SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Pancreatic Cancer Treatment Options

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

Disclosures

- I will be discussing off-label use of some drugs and devices

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Objectives

1. Review standard as well as new treatment options for metastatic disease
2. Review new treatment algorithms for locally advanced disease
3. Review ongoing trials for adjuvant therapy
4. Introduce new data on a promising vaccine approach in pancreatic cancer

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 scores and inanition
- 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

Estimated New Cases*

Males			Females		
Prostate	241,740	29%	Breast	226,870	29%
Lung & bronchus	116,470	14%	Lung & bronchus	109,690	14%
Colon & rectum	73,420	9%	Colon & rectum	70,040	9%
Urinary bladder	55,600	7%	Uterine corpus	47,130	6%
Melanoma of the skin	44,250	5%	Thyroid	43,210	5%
Kidney & renal pelvis	40,250	5%	Melanoma of the skin	32,000	4%
Non-Hodgkin lymphoma	38,160	4%	Non-Hodgkin lymphoma	31,970	4%
Oral cavity & pharynx	28,540	3%	Kidney & renal pelvis	24,520	3%
Leukemia	26,830	3%	Ovary	22,280	3%
Pancreas	22,090	3%	Pancreas	21,830	3%
All Sites	**848,170**	**100%**	**All Sites**	**790,740**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	87,750	29%	Lung & bronchus	72,590	26%
Prostate	28,170	9%	Breast	39,510	14%
Colon & rectum	26,470	9%	Colon & rectum	25,220	9%
Pancreas	18,850	6%	Pancreas	18,540	7%
Liver & intrahepatic bile duct	13,980	5%	Ovary	15,500	6%
Leukemia	13,500	4%	Leukemia	10,040	4%
Esophagus	12,040	4%	Non-Hodgkin lymphoma	8,620	3%
Urinary bladder	10,510	3%	Uterine Corpus	8,010	3%
Non-Hodgkin lymphoma	10,320	3%	Liver & intrahepatic bile duct	6,570	2%
Kidney & renal pelvis	8,650	3%	Brain & other nervous system	5,980	2%
All Sites	**301,820**	**100%**	**All Sites**	**275,370**	**100%**

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

Patients Often Staged Clinically, Not by TNM

- Resectable
  - No metastases
  - No vascular encasement or abutment
- Locally advanced - Borderline resectable
  - No metastases
  - SMA encasement < 180º SMV/portal impingement, short segment SMV occlusion, celiac encasement < 180º (tail), abutment/encasement of hepatic artery
- Locally advanced - Unresectable
  - No metastases
  - SMA encasement > 180º, unreconstructable SMV/portal vein occlusion; any celiac abutment (head) or celiac encasement > 180º (body/tail), aortic invasion or encasement, lymph node metastases beyond field of resection
- Metastatic

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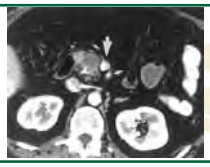
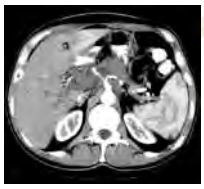
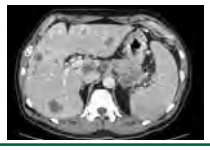
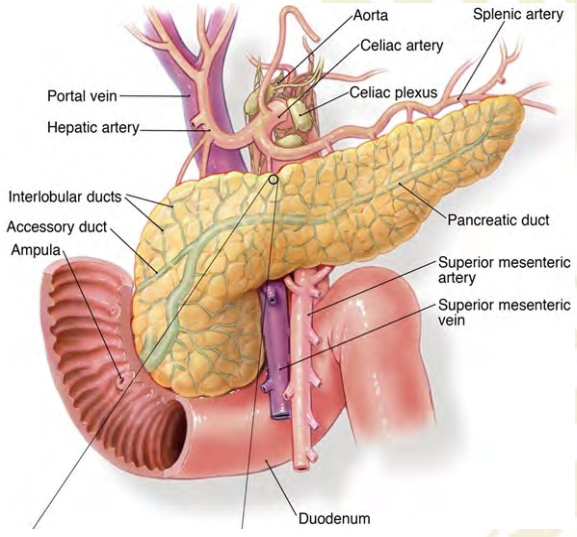
Pancreatic Cancer by Stage (SEER Database)

Stage Classification		Proportion
Localized		10%
Locally advanced/ unresectable		30%
Metastatic		50%

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

The Pancreas



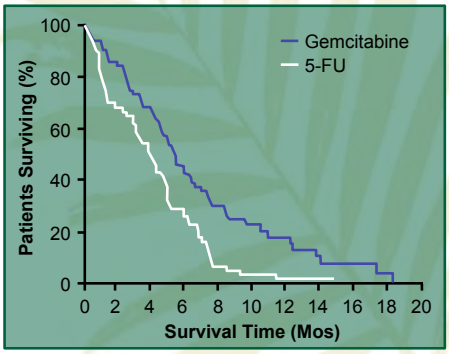
Chemotherapy for advanced/metastatic pancreatic cancer

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.

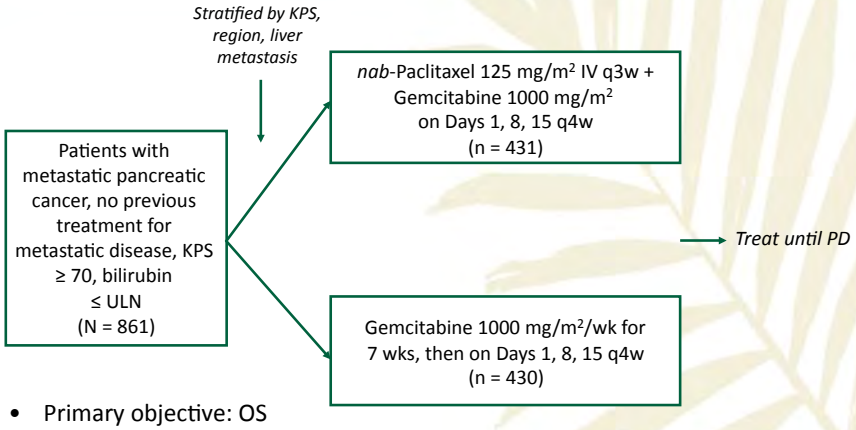
Phase III trials: Gemcitabine doublets vs Monotherapy

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.

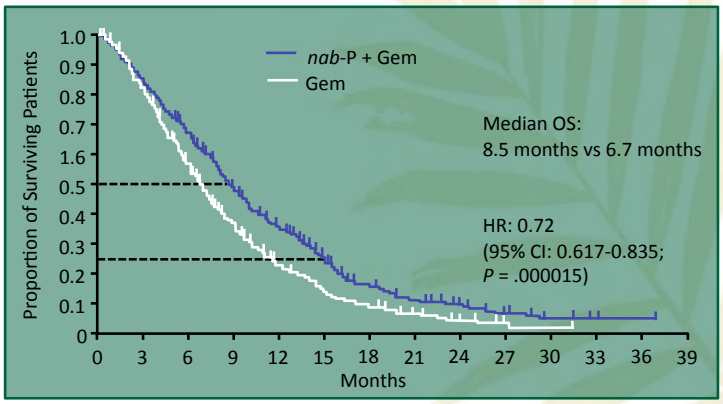
Phase III MPACT Trial: Gemcitabine ± *nab*-Paclitaxel



- Primary objective: OS
- Secondary endpoints: PFS, ORR, safety

Von Hoff DD, et al. ASCO GI 2013. Abstract LBA148.

Phase III MPACT Trial: Gemcitabine ± *nab*-Paclitaxel



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 DD, et al. ASCO GI 2013. Abstract LBA148.

Phase III MPACT Trial: Gemcitabine ± *nab*-Paclitaxel

Adverse Event	*nab*-P + Gem n = 421	Gem n = 402
≥ 1 AE leading to death, %	4	4
Grade ≥ 3 hematologic AE,* %		
Neutropenia	38	27
Leukopenia	31	16
Thrombocytopenia	13	9
Anemia	13	12
Receipt of growth factors %	26	15
Febrile neutropenia†, %	3	1
Grade ≥ 3 nonhematologic AE† in > 5% pts, %		
Fatigue	17	7
Peripheral neuropathy	17	< 1
Diarrhea	6	1
Grade ≥ 3 neuropathy		
Time to onset, median days	140	113
Time to improvement by grade, median days	21	29
Time to improvement to grade ≤ 1, median days	29	--
Resumed *nab*-P, %	44	--

*Based on lab values
†Based on investigator assessment of treatment-related events

Von Hoff DD, et al. ASCO GI 2013. Abstract LBA148.

Phase III MPACT Trial: Gemcitabine ± *nab*-Paclitaxel

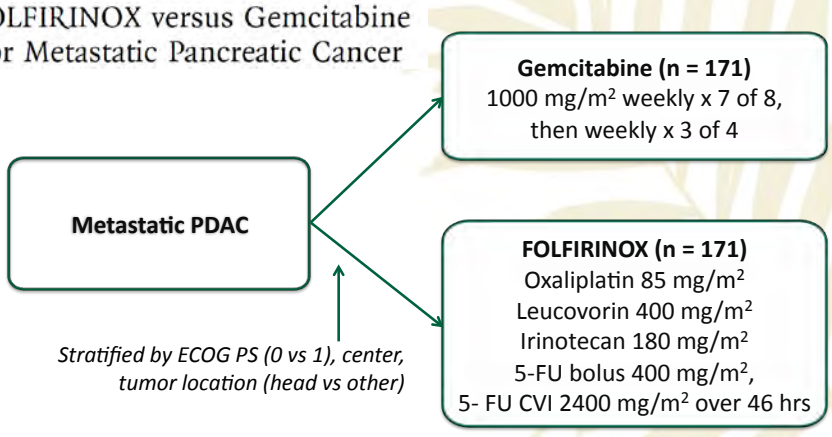
- Addition of *nab*-paclitaxel to gemcitabine significantly improved survival
  - Across entire curve at all time points
  - Median OS: 8.5 vs 6.7 mos with gemcitabine alone
- Metabolic response rates (by PET and CA19-9) significantly increased with addition of *nab*-paclitaxel to gemcitabine
  - Predictive of OS
- Serious side effects not increased, remain acceptable and manageable
- ***Nab*-paclitaxel + gemcitabine potentially a new standard for the treatment of metastatic pancreatic cancer**
  - Could become backbone of new regimens

Von Hoff DD, et al. ASCO GI 2013. Abstract LBA148.

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 Eng J Med. 2011;364:1817-1825.

Phase III Trial of FOLFIRINOX vs Gemcitabine

Table 1. Demographic and Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	FOLFIRINOX (N=171)	Gemcitabine (N=171)
Age — yr		
Median	61	61
Range	25–76	34–75
Sex — no. (%)		
Male	106 (62.0)	105 (61.4)
Female	65 (38.0)	66 (38.6)
ECOG performance status score — no. (%)		
0	64 (37.4)	66 (38.6)
1	106 (61.9)	105 (61.4)
2	1 (0.6)	0
Pancreatic tumor location — no. (%)		
Head	67 (39.2)	63 (36.8)
Body	53 (31.0)	58 (33.9)
Tail	45 (26.3)	45 (26.3)
Multicentric	6 (3.5)	5 (2.9)
Biliary stent — no. (%)		
Yes	27 (15.8)	22 (12.9)
No	144 (84.2)	149 (87.1)
No. of metastatic sites involved		
Median	2	2
Range	1–6	1–6
Level of carbohydrate antigen 19-9 — no./total no. (%)		
Normal	24/164 (14.6)	23/165 (13.9)
Elevated, <39× ULN	72/164 (43.9)	65/165 (39.4)
Elevated, ≥39× ULN	68/164 (41.5)	77/165 (46.7)
Unknown	7/171 (4.1)	6/171 (3.5)
No. of measurable metastatic sites — no. of patients/total no. (%)		
Liver	149/170 (87.6)	150/171 (87.7)
Pancreas	90/170 (52.9)	91/171 (53.2)
Lymph node	49/170 (28.8)	39/171 (22.8)
Lung	33/170 (19.4)	49/171 (28.7)
Peritoneal	33/170 (19.4)	32/171 (18.7)
Other	18/170 (10.6)	29/171 (17.0)

ECOG performance status score — no. (%)		
0	64 (37.4)	66 (38.6)
1	106 (61.9)	105 (61.4)
2	1 (0.6)	0
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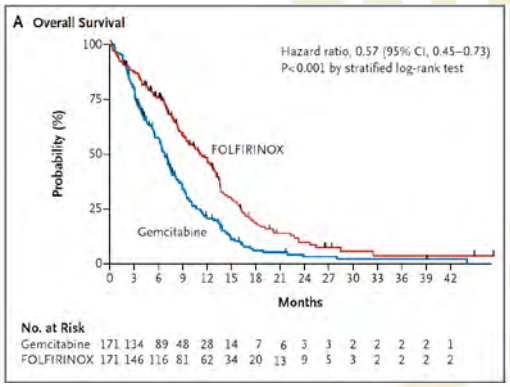
Phase III Trial of FOLFIRINOX vs Gemcitabine



	Median Overall Survival	Response Rate
FOLFIRINOX	11.1 months	31.6%
Gemcitabine	6.8 months	9.4%

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

Phase III Trial of FOLFIRINOX vs Gemcitabine

Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

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

Phase III Trial of FOLFIRINOX vs Gemcitabine

- Markedly positive survival results; exceeds those seen in any previous randomized phase III trial in advanced PDAC
- New gold standard for first-line metastatic pancreatic cancer for patients with good performance status
- Do we consider the study patient population representative (majority non-head tumors)?
- Do we consider the toxicity profile acceptable for this patient population?

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Approach to patients with locally advanced pancreatic cancer

Locally Advanced Pancreatic Cancer (LAPC)

- Need to treat differently than metastatic disease
- To radiate or not to radiate?
  - Up-front vs delayed radiation

Radiation First, Chemotherapy Later	Chemotherapy First, Radiation Later
▪ Importance of obtaining optimal local control ▪ Better palliation of symptoms? ▪ Better likelihood of cytoreduction to downstage a patient for potential surgery	▪ Greatest imperative is to eradicate micrometastatic disease ▪ Limits XRT to subgroup of patients whose tumors do not spread and are well-controlled with a period of up-front systemic therapy (series suggest 25% to 35% dropout rate with this strategy)

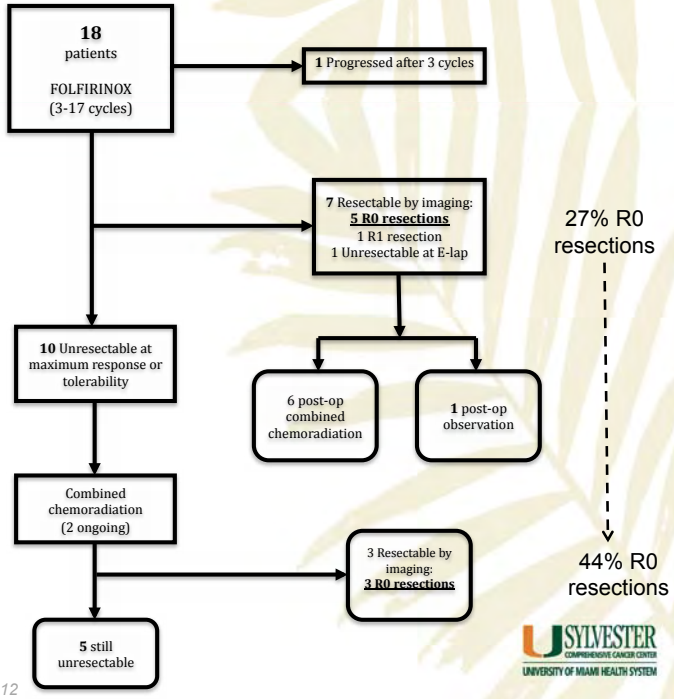
University of Miami LAPC experience

A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma

Peter J. Hosein[1*], Jessica Macintyre[2], Carolina Kawamura[3], Jennifer Cudris Maldonado[4], Vinicius Ernani[5], Arturo Loaiza-Bonilla[6], Govindarajan Narayanan[7], Afonso Ribeiro[8], Lorraine Portelance[9], Jaime R. Merchan[10], Joe U. Levi[11] and Caio M. Rocha-Lima[12]

Hosein P, et al, BMC Cancer 2012

Results



Hosein P, et al, BMC Cancer 2012

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

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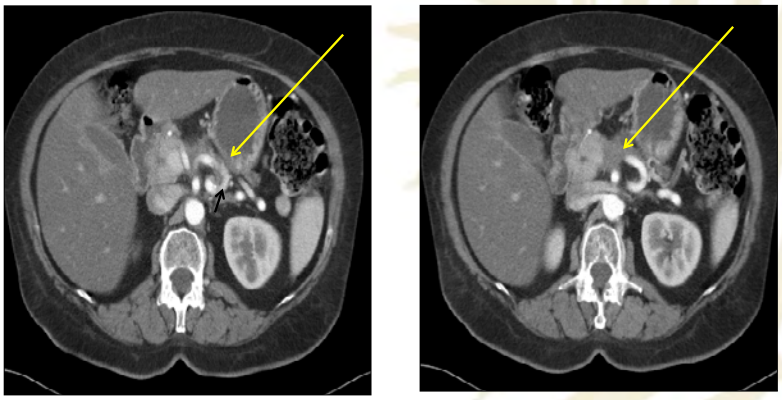
Narayanan G, et al, JVIR 2013

IRE (Nanoknife) example



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

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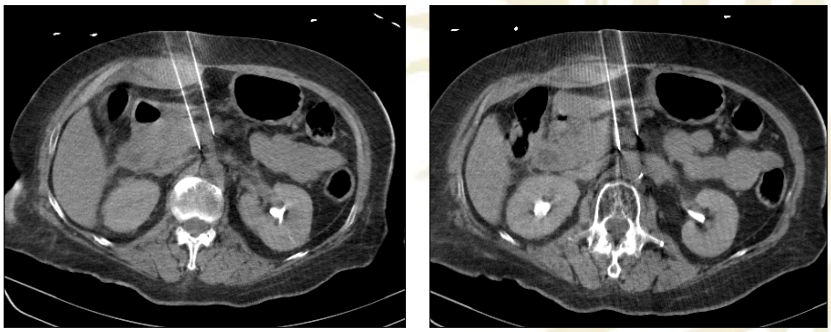
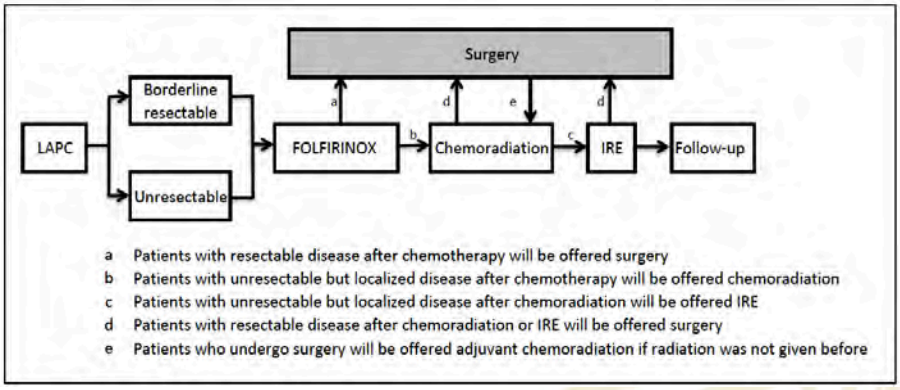
IRE (Nanoknife) example



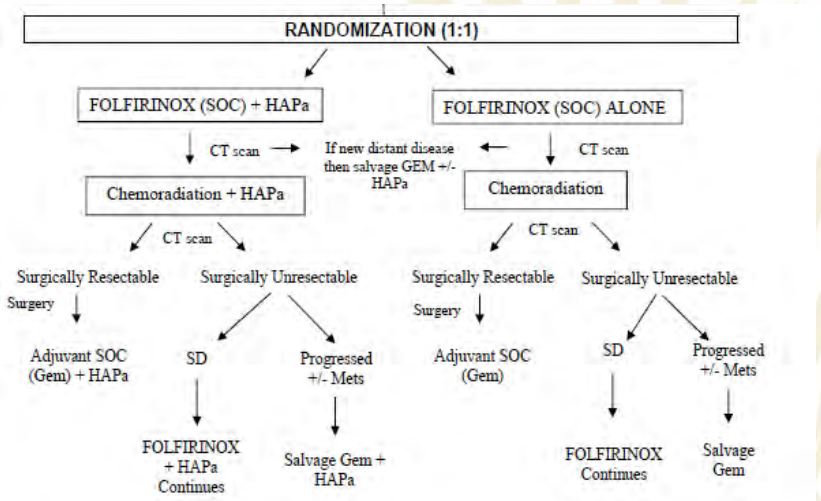
Percutaneous placement of 4 probes around the tumor followed by delivery of an electric current between pairs or probes, leading to irreversible electroporation

University of Miami 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

LAPC vaccine trial (Newlink Genetics)



Adjuvant therapy for resected pancreatic adenocarcinoma

Phase III Postop Adjuvant Therapy Trials

				European Standard	USA Standard
Patient Factor	**GITSG**	**EORTC**	**ESPAC-1***	**CONKO-001 (Gem only)**	**RTOG 9704 (XRT + Gem)**
Microscopically positive margins	0	19%†	28%	19%	35%
T3 or T4	NA	0	NA	86%	81%
Node–positive	30%	47%	50%	71%	68%
Local recurrence rate	47%	51%†	63%‡	37%	23%
Median survival	21mos	17mos	20mos	22mos	21mos
3-year survival	24%	30%	30%	34%	31%
5-year survival	19%	20%	21%	22.5%	NA

*Chemotherapy only group.
†Includes patients with periampullary cancers.
‡Among all patients.

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

The future of adjuvant therapy

- Ongoing trials
  - Role of combination chemotherapy
    - Gemcitabine/capecitabine (ESPAC-4)
    - FOLFIRINOX (French cooperative group)
  - Role of radiation
    - **RTOG 0848 trial (Gem ± erlotinib ± XRT) – Accruing at UM**
  - Role of immunotherapy
    - **ChemoXRT ± HAPa vaccine – Accruing at UM**
- Future trials
  - Neoadjuvant therapy
    - Up-front chemotherapy ± XRT may allow appropriate selection of patients truly likely to benefit from surgery[1,2]
  - Biomarker-driven trials
    - Possibilities: hENT1 (nucleoside transporter); DPC4

1. Evans DB, et al. J Clin Oncol. 2008;26:3496-3502.
2. Varadhachary GR, et al. J Clin Oncol. 2008;26:3487-3495.

New insights into pancreatic cancer – Immunotherapy

GVAX Pancreas + CRS-207
in Metastatic Pancreatic Cancer

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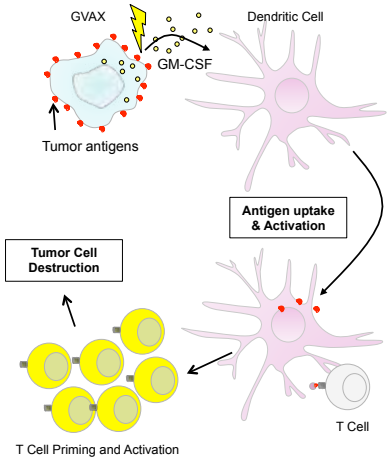
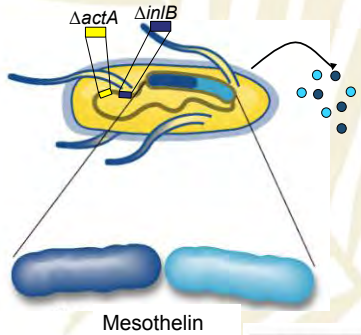
How do the vaccines work?

GVAX Pancreas
Irradiated, whole-cell tumor vaccine



LADD Listeria
Live-attenuated *Listeria monocytogenes*



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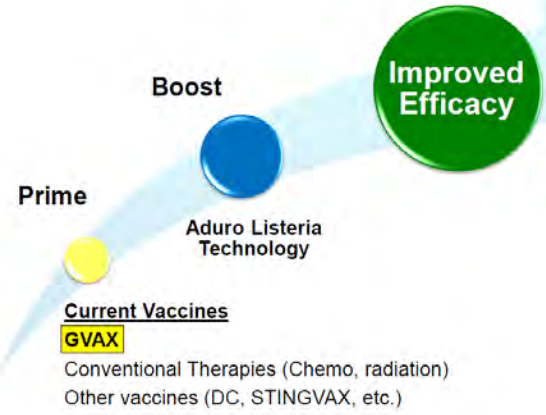
How do the vaccines work?



Current Vaccines

GVAX

Conventional Therapies (Chemo, radiation)

Other vaccines (DC, STINGVAX, etc.)

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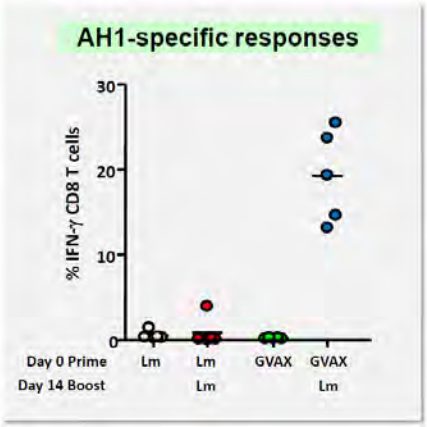
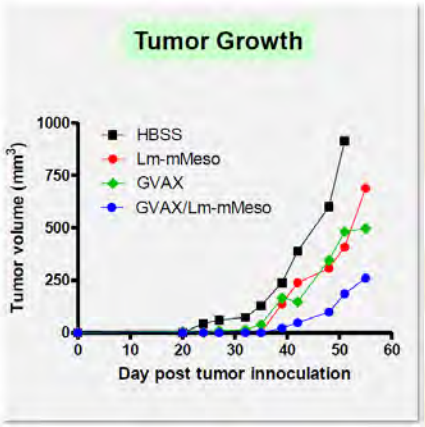
Results of the vaccine combination in mice





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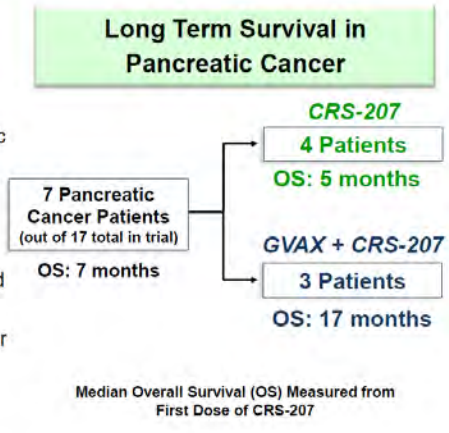
Results of the vaccine combo in a phase I study

- Established safe, immunogenic dose
- No shedding observed
- 6 of 17 end-stage cancer patients survived ≥15 months
  - Long-term survival observed in pancreatic cancer, mesothelioma and NSCLC pts.
- All 6 extended survivors given prior immunotherapy or subsequent local radiation therapy
  - 3 of 3 pancreatic cancer patients received prior treatment with GVAX
  - 1 of 1 mesothelioma patient received prior treatment with adenovirus expressing interferon β
  - 2 of 2 NSCLC patients received subsequent local radiation therapy



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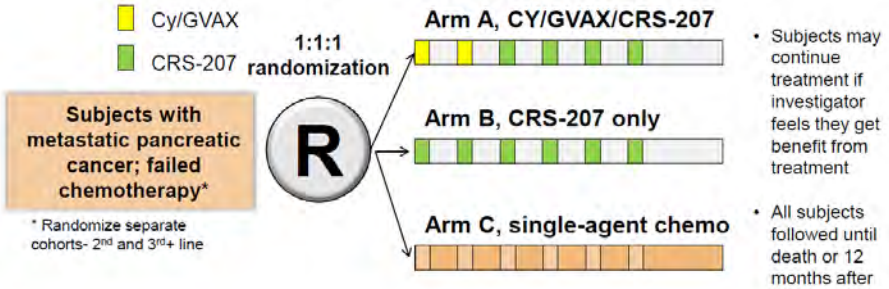
Upcoming Phase 2B trial (opening soon at Sylvester)



- Subjects may continue treatment if investigator feels they get benefit from treatment
- All subjects followed until death or 12 months after last subject enrolled

- Goals of study
  - Confirm results from the 1st Phase 2 study
  - Assess the contribution of CY/GVAX by testing CRS-207 alone
  - Compare to chemotherapy control (MD-choice single-agent chemo)
  - Obtain data on 2nd-line patients (exploratory)

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Conclusions

- Chemotherapy options are improving in advanced pancreatic cancer (e.g. gemcitabine/*nab*-paclitaxel and FOLFIRINOX)
- Combination chemotherapy and multimodality therapy for locally advanced appears promising
- New adjuvant strategies to improve cure rate after surgery are being investigated
- A new vaccine combination appears promising in early testing

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Thank

Questions?

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