Immune Therapy for Pancreatic Cancer

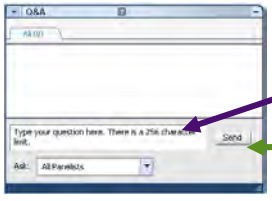
December 16, 2014

If you experience technical difficulty during the presentation:

Contact WebEx Technical Support directly at:
US Toll Free: 1-866-229-3239
Toll Only: 1-408-435 -7088
or
Submit a question to the Event Producer via the Q&A Panel

For international support numbers visit:
http://support.webex.com/support/phone-numbers.ht

Questions may be submitted anytime during the presentation.



To submit questions:

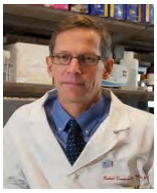
Type your questions in the text entry box

Click the Send Button

Please direct your questions to "All Panelists" in the drop down

Immune therapy for pancreatic cancer

Robert Vonderheide, MD, DPhil
Abramson Cancer Center
University of Pennsylania
Philadelphia, PA



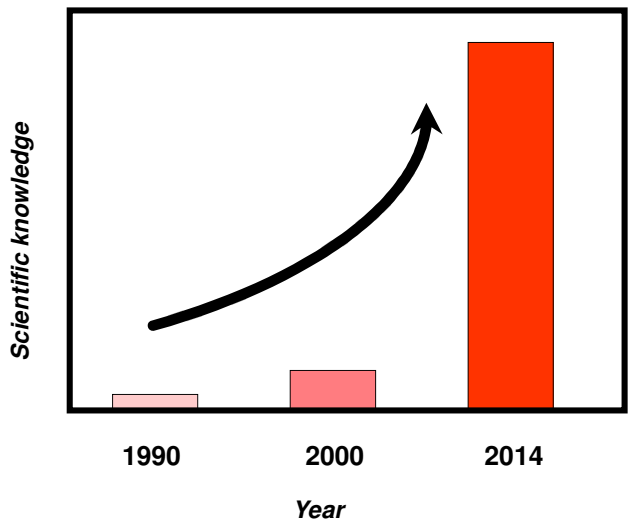
December 16, 2014

Abramson Cancer Center
Penn Medicine

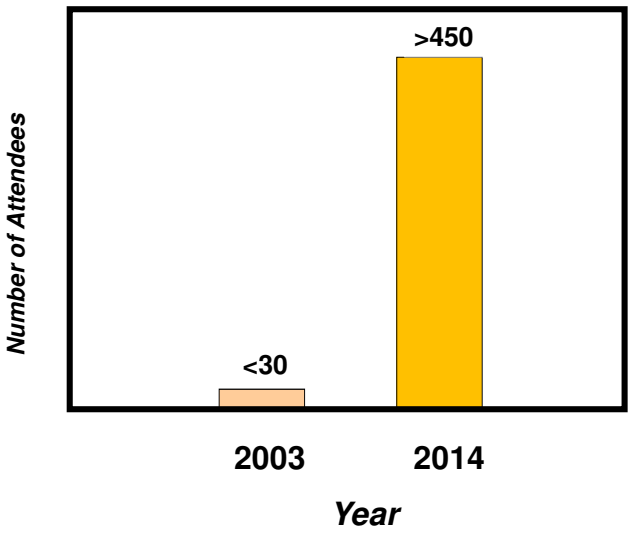
The clinical and biological challenges:

Early detection is difficult
Suboptimal response to standard therapies
Main tumor mutation (Kras) is currently 'undruggable'
Hostile microenvironment in pancreatic cancer

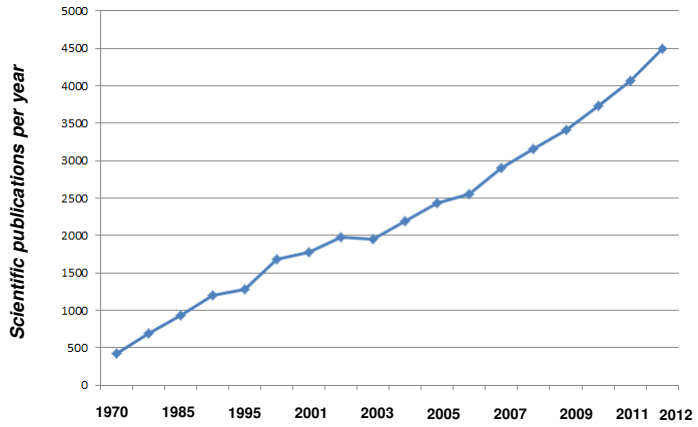
What we know about pancreatic cancer



Attendance at a national scientific meeting on pancreatic cancer

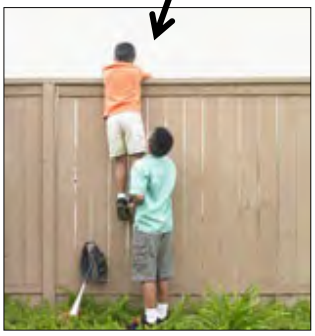


Massive increase in the depth and breadth of research activity in pancreatic cancer



Publications on breast cancer
in 2012: **13,925**
in 2002: **5,090**

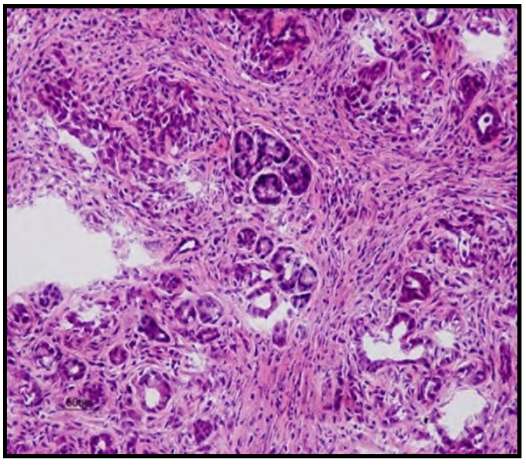
We are here



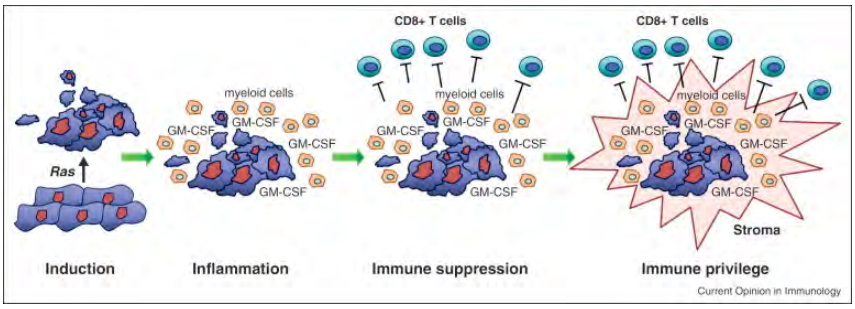
Redesigned chemotherapy for pancreatic cancer

- Two new combinations of drugs for patients with metastatic disease
  - FOLFIRINOX (Conway et al, NEJM, 2011)
  - Gemcitabine/Abraxane (Von Hoff et al, NEJM, 2013)
- Rates of major tumor regression to initial therapy for metastatic disease have gone from <5% to 25%-30%, with better survival
  - But still not a 'cure'
- Implications and next steps
  - It's not just gemcitabine alone anymore
  - Provides a better initial approach to stabilize our patients so additional therapies, such as immune therapy, can be added
  - Chemotherapy does not 'ruin' the immune system

The challenge and opportunity of stroma



Immune biology of pancreatic cancer



Bayne and Vonderheide, Curr Opin Immunol, 2013

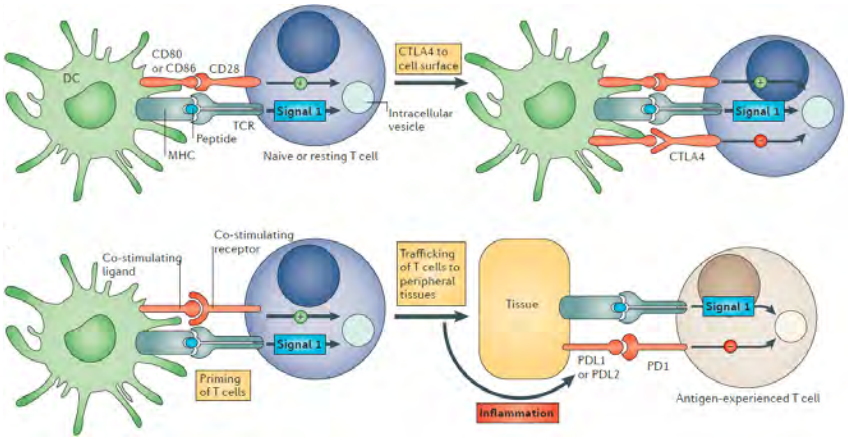
Cancer immunotherapy trials for patients with pancreatic cancer

	2014	2013
Treatment clinical trials for PDA *		
• Open trials	372	385
• Immunotherapy trials	20	13
Percentage of all trials exploring immunotherapy for PDA	**5.4%**	**3.0%**
• Same calculation in melanoma:	22.1%	17.0%
• Same calculation in breast cancer:	3.9%	1.0%

* Clinicaltrials.gov, assessed by RHV

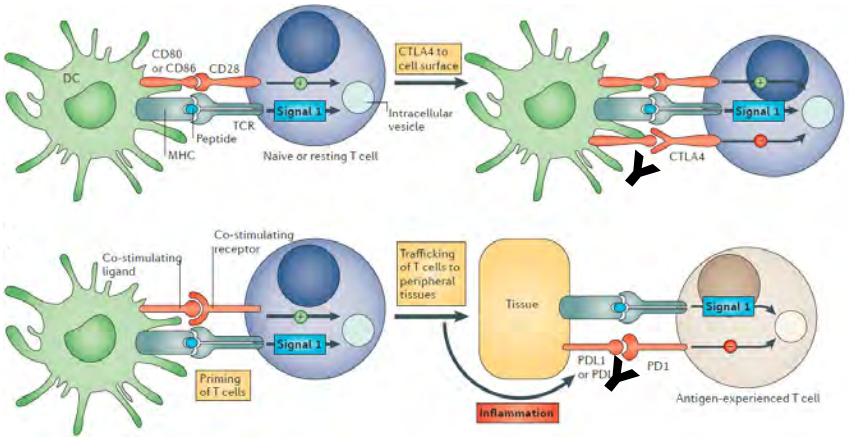
Monoclonal antibodies can stimulate the immune system

Negative immune checkpoints: the 'brakes'



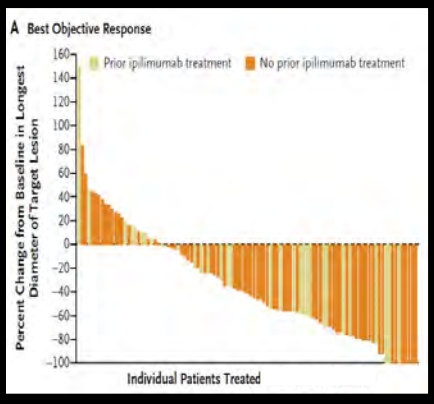
Pardoll, Nat Rev Can, 2012

Negative immune checkpoints: the 'brakes'



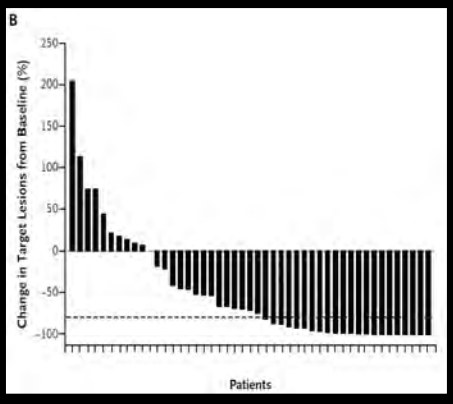
Pardoll, Nat Rev Can, 2012

PD-1 antibody with and without CTLA-4 antibody



Pembrolizumab for patients with metastatic melanoma

Hamid et al, NEJM, 2013



Nivolumab plus ipilimumab for patients with metastatic melanoma

Wolchok et al, NEJM, 2013

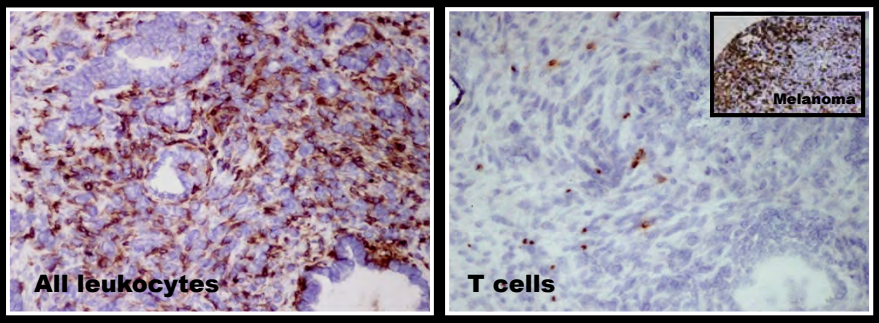
Checkpoint antibody clinical trials in patients with pancreatic cancer

Results so far using antibodies against negative immune checkpoints in patients with pancreatic cancer

- Single agent ipilimumab – no responses (Royal et al., *J Immnunother*, 2010; Le et al, *J Immunother*, 2013)
- Single agent αPD-L1 – no responses (Brahmer et al., *NEJM*, 2012)

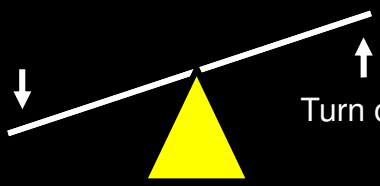
Clinicaltrials.gov

Immune cells in pancreatic cancer



Strategies to tip the balance of immunity

Turn on T cells



Turn off negative factors

Immunity **No immunity**

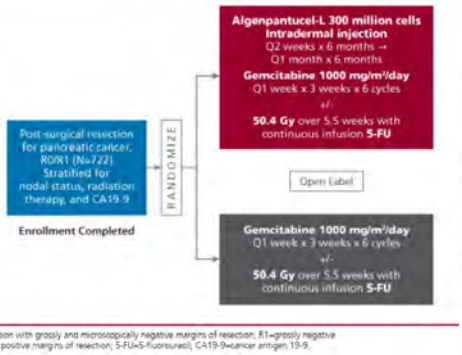
IMPRESS Trial: Algenpantucel-L vaccine with chemoradiation therapy for patients with resectable PDA

IMPRESS: Immunotherapy for **P**ancreatic **R**esectable Cancer **S**urvival **S**tudy[1]

Study Status[1]

ENROLLMENT COMPLETED[2] **(722 Patients)**

IMPRESS Phase 3 Study Schema[1]



R0=complete resection with grossly and microscopically negative margins of resection; R1=grossly negative but microscopically positive margins of resection; 5-FU=5-fluorouracil; CA19-9=cancer antigen 19-9.

Tumor-specific cancer cell lines modified to express the carbohydrate alpha-gal

Study Details[1]

Study Design	• Randomized phase 3 study of standard adjuvant therapy alone or in combination with algenpantucel-L in patients who have undergone surgical resection for pancreatic cancer
Key Inclusion Criteria	• Surgical resection for adenocarcinoma of the pancreas; extent of resection must be R0 or R1 • ECOG PS ≤ 2 • First vaccination within 10 weeks of surgery
Key Exclusion Criteria	• Active metastases • Current immunosuppressive therapy • Chronic systemic corticosteroid therapy
Key Endpoints	• **Primary:** Overall survival (OS) • **Secondary:** Disease-free survival (DFS)

PILLAR trial open for patients with locally advanced non resectable disease NCT01836432

Combining vaccines with checkpoint antibody for patients with pancreatic cancer

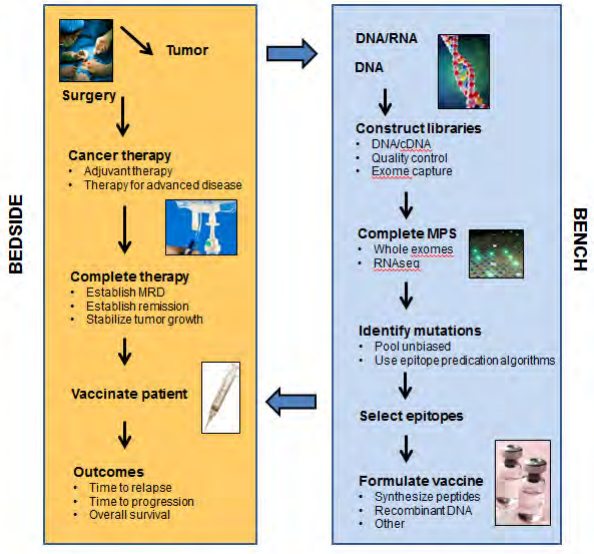
Dual component gene therapy vaccine

- GVAX pancreas – irradiated, whole cell tumor vaccine, secretes GM-CSF
- LADD Listeria – live, attenutated *Listeria monocytogenes* expressing mesothelin
- Survival benefit in patients given both components rather than GVAX alone, now a randomized study nationwide, NCT02004262
- Next step is to add anti-PD-1 antibody (trial at Johns Hopkins to open soon, NCT02243371)

GVAX plus ipilimumab

- Patients who receive FOLFIRINOX then go on to receive GVAX pancreas plus anti-CTLA-4 antibody (trial at Johns Hopkins, NCT01896869)

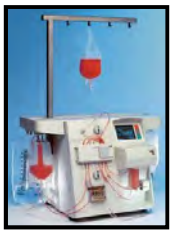
The road to personalized cancer vaccines



Vonderheide and Nathanson, Nature Medicine, 2013

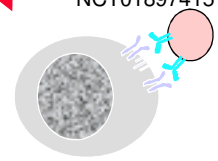
Engineered T cell therapy for pancreatic cancer

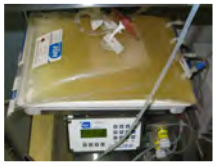
1. Remove the immune cells from blood



2. Engineer killer lymphocytes in a clinical laboratory

Anti-mesothelin"
NCT01897415

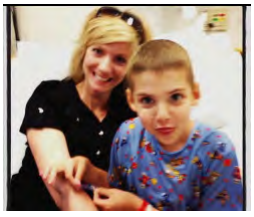




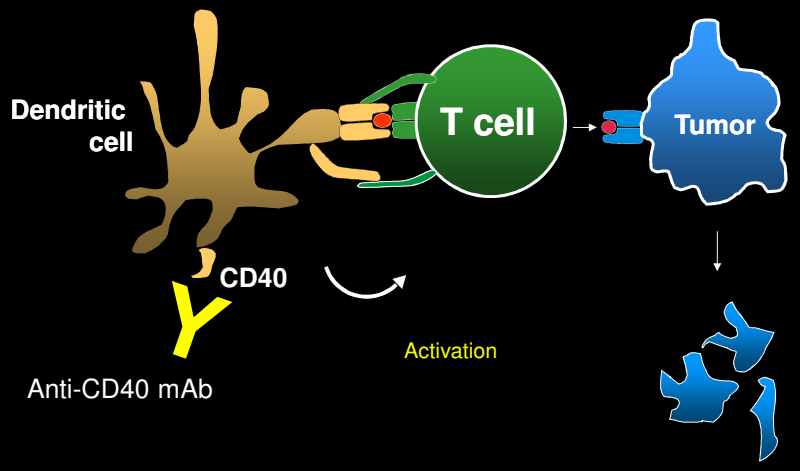
3. Prepare cells for re-infusion

4. Give patient engineered T cells

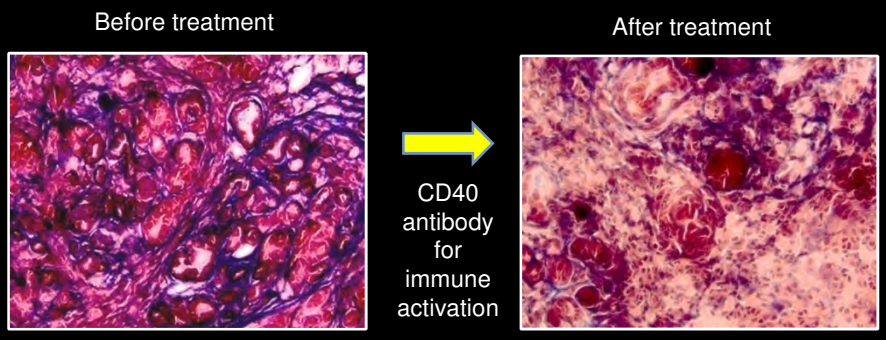
Porter et al, NEJM, 2011
Grupp et al, NEJM, 2013
Maude et al, NEJM, 2014
Beatty et al, Can Immunol Res, 2014



Testing CD40 antibodies as immune therapy for pancreatic cancer in the laboratory

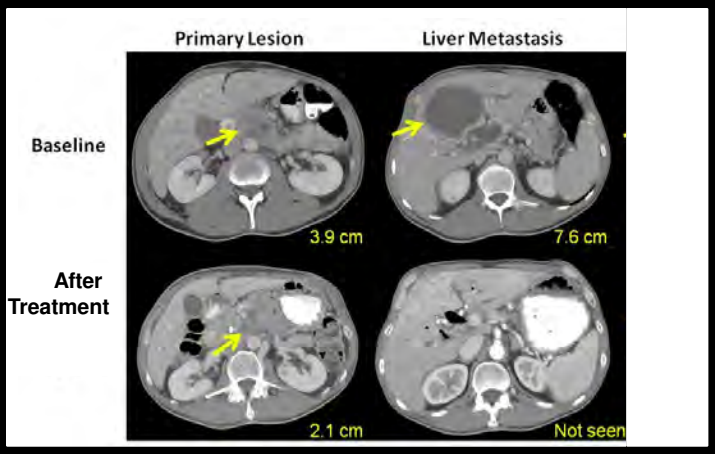


Testing CD40 antibodies as immune therapy for pancreatic cancer in the laboratory



Beatty et al, Science, 2011

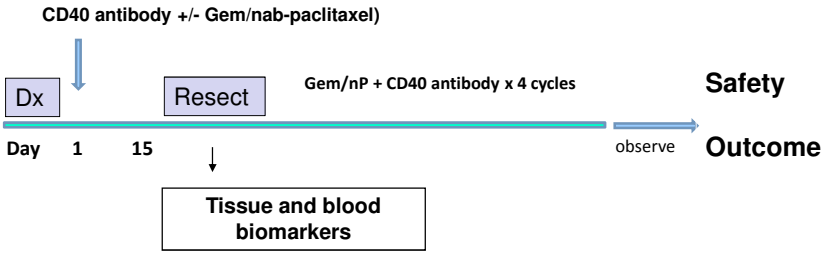
CD40 antibody immune therapy for pancreatic cancer



Beatty et al, Science, 2011

CD40 antibody for patients undergoing surgery

To open soon at Penn: Phase I study of preoperative CD40 antibody +/- chemo for patients with newly diagnosed resectable pancreatic carcinoma



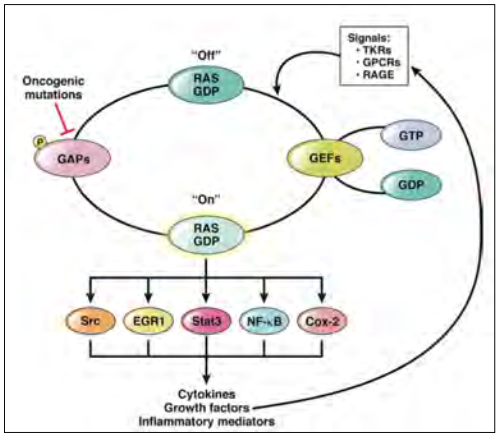
Recalcitriol with chemotherapy for patients with resectable pancreatic cancer

- Expression profiling of tumor stellate cells revealed Vitamin D receptor as a potential regulator of function *Sherman et al, Cell, 2014*
- Vitamin D agonists alter tumor stroma and facilitate tumor death in combination with chemotherapy in laboratory studies
- Phase I study of paricalcitol and chemotherapy delivered prior to, and again after, surgical resection of primary tumor
  - At Penn, NCT02030860

STAND UP TO CANCER
standup2cancer.org

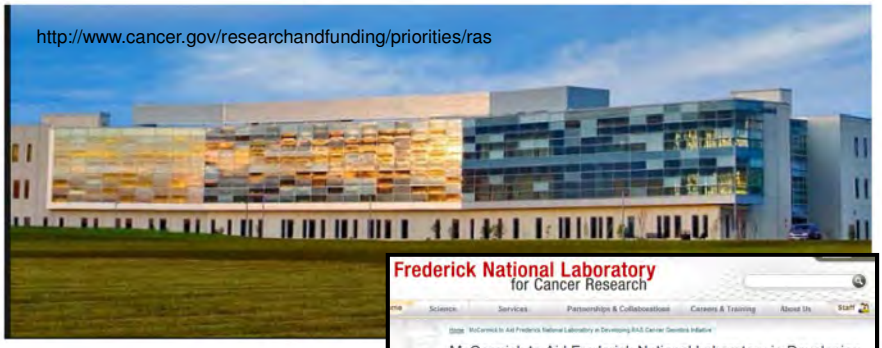
Mutant Kras oncogene

- More than 95% of all patients with pancreatic ductal adenocarcinoma have mutations in Kras in the tumor
- There are cooperating mutations but no other common 'driver' mutations
- Does mutant Kras cause such immune suppression?



Pasca di Magliano and Logsdon, Gastroenterology, 2013
Biakin et al, Nature, 2012

The Ras Initiative



Pancreatic cancer is a clinical EMERGENCY

Research in clinical trials are critical

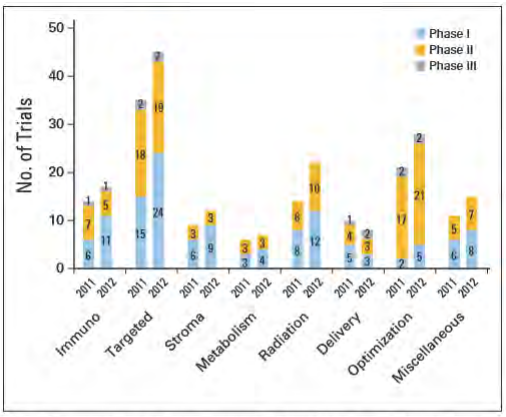


Fig 3. Pancreatic ductal adenocarcinoma clinical trials open in United States in 2011 and 2012 by treatment type. Targeted indicates those targeted to signal

Hoos et al, J Clin Oncology, 2013

Still, only 4% of patients with pancreatic cancer ever go on a clinical trial

Conclusions

- **Research efforts in pancreatic cancer are accelerating**
- **New discoveries are driving novel therapies, especially immune therapies**
- **Clinical trials are critical**

Thank you for your participation.

If you have questions, please contact our Patient and Liaison Services (PALS) program at
(877) 272-6226 or e-mail pals@pancan.org.

www.pancan.org or wagehope.org