Pancreatic Cancer: The Time is Now

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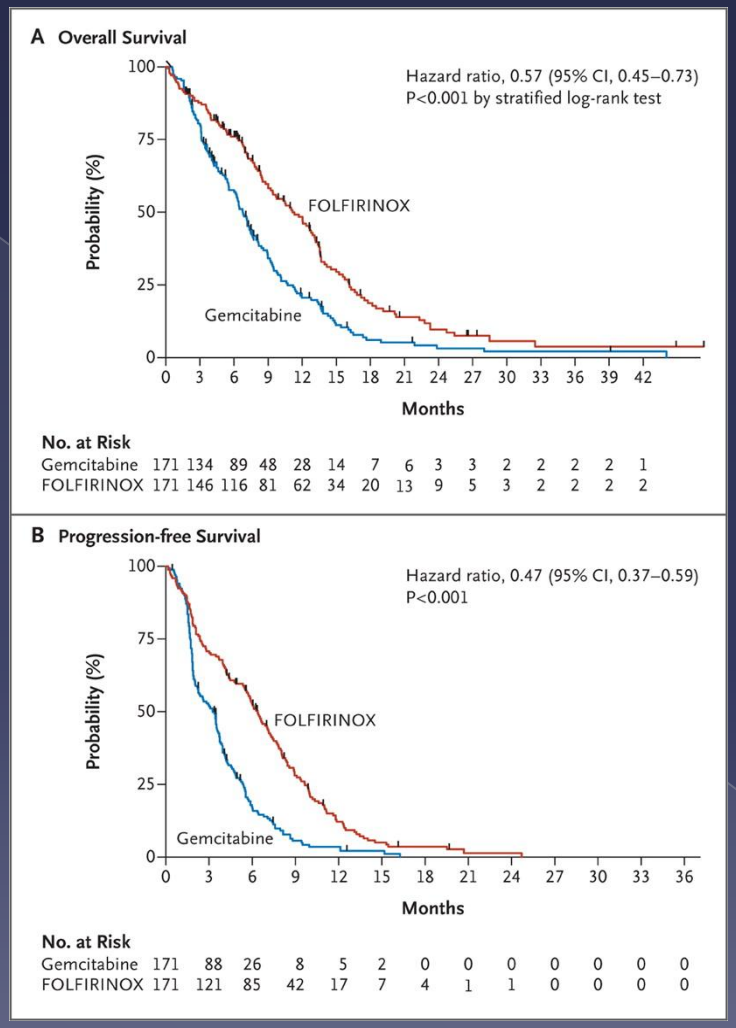
Outline

- Brief history of pancreatic cancer therapeutics
- The unique challenges of this disease
- New approaches: sequencing, immunotherapy, multimodality strategies
- Improving patient education and clinical trial enrollment

How far we have come…

- Prior to 2001, unresectable pancreatic adenocarcinoma had a median overall survival of 3-5 months
- Not a single agent was known to provide benefit…
- Gemcitabine, which provided clinical benefit in 20-30% of patients and extended overall survival, was a major breakthrough (Heinemann, 2001)

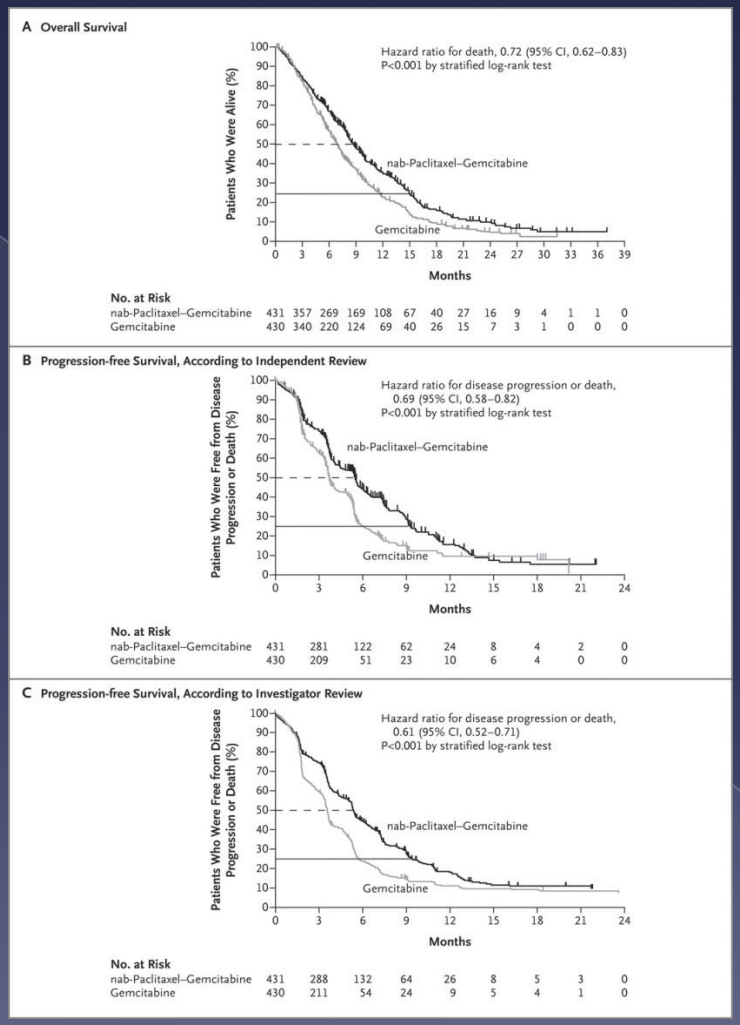
Kaplan–Meier Estimates of Overall Survival and Progression-free Survival, According to Treatment Group.



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

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Curves for Survival and Progression-free Survival in the Intention-to-Treat Population.



Von Hoff DD et al. N Engl J Med 2013;369:1691-1703.

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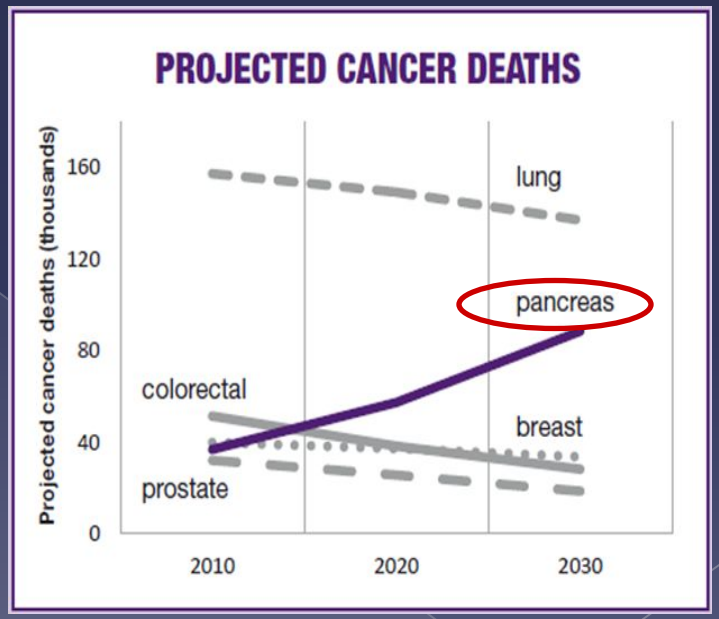
The challenges of pancreatic cancer

- Diagnosed at late stage
  -Only ≈10% are curable at diagnosis
  -Of those who undergo curative resection surgery, many relapse, even after adjuvant therapy
- Lack of early detection methods
- Aggressive disease biology
- Hostile microenvironment
- Stromal blockade of therapeutics
- "One basket" treatment strategies
- Low rates of clinical trial enrollment

Clinical challenge: High and growing number of deaths from pancreatic cancer

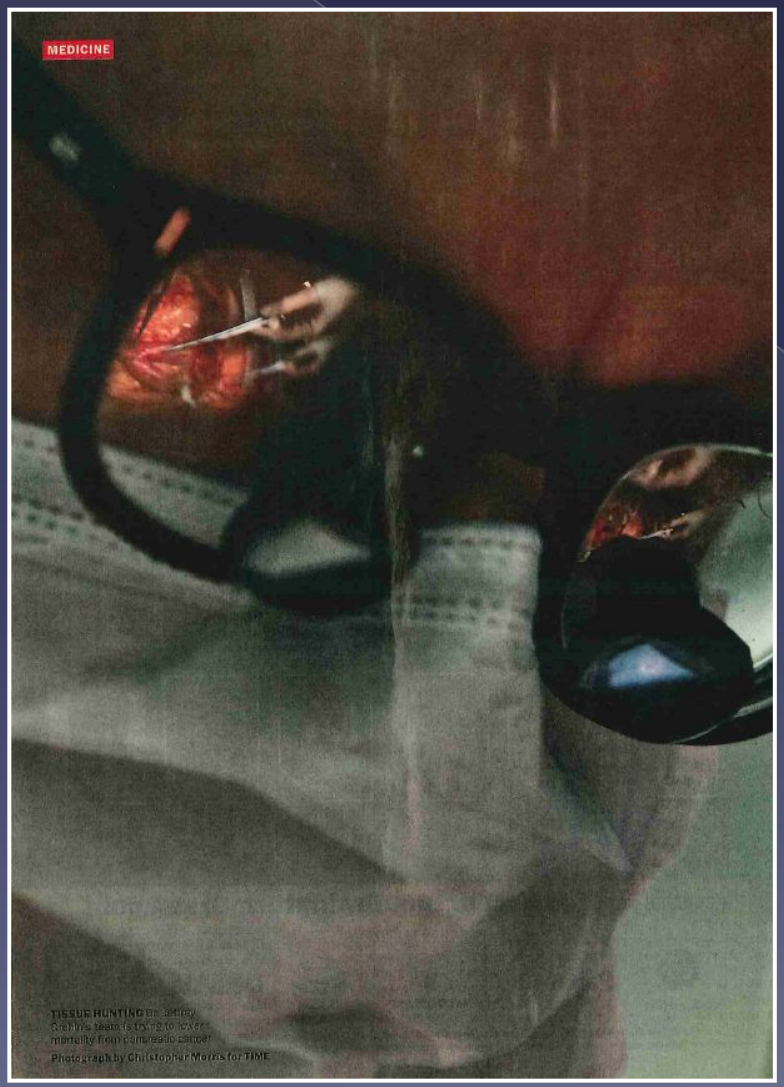
Cancer	Total est 2012 Incidence*	Total est 2012 deaths*	Change in Death Rates 1990-2008 Female		Male	
All Malignant Cancers	1,638,910	577,190	↓↓	-15.1	↓↓↓	-22.9
Oral Cavity & Pharynx	40,250	7,850	↓↓↓	-30.0	↓↓↓↓	-32.1
Esophagus	17,460	15,070	↓↓	-11.1	↑	5.6
Stomach	21,320	10,540	↓↓↓↓	-40.5	↓↓↓↓	-44.9
Colon and Rectum	143,460	51,690	↓↓↓↓	-33.0	↓↓↓↓	-36.0
Liver & Intrahepatic Bile Duct	28,720	20,550	↑↑↑↑	33.3	↑↑↑↑	58.5
Pancreas	43,920	37,390	↑	3.2	–	0.0
Larynx	12,360	3,650	–	0.0	↓↓↓	-30.0
Lung & Bronchus	226,160	160,340	↑	6.0	↓↓↓	-29.4
Melanoma of the skin	76,250	9,180	↓↓	-20.0	↑	7.9
Breast	229,060	39,920	↓↓↓	-32.0		
Cervix Uteri	12,710	4,220	↓↓↓↓	-35.1		
Corpus and Uterus, NOS	47,130	8,010	↓	-2.3		
Ovary	22,280	15,500	↓↓	-14.0		
Prostate	241,740	28,170			↓↓↓↓	-40.9
Urinary Bladder	73,510	14,880	↓	-8.3	↓	-5.0
Kidney & Renal Pelvis	64,770	13,570	↓	-10.7	↓	-6.5
Brain & Other Nervous System	22,910	13,700	↓↓	-12.5	↓↓	-11.7
Hodgkin Lymphoma	9,060	1,190	↓↓↓↓	-40.0	↓↓↓↓	-44.4
Non-Hodgkin Lymphoma	70,130	18,940	↓↓	-20.6	↓↓	-18.0
Myeloma	21,700	10,710	↓↓	-16.1	↓	-10.4
Leukemia	47,150	23,540	↓↓	-14.5	↓↓	-11.2

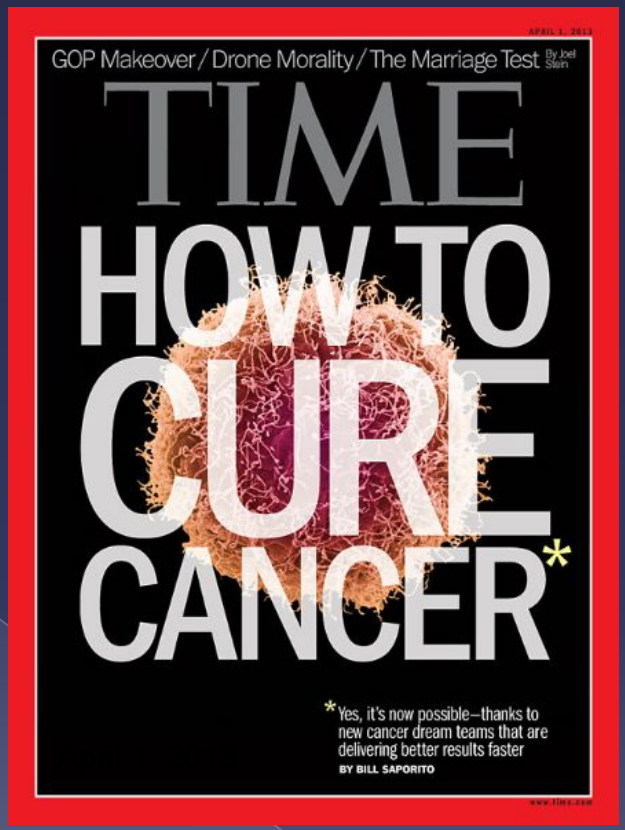
AACR Cancer Progress Report 2012



Pancreatic Cancer Action Network Report 2012

Next generation genetic sequencing of pancreatic cancer





STAND UP TO CANCER™
standup2cancer.org

NGS for pancreatic cancer

- Majority driven by KRAS and p53
- Subsets fueled by other "driver" mutations
- Sequencing panels look at 70-150 "hot spots" for common cancer drivers
- More and more usable targets being identified
- Turnaround time 2-4 weeks (room for improvement!)

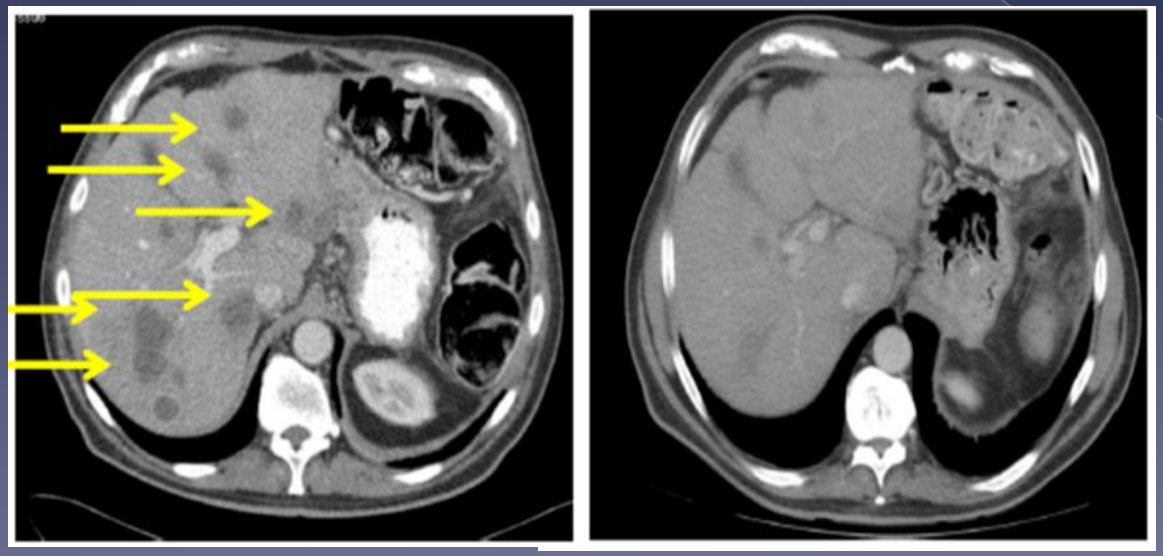
Personalized therapeutics: BRCA

- BRCA mutations are a well-known set of mutations that affect homologous recombination
- If BRCA is mutated, cells cannot adequately repair double-stranded DNA breaks
- Cells are hypersensitive to DNA damaging agents and agents that additionally injure other DNA repair pathways (PARP inhibitiors)
- BRCA mutations can be germline or somatic. Germline BRCA mutations increase risk for breast cancer, ovarian cancer, prostate cancer, melanoma and pancreatic cancer

Personalized therapeutics: BRCA

- PARP inhibitors block a back-up DNA repair pathway
- Olaparib showed 23% response in pancreatic cancer patients on second line or higher chemotherapy (Kaufman et al, ASCO, 2013)

  -Germline only; no platinum sensitivity clause
- Phase II study of PARP inhibitor rucaparib for patients with metastatic disease after 1st or 2nd line of chemotherapy; **+platinum sensitive!**
  - -For patients with BRCA1, BRCA2 or PALB2 mutation
  - Germline or somatic



RUCA PANC

BASSER RESEARCH CENTER *for* BRCA

Abramson Cancer Center

Penn Medicine

Personalized therapeutics: BRCA

- Upfront trials
  - -Cisplatin + Gemcitabine + Veliparib
  - -FOLFOX6 + Veliparib
- Maintenance trials
  - -Precision Promise (PANCAN)
  - -Rucaparib after platinum-stability (BRCA or PALB2)
  - -Others are coming…
- Prevention trials
  - -CAPS5

PANCREATIC CANCER ACTION NETWORK

JOHNS HOPKINS MEDICINE
THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER

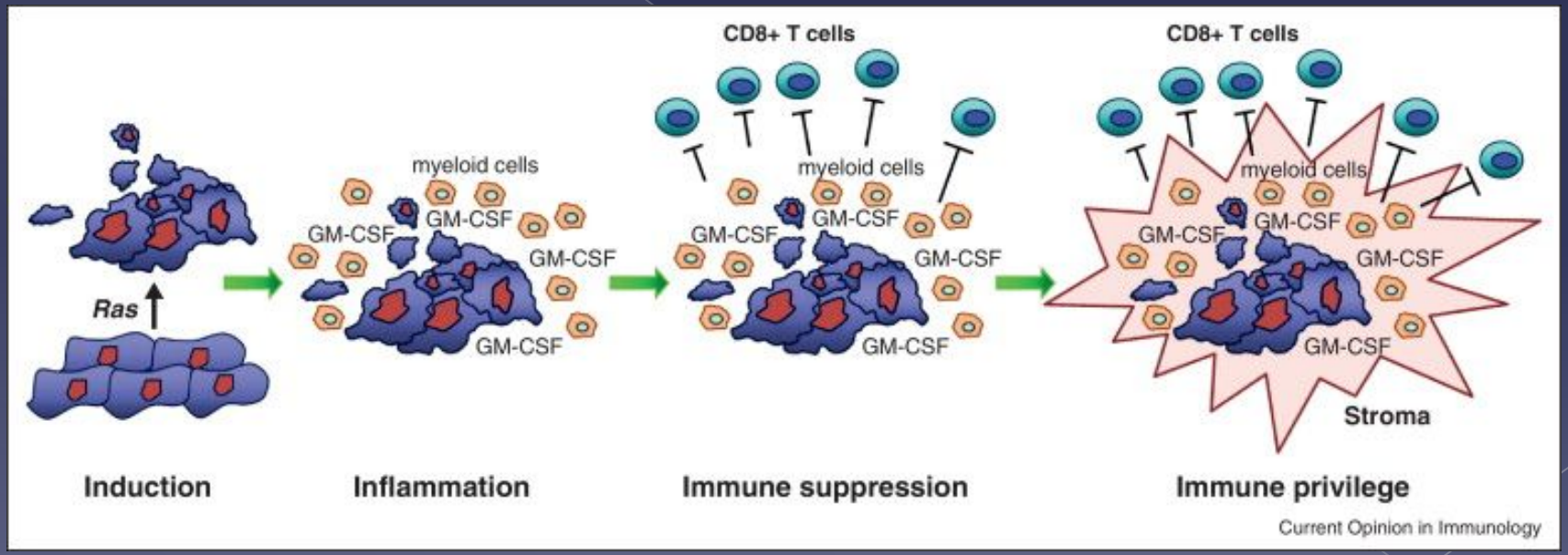
MEMORIAL SLOAN-KETTERING CANCER CENTER
ESTABLISHED 1884

Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER

UNIVERSITY OF PENNSYLVANIA
Abramson Cancer Center

Immunotherapy

- **"The Future in Now"** (AACR meeting, 2012)
- **"A development as exciting as The Beatles were to music"** (AACR Special Conference on Pancreatic Cancer, 2012)



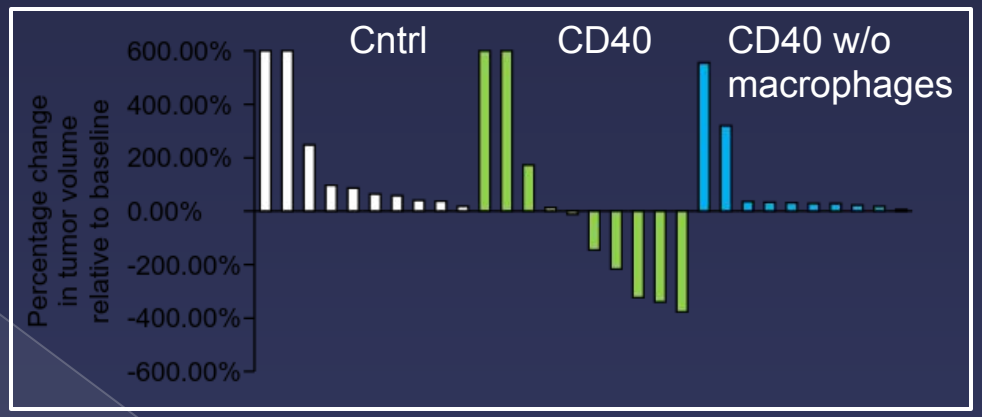
Bayne and Vonderheide, Curr Opin Immunol, 2013

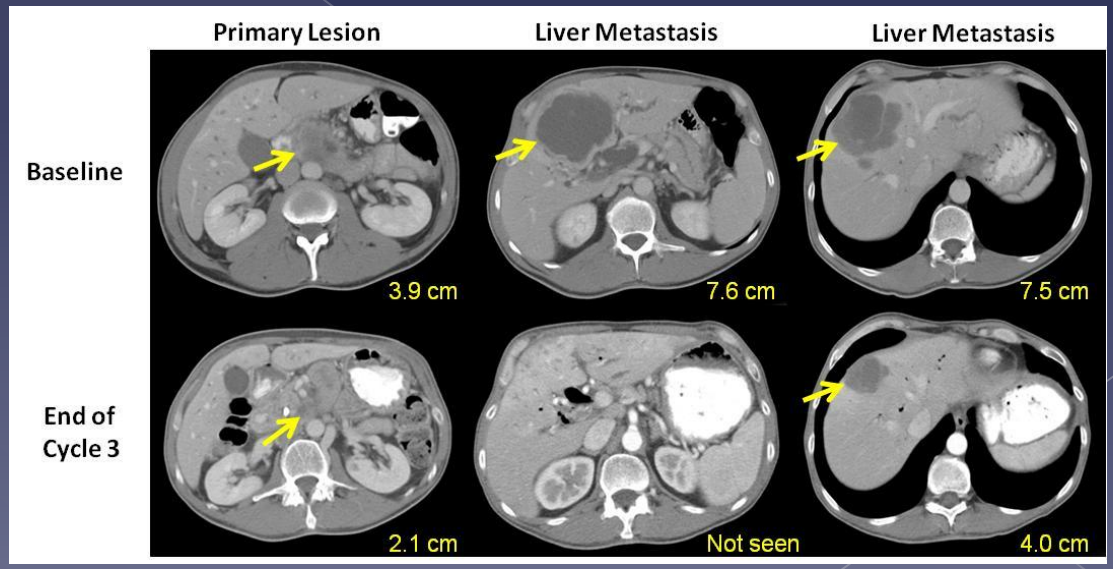
CD40 antibody as immune therapy for pancreatic cancer

A costimulatory protein found on APCs (macrophages), required for their activation

Tumor regressions after agonist CD40 mAb in laboratory experiments

Major and durable tumor regressions in metastatic patients receiving CD40 mAb and gemcitabine

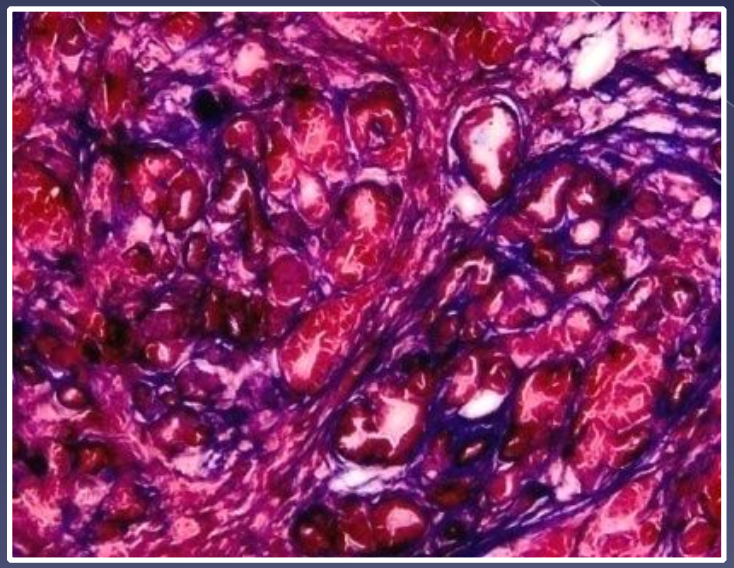


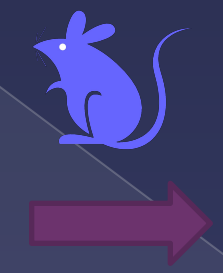


Beatty GL et al, Science, 2011

CD40 antibody as immune therapy for pancreatic cancer

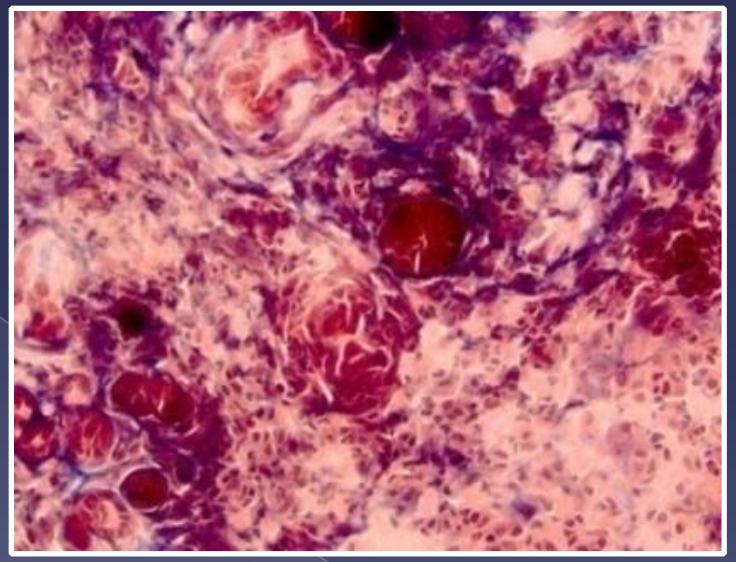
Before treatment





CD40 immune activation

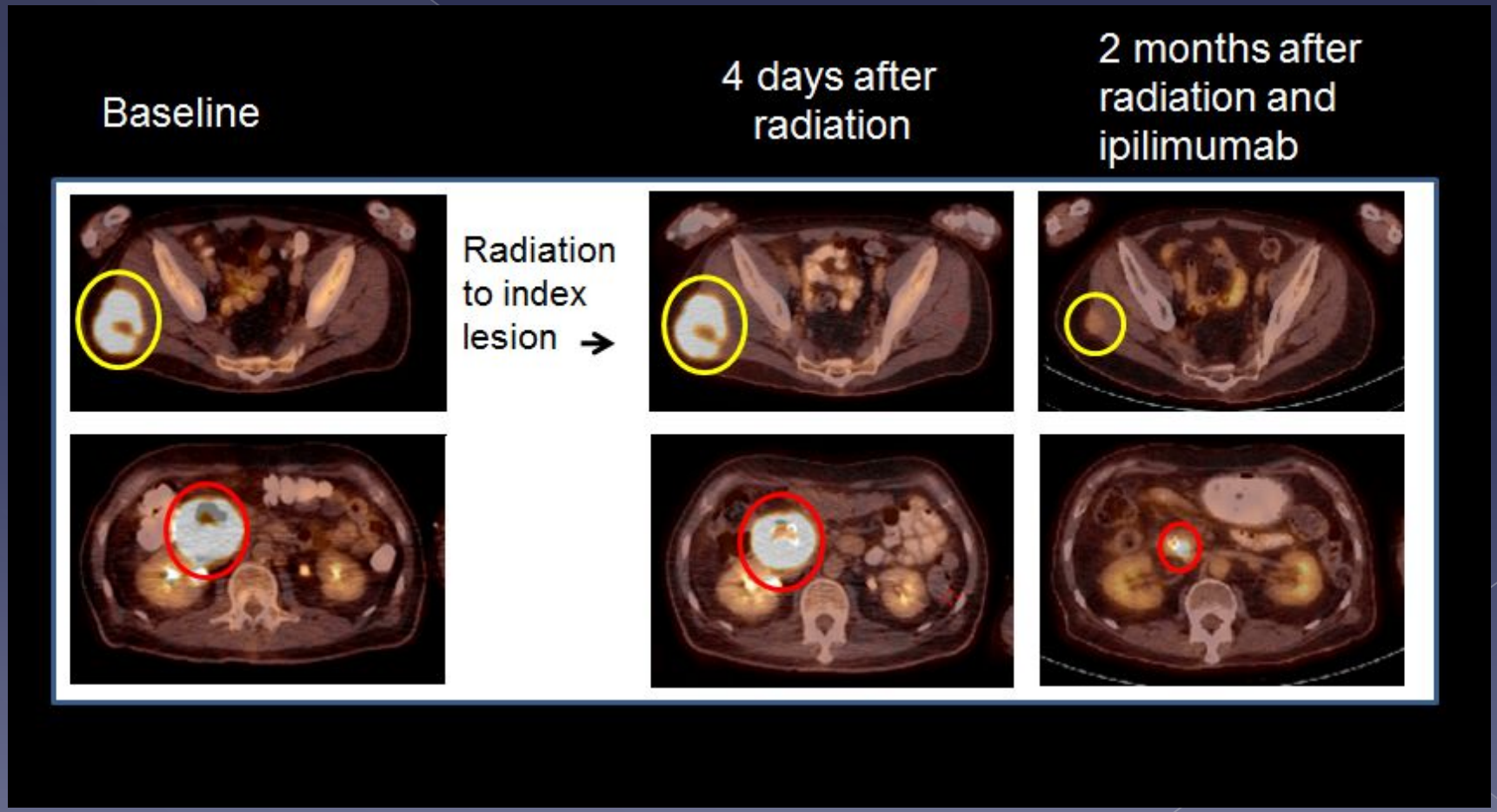
After treatment



Beatty et al, Science, 2011

‘RadVax’ – combining radiation with immune therapy

Radiation -> antigen release -> in-situ vaccine



Improving access to trials and standard of care

- 4.1% of cancer patients in the USA enroll in clinical trials
- Education is lacking
- Access/availability is lacking
- Funding for outreach is lacking

Let's Win!

Sharing science solutions for Pancreatic Cancer

ClinicalTrials.gov

The mission

- Strong scientific research
  -"Know your enemy"
- Strong translational partnerships with clinician researchers
- Increase in outreach efforts, education, trial availability
- Improve the discussions between patients and providers
- Increase in multi-institutional, national and international partnerships

Together, we have the power to be the next great story in cancer history…