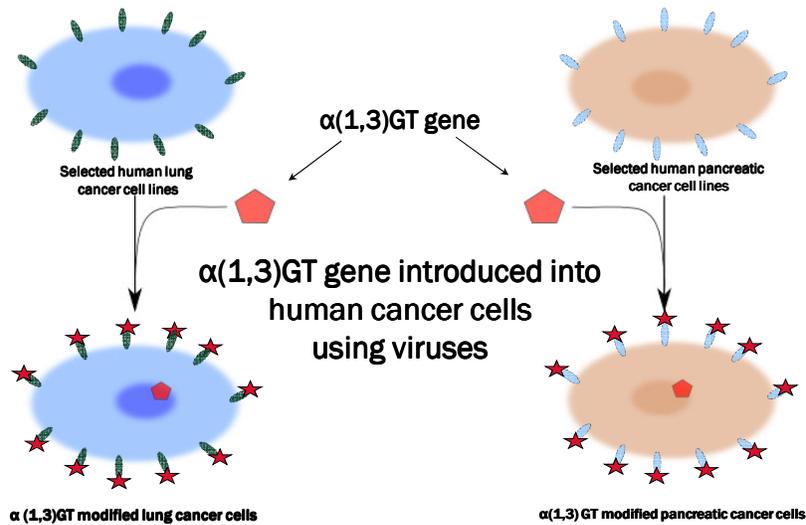


LADD Listeria Live-attenuated *Listeria monocytogenes*

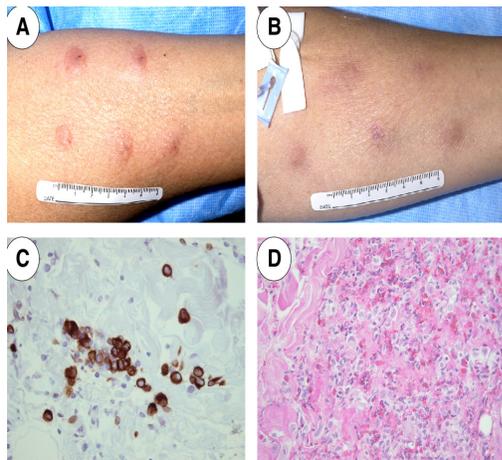




Hyperacute vaccine (Algenpantucel-L)

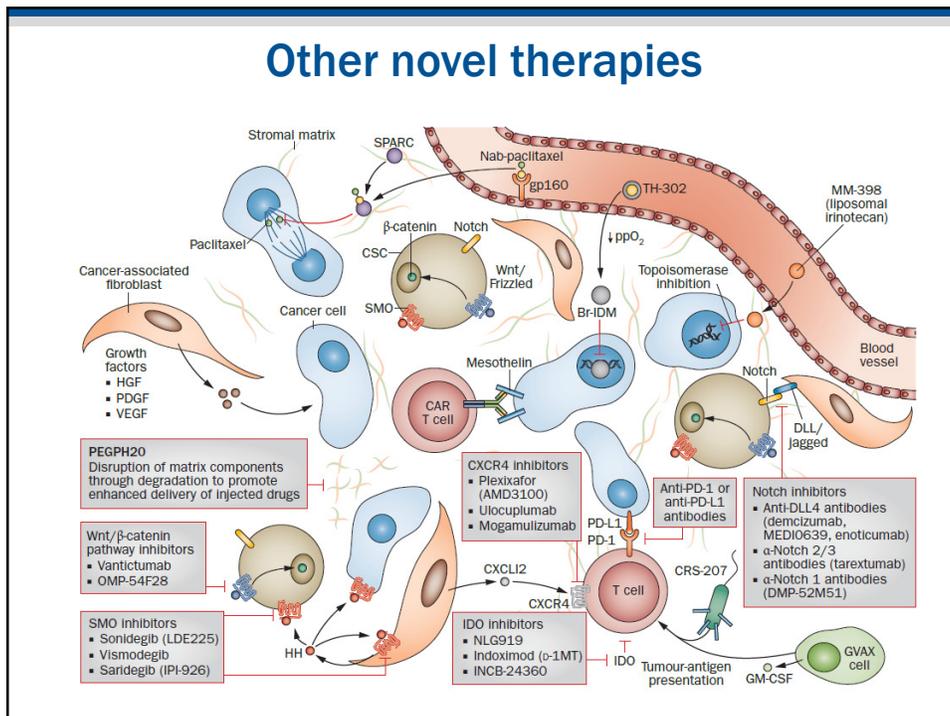
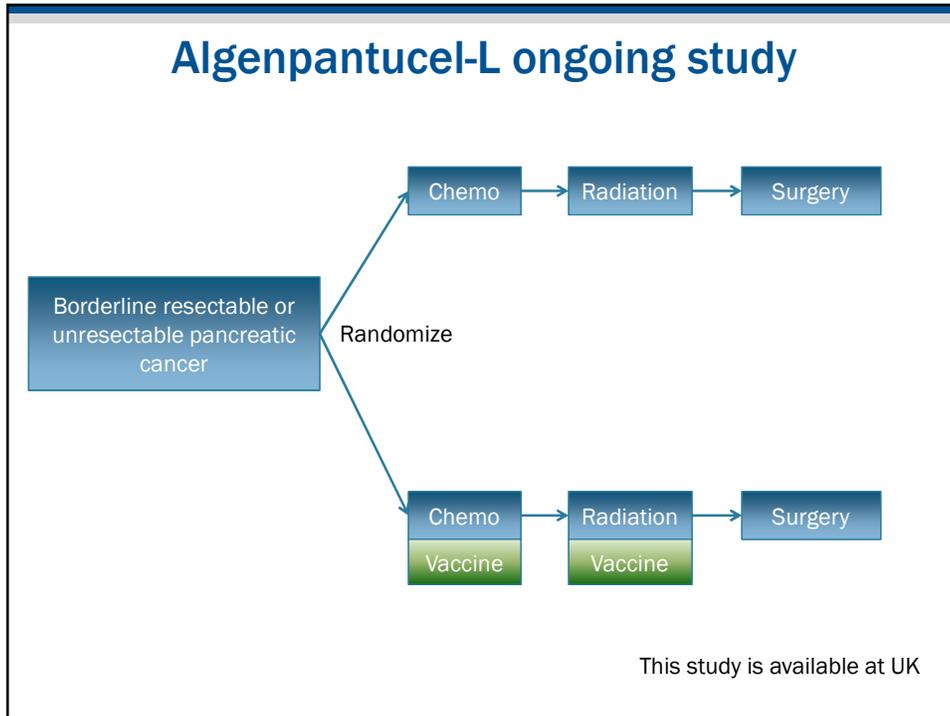


Hyperacute vaccine (Algenpantucel-L)



- Persistent erythema and Induration 24-48 hrs. post injection.

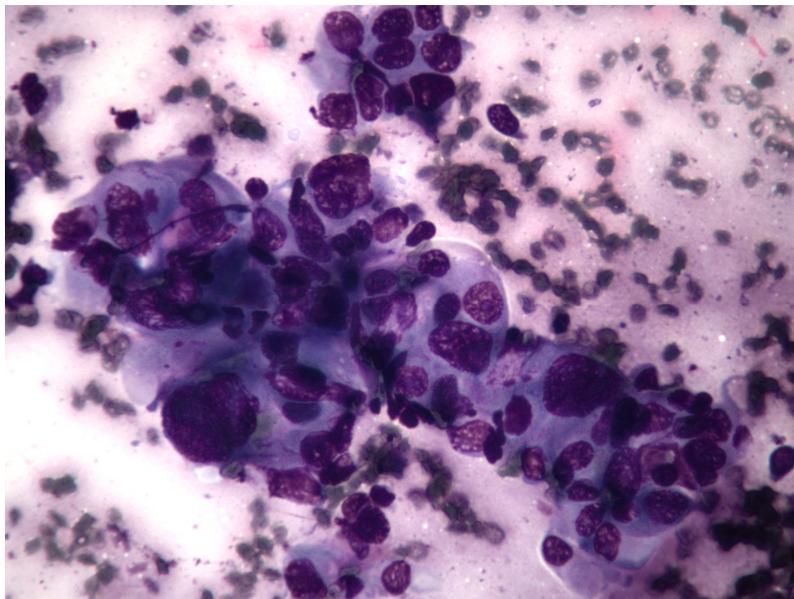
- Skin biopsies of skin injection site shows significant cellular infiltration of various immune cells.



Case presentation

- 46 year-old female
 - Presented with abdominal pain
 - CT scan showed a pancreatic tumor with no evidence of spread but the tumor was touching the superior mesenteric vein for a short segment
 - Endoscopy (endoscopic ultrasound - EUS) was performed

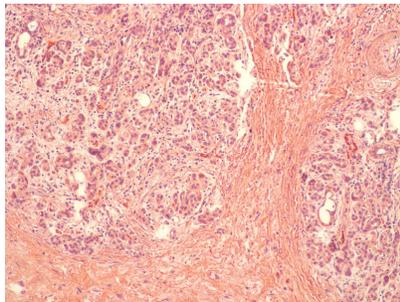
Case presentation



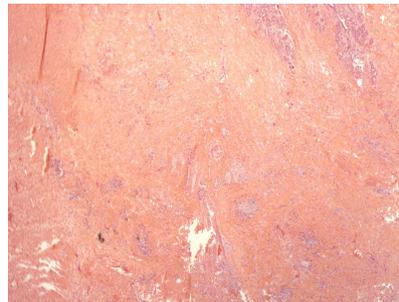
Case presentation

- Pancreatic cancer confirmed
- Tumor classified as “borderline resectable”
- Started chemotherapy with FOLFIRINOX
 - Received 8 cycles of chemotherapy (4 months)
- Then received radiation plus chemotherapy (6 weeks)
- Taken to surgery 7 months after diagnosis for Whipple resection

Case presentation



Unaffected area of the pancreas



Area where the tumor was, now showing extensive fibrosis but no active cancer

Overall result – no further evidence of cancer after intensive chemotherapy, radiation therapy and surgery

Conclusions

- Cancer is a systemic disease but can sometimes be cured with the correct sequence of treatments
- Chemotherapy options are improving in advanced pancreatic cancer (e.g. gemcitabine/*nab*-paclitaxel and FOLFIRINOX)
- Clinical trials are the way that we make advances. This is the best way to help yourself and others

Thank you!
Questions?