Recent Advances in the Management of Pancreatic Cancer

Session VII: Innovation in Oncology Treatment
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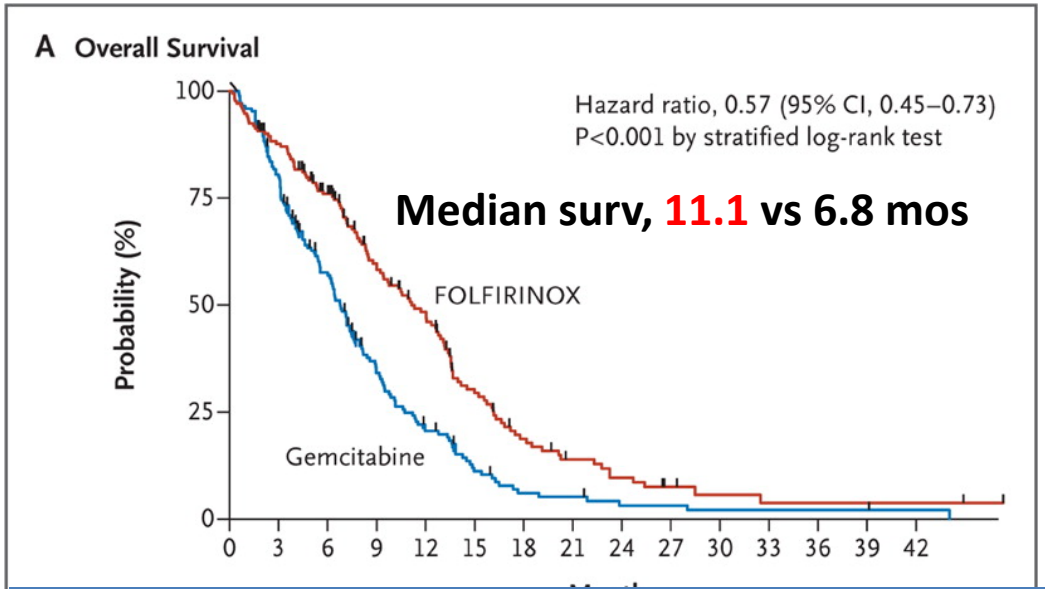
Andrew H. Ko, MD
Professor of Medicine, Division of Hematology/Oncology
UCSF Comprehensive Cancer Center

Pancreatic cancer: Scope of the problem

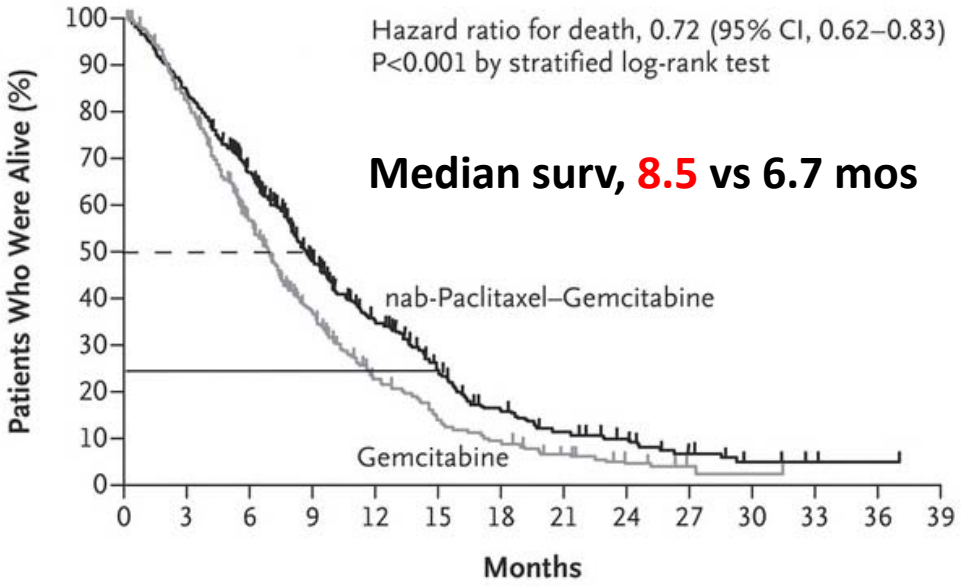
- Stage for stage, pancreatic cancer is associated with the lowest survival rates of any major cancer type
- Within the decade, pancreatic cancer is expected to rise to the **#2 leading cause of cancer-related mortality** in the United States (behind lung cancer)
- The vast majority of patients (80-85%) are inoperable at the time of diagnosis
- Many patients suffer from cachexia, anorexia, and rapidly declining performance status, making them poor candidates for participating in experimental therapy

There are currently two first-line standards for the treatment of advanced metastatic pancreatic cancer…

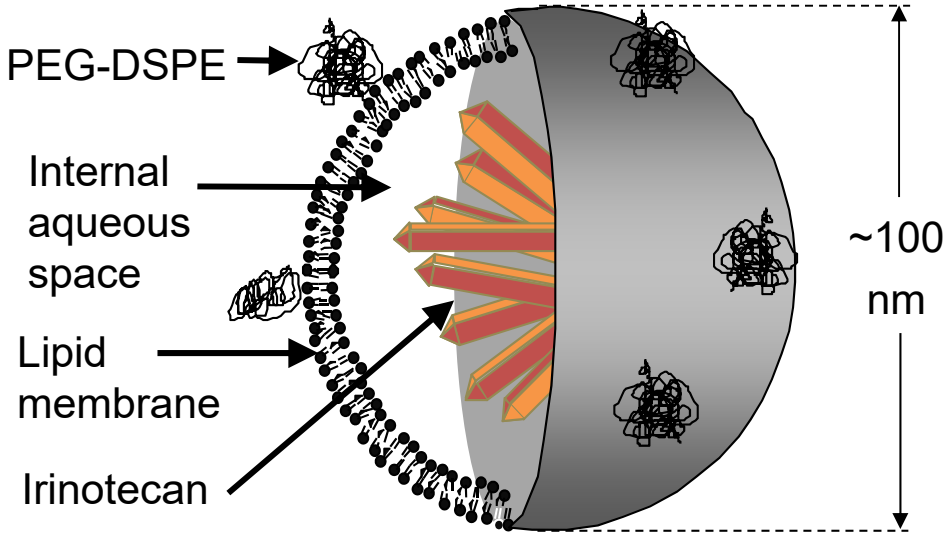


FOLFIRINOX vs gemcitabine
Conroy et al, N Eng J Med 2011, 364:1817-25.

Gemcitabine/nab-paclitaxel vs gemcitabine
Von Hoff, *N Engl J Med* 2013; 369:1691-703.



As well as the first agent approved for the *2nd-line* setting = nanoliposomal irinotecan (nal-IRI)



~80,000 irinotecan molecules/liposome

- MM-398 (120 mg/m^2) clinical PK show extended circulation
  - 70x higher AUC of total irinotecan in blood *vs* conventional irinotecan (300 mg/m^2)
- MM-398 achieved 5x higher levels of SN-38 (active metabolite) in tumor compared to blood at 72 hours

NAPOLI-1 trial: Improvement in median survival by ~ 2 months (nal-IRI/5-FU/LV vs 5-FU/LV, 6.1 vs. 4.2 months, HR 0.67, p=0.012)

1. Roy AC et al. *Ann Oncol*. 2013;24:1567-1573. 2. Ramanathan RK et al. Proc.105th AACR; 2014. CT224. 3. Ko AH et al. *Br J Cancer*. 2013;109:920-925. 4. Wang-Gillam A et al. Lancet 2016;387:545-557.

What are the challenges of moving beyond conventional cytotoxic therapies in pancreatic cancer?

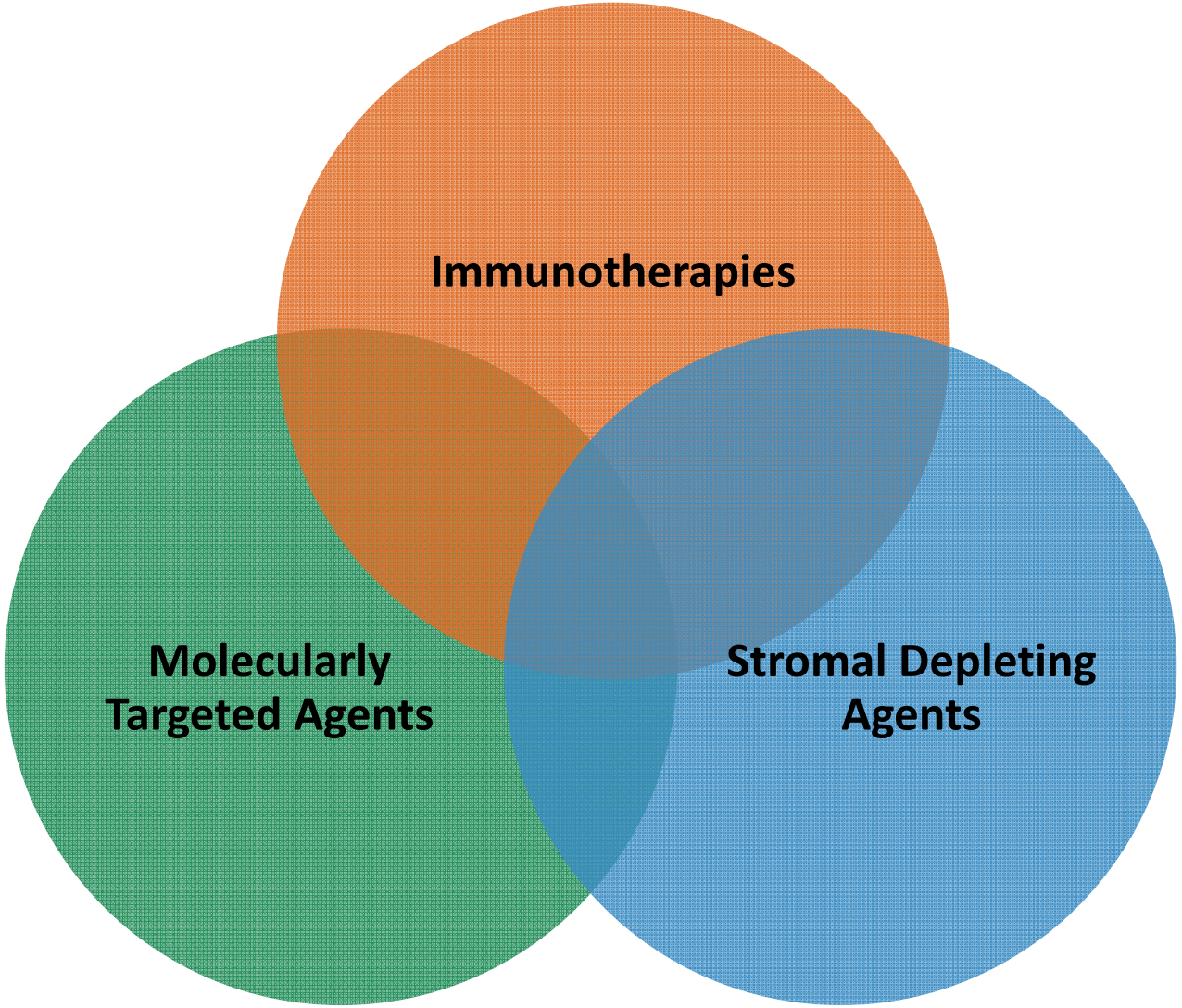
- *The pancreatic cancer microenvironment includes a dense, desmoplastic **stroma** that impedes effective drug delivery.*
- *Pancreatic cancer is generally felt to be a **non-immunogenic** tumor.*
- *There are **no validated therapeutic targets** in pancreatic cancer, and **no predictive molecular biomarkers** that allow us to "personalize" treatment for patients with pancreatic cancer.*

Novel drugs in development for advanced pancreatic cancer

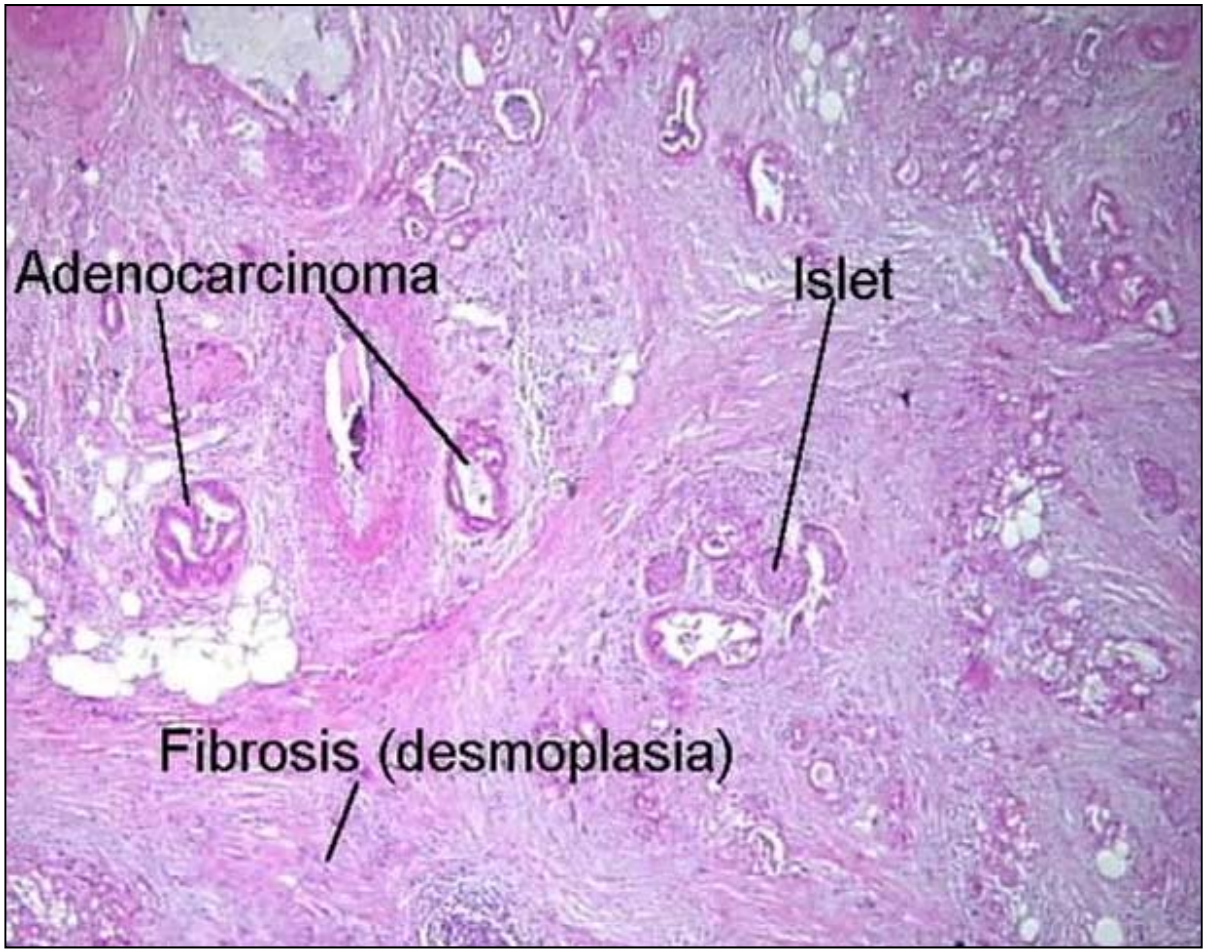
Class	Examples
Novel cytotoxics	• MM-398 (nanoliposomal irinotecan) • ~~TH-302 (hypoxia-activated mustard)~~
Stromal modifying agents	• PEGPH20 (recombinant hyaluronidase) • CD40 mAb • Vitamin D analogues
Immunotherapies	• ~~CRS-207 (attenuated Listeria vaccine)~~ • Immune checkpoint inhibitors/PD-1 mAbs • IDO Inhibitors • Chimeric antigen receptor (CAR) T cells?
Signal transduction inhibitors	• ~~Ruxolitinib (JAK-STAT inhibitor)~~ • Istiratumab (MM-141; bispecific IGFR/HER3 mAb) • Ibrutinib (BTK inhibitor) • Notch inhibitors (demcizumab~~, tarextumab~~) • PARP inhibitors

Negative phase II/III trials in 2016 alone

Novel therapeutics beyond chemotherapies cross mechanistic boundaries



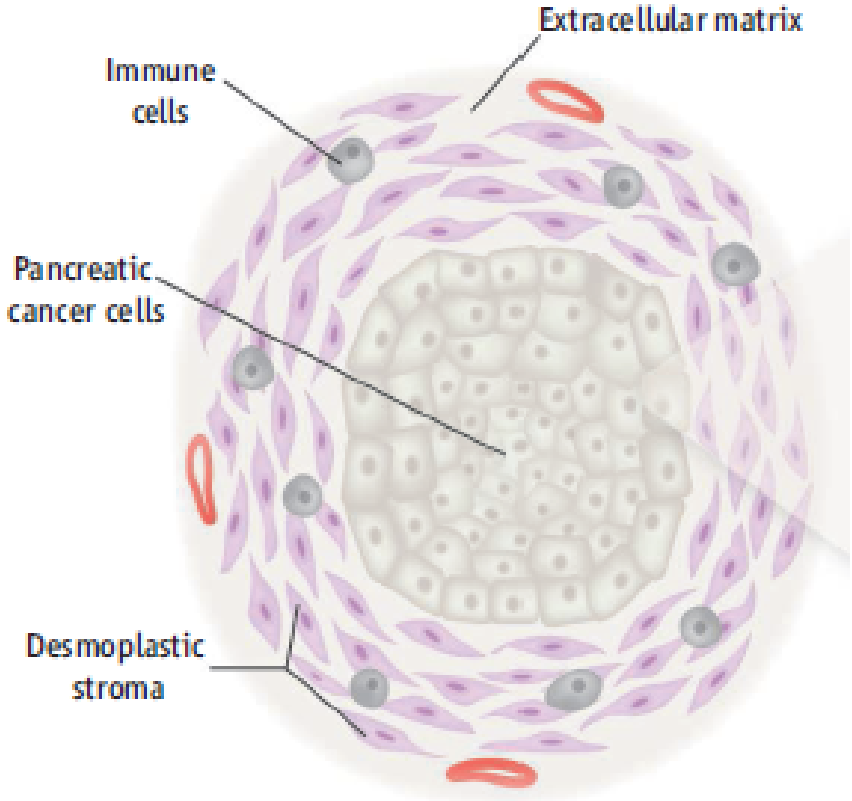
The importance of the tumor stroma in pancreatic cancer: Is this a viable therapeutic target?



Courtesy of Eric Collisson, MD.

Breaching the Cancer Fortress

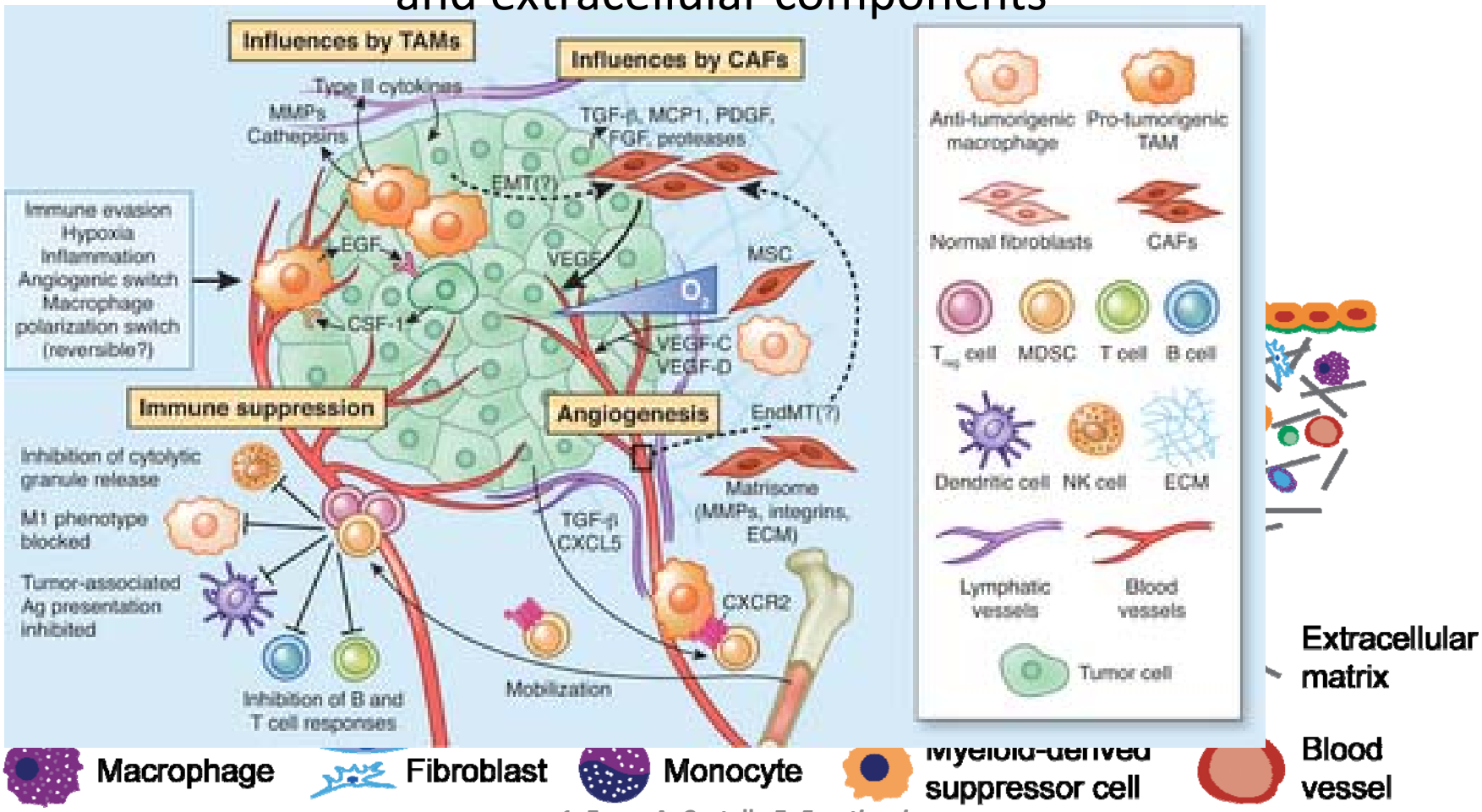
The predominant and invariably lethal form of pancreatic cancer—ductal adenocarcinoma—is characterized by an enveloping fibrotic stroma of excessive connective tissue and cells that forges rock-hard tumors. These tumors are refractory to essentially all therapies; gemcitabine, the standard-of-care chemotherapeutic drug, extends survival by only a few weeks. It has long been surmised that these pathological and clinical features are interconnected. On page 1457 in this issue, Olive *et al.* (*1*) confirm this notion, showing that cancer-associated fibroblasts in pancreatic ductal adenocarcinoma are responsible for a poorly vascularized architecture that imposes a barrier to drug



Science 2009;324(5933):1400-1.

The pancreatic tumor stromal microenvironment

A complex and dynamic interplay between multiple cellular and extracellular components



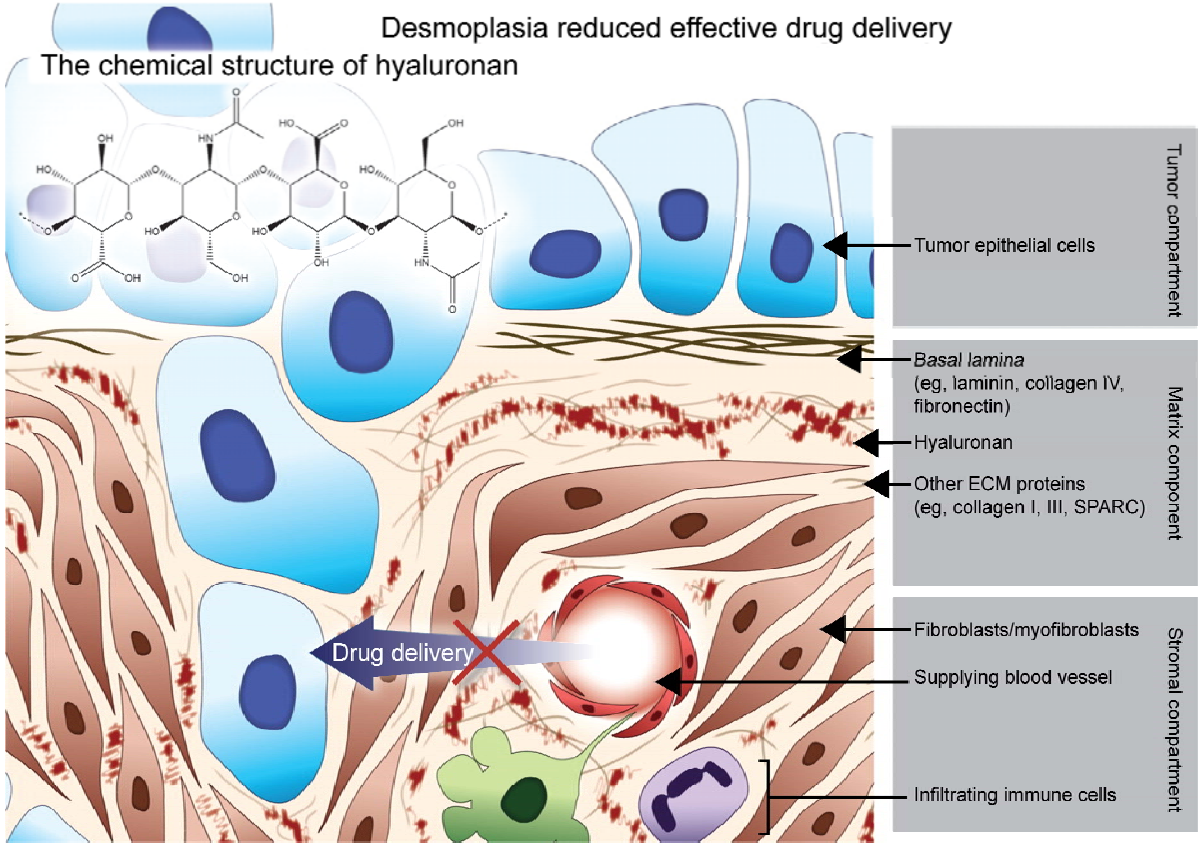
1. Evans A, Costello E. *Frontiers in Physiology*. 2012;3:270. 2. Quail DF, Joyce JA. *Nat Med*. 2013;19:1423-1437.

Stromal depleting/modifying agents

- Hedgehog inhibitors[1]
- Recombinant human hyaluronidase: PEGylated-rHuPH20[2]
- Vitamin D analogues[3]
- Nab-paclitaxel?[4]

1. Olive KP et al. *Science.* 2009;324:1457-1461. 2. Provenzano PP et al. *Cancer Cell* 2012;21:418-429.
3. Sherman MH et al. *Cell.* 2014;159:80-93.
4. Alvarez R et al. *Br J Cancer.* 2013;109:926-933.

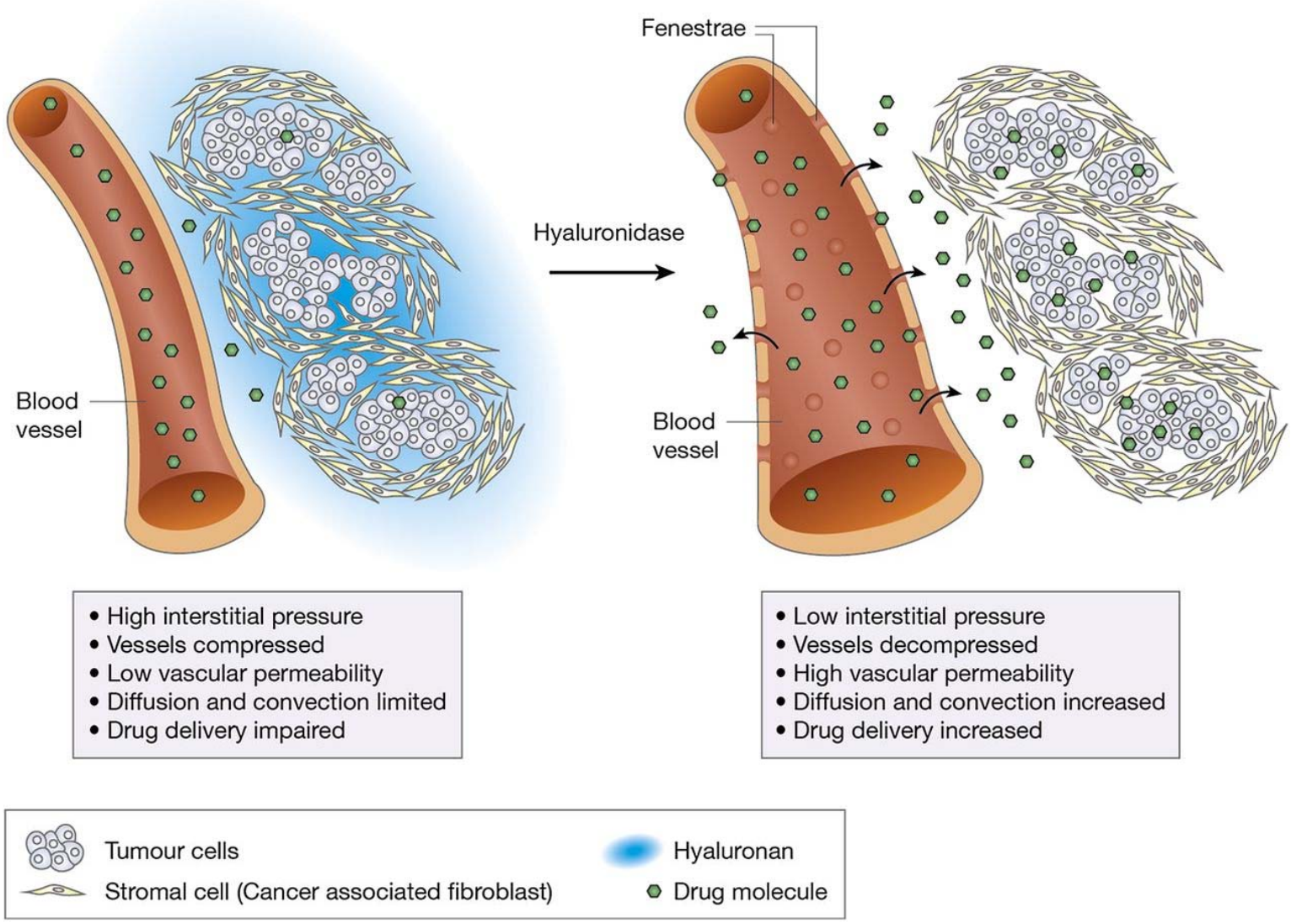
Hyaluronan is a major component of the extracellular matrix (ECM)



- Hyaluronan is degraded by hyaluronidase
- Recombinant human hyaluronidase: PEGylated-rHuPH20

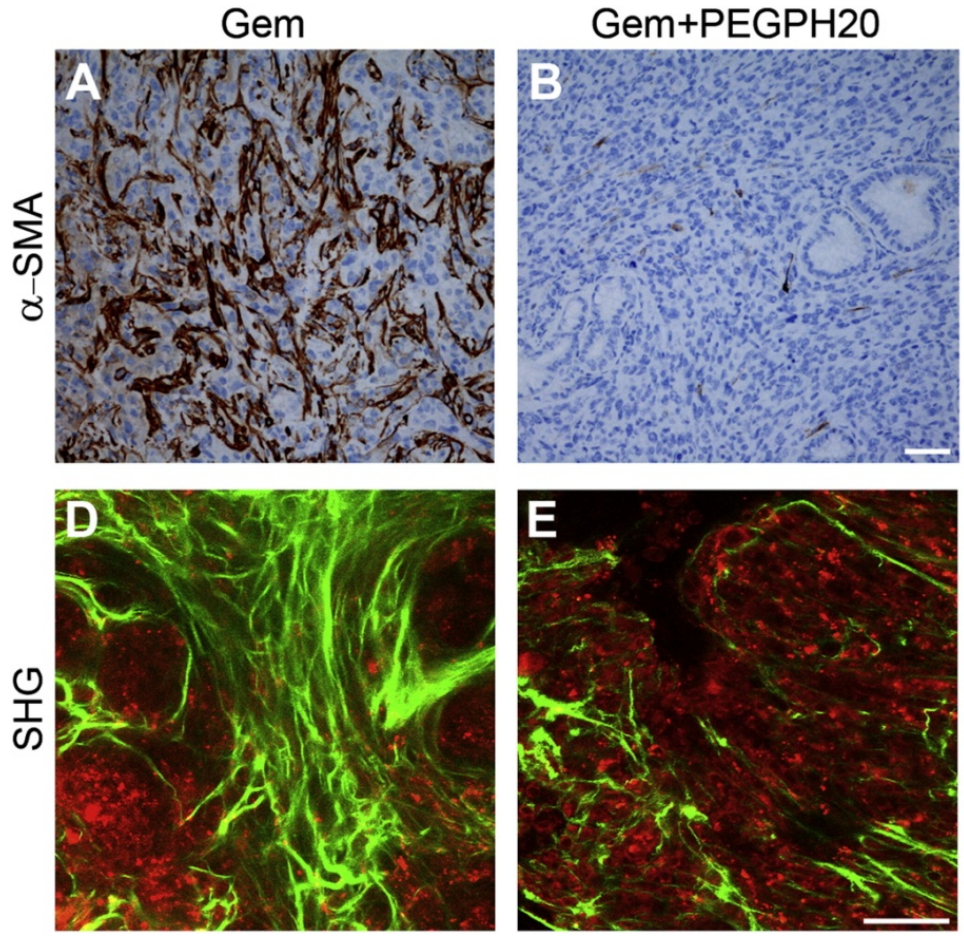
Whatcott et al. *Cancer Discovery.* 2011;1:291-296.

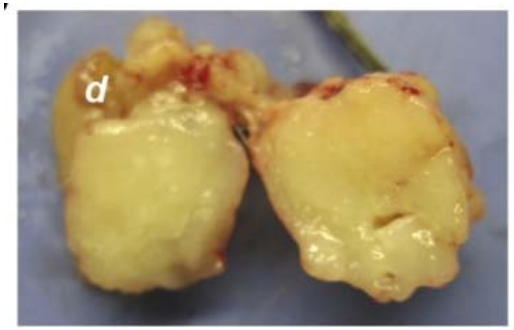
Effects of hyaluronidase on the tumour vasculature and interstitial pressure in pancreatic cancer



Michl and Gress, Gut 2012;61:1377-1379.

PEGPH20 combined with chemotherapy remodels tumor stroma and re-expands microvasculature



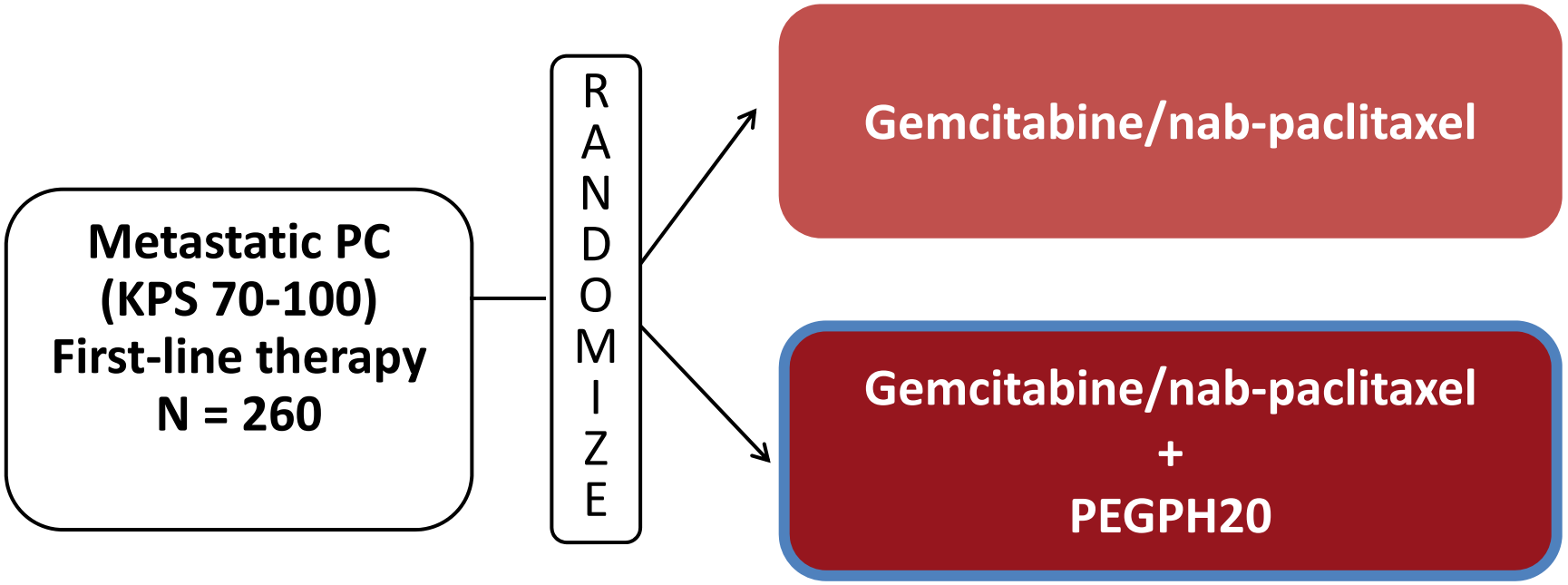


GEMCITABINE ALONE

GEMCITABINE + PEGPH20

Provenzano et al, Cancer Cell 2012.

Phase 2 HALO-109-202 trial



Primary endpoint: Progression-free survival

Hingorani SR et al. *J Clin Oncol*. 2015;33(suppl; abstr 4006).

Phase 2 HALO-109-202 trial results (preliminary)

	Gemcitabine-Nab-Paclitaxel + PEGPH20	Gemcitabine-Nab-Paclitaxel	Statistical Significance
TOTAL STUDY POPULATION			
Progression-free survival	5.7 months	5.2 months	HR 0.69, *P* = .11
Response rate	41% (30/74)	34% (21/61)	*P* = .48

- Higher rate of **thromboembolic events** on PEGPH20 arm during first stage of enrollment (42% vs 25%); mitigated during second stage with addition of prophylactic enoxaparin

Hingorani SR et al. *J Clin Oncol*. 2015:33(suppl; abstr 4006).

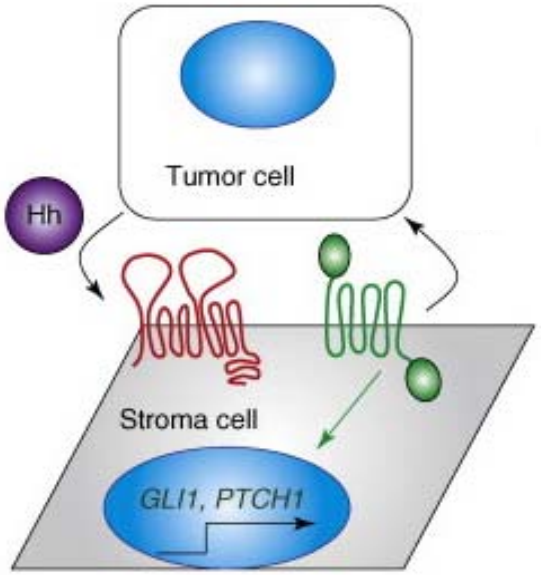
Current/future PEGPH20 clinical trials

- **SWOG phase I/II trial (S1313): modified FOLFIRINOX +/- PEGPH20**

- **Phase III trial of gemcitabine/nab-paclitaxel PLUS PEGPH20**
  - Limited to patients with tumors exhibiting high levels of HA expression

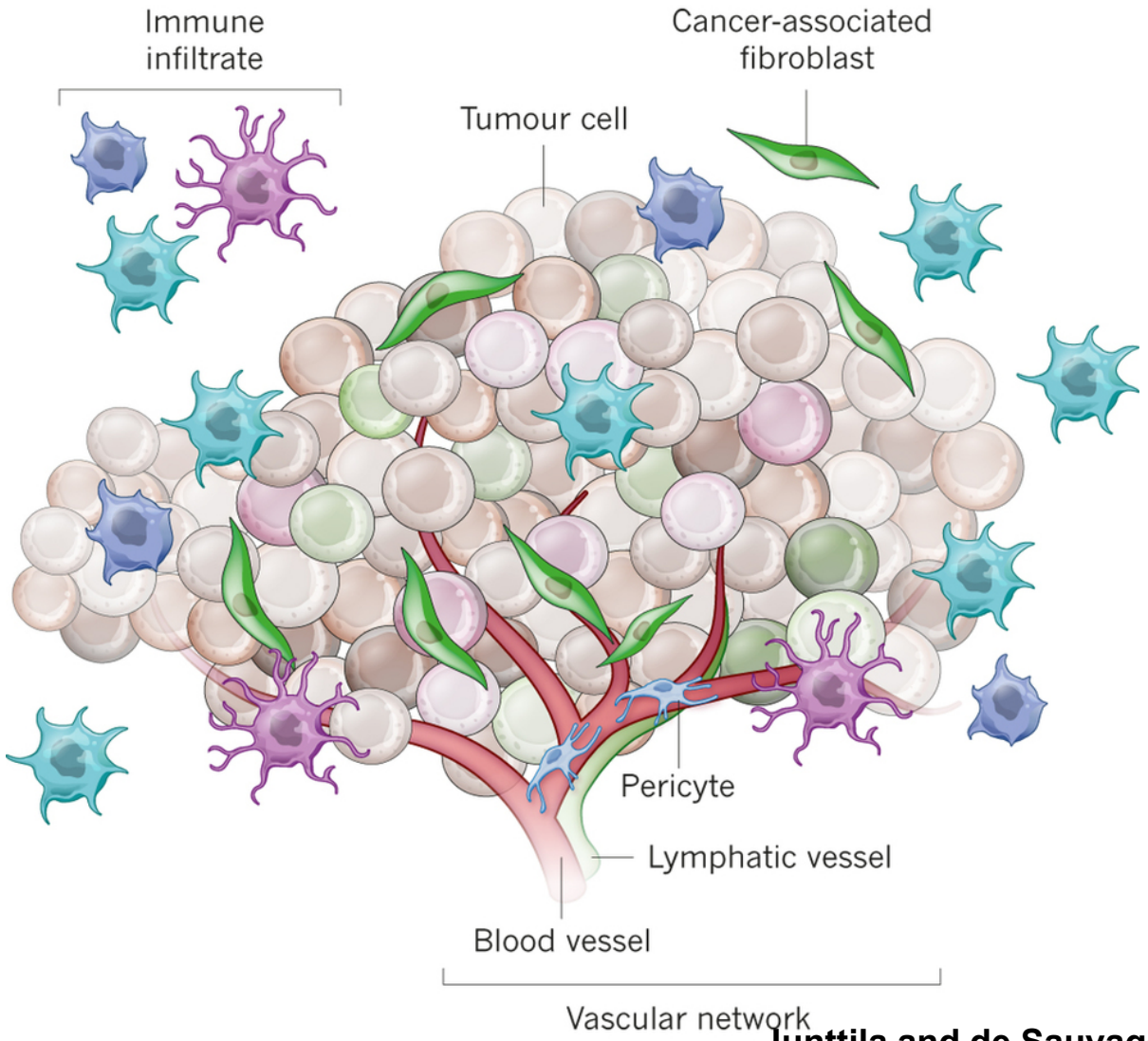
Stromal depleting strategies: Proceed with caution?

- Lessons learned from **Hedgehog story** in pancreatic cancer (Olive, *Science* 2009)
- The tumor stroma may be a physical barrier hampering drug delivery… but also may have *protective* effects in restraining tumor growth/progression!
  - **Stromal depletion may result in more aggressive tumor phenotype** (Rhim et al, Cancer Cell 2014; Ozdemir et al, Cancer Cell 2014)
  - **Dense stroma reaction a/w improved DFS and OS** in patients with resectable pancreatic cancer (Sinn et al, Br J Cancer 2014; Torphy et al, ASCO 2015; abstract 4021).



Scales and de Sauvage, Trends Pharmacol Sci 2009; 30:303-12.

The immunotherapy revolution in cancer: How will it impact pancreatic cancer?



Junttila and de Sauvage, Nature 2013.

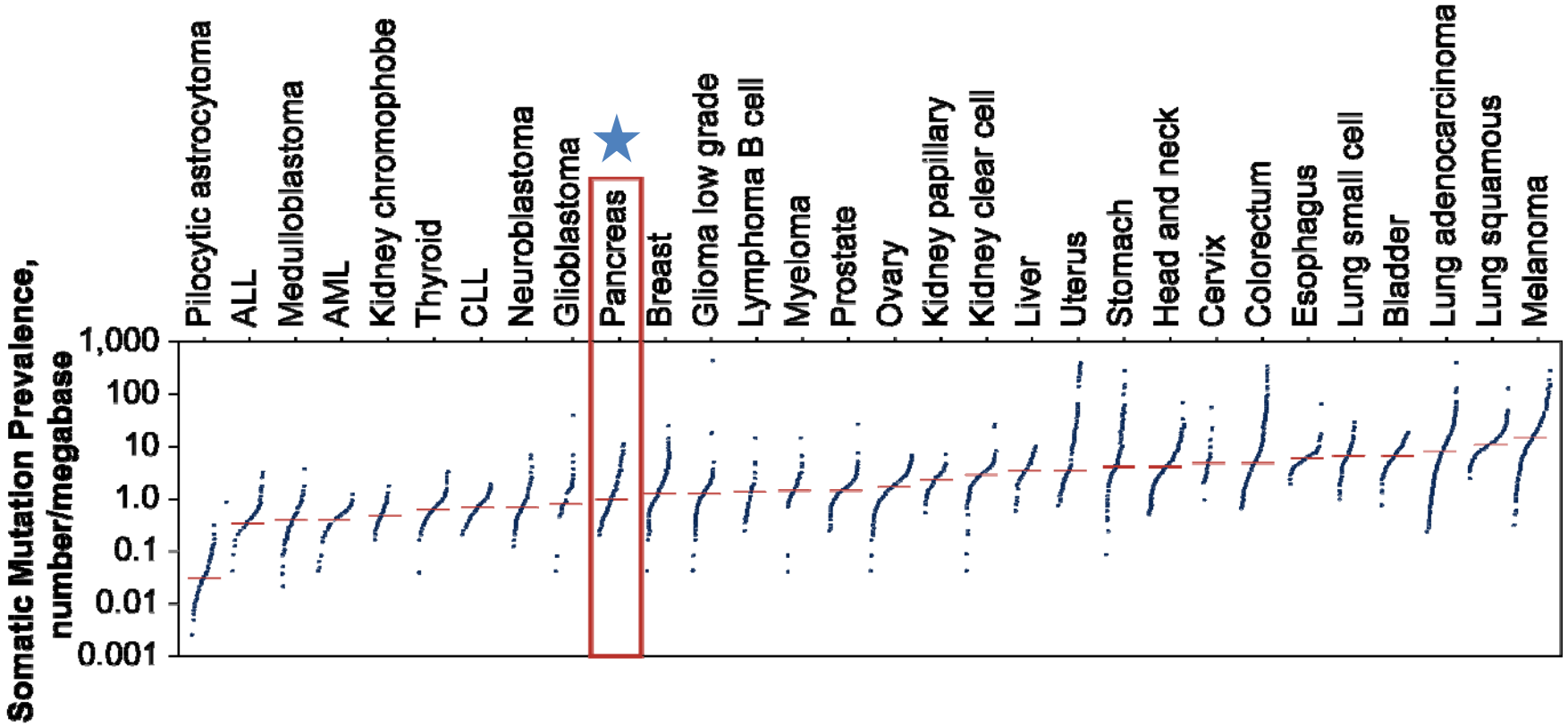
Pancreatic cancer: a non-immunogenic tumor?

- Genetically engineered mouse models of show pancreatic cancer development is associated with a rich and progressive infiltration of leukocytes dominated by immune-suppressive cells:
  - *Tumor-associated macrophages (TAMs)*
  - *Myeloid-derived suppressor cells (MDSCs)*
  - *Regulatory T cells (Tregs)*

- Conversely, there is striking **paucity** of activated cytotoxic (effector) CD8+ T cells or NK cell

Clark, *Cancer Res* 2007;67:9518-27

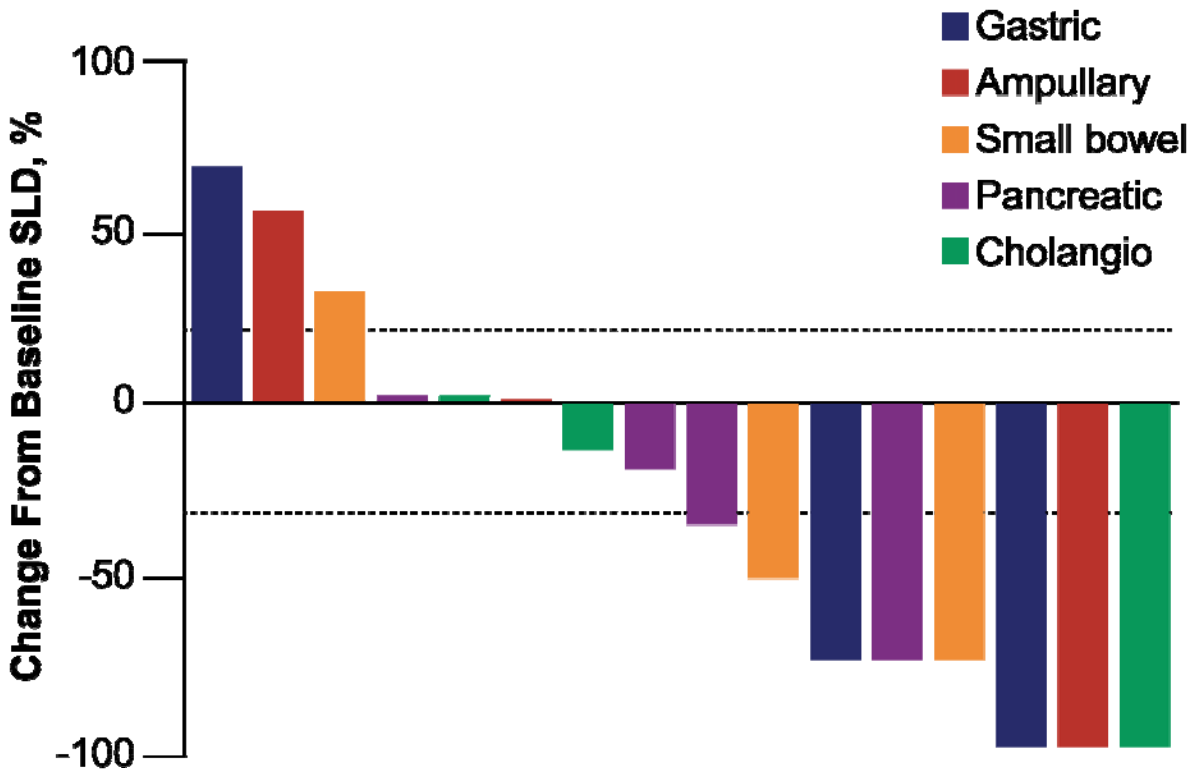
Pancreatic cancer is also on the lower end of the mutational burden spectrum compared to other solid tumors



Alexandrov LB et al. *Nature*. 2013;500:415-421.

Immune checkpoint inhibitors in pancreatic cancer

- Early studies of CTLA-4 and PD-1/PD-L1 antibodies showed minimal to no activity in advanced pancreatic cancer
- One exception: 1-2% of pancreatic cancers associated with defective mismatch repair (dMMR/MSI-high)



KEYNOTE-028:
4 patients with pancreatic cancer
➔ **2 objective responses**

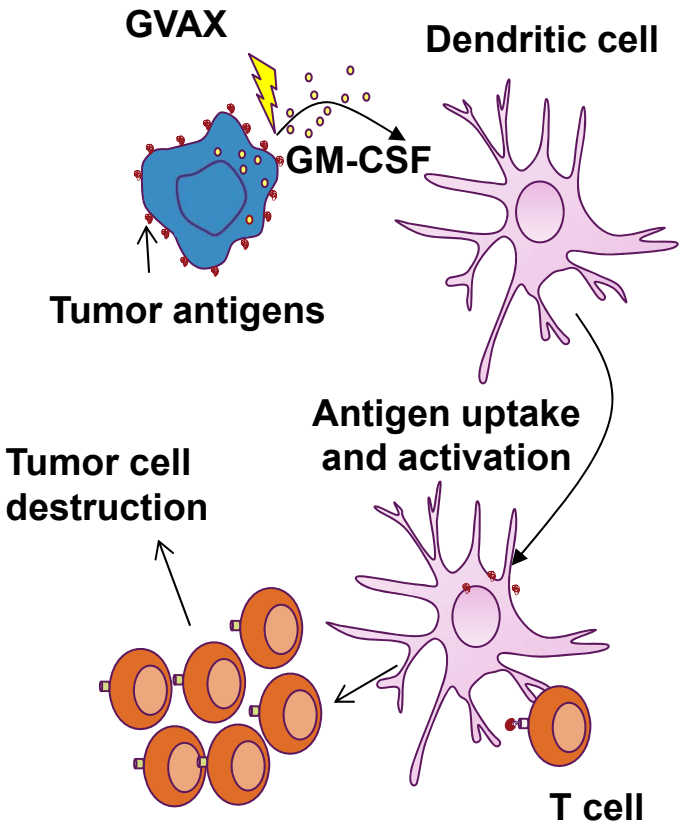
1. Le DT et al. *J Clin Oncol.* 2016;34(suppl 4S; abstr 195).

Immunotherapies undergoing evaluation for advanced/metastatic pancreatic cancer

Category	Description/Examples
Immune checkpoint inhibitors	• PD-1 and PD-L1 mAbs • CTLA-4 mAbs • IDO inhibitors
Vaccines	• CRS-207 = attenuated mesothelin-expressing Listeria • GVAX • Algenpantucel-L (“hyperacute” vaccine)
CD40 agonist mAbs	• CP-870,893, APX-005M
CCR2 antagonists	• PF-04136309
Bruton’s tyrosine kinase (BTK) inhibitors	• Ibrutinib • ACP-196
CAR (chimeric antigen receptor) T cells	• Pilot studies ongoing • Mesothelin represents frequent target

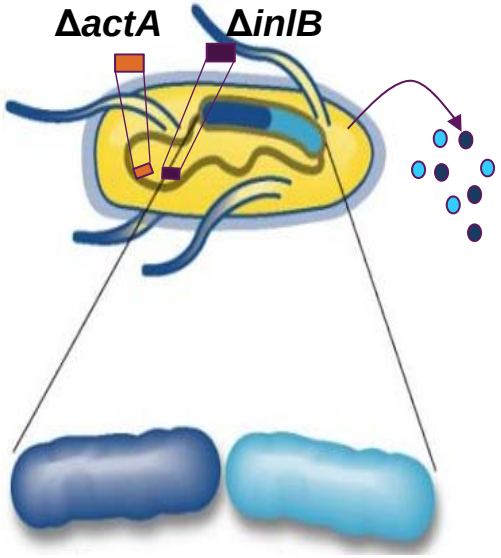
CRS-207 (Mesothelin-Expressing Listeria Vaccine)

GVAX Pancreas
Irradiated, whole-cell tumor vaccine



CRS-207
Live-attenuated *Listeria monocytogenes*

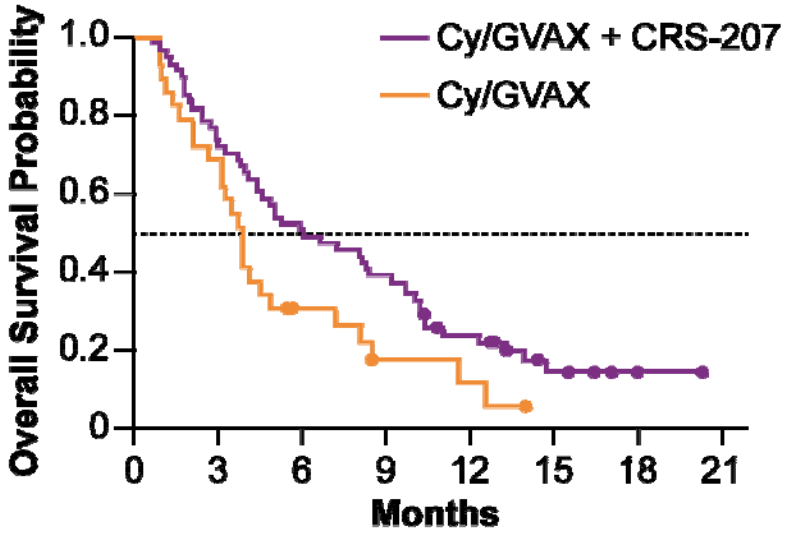
- Potent activation of innate and antigen-specific immune response



- Deletion of virulence genes (*actA, inlB*)
- Insertion of **mesothelin** expression cassette—validated immune target

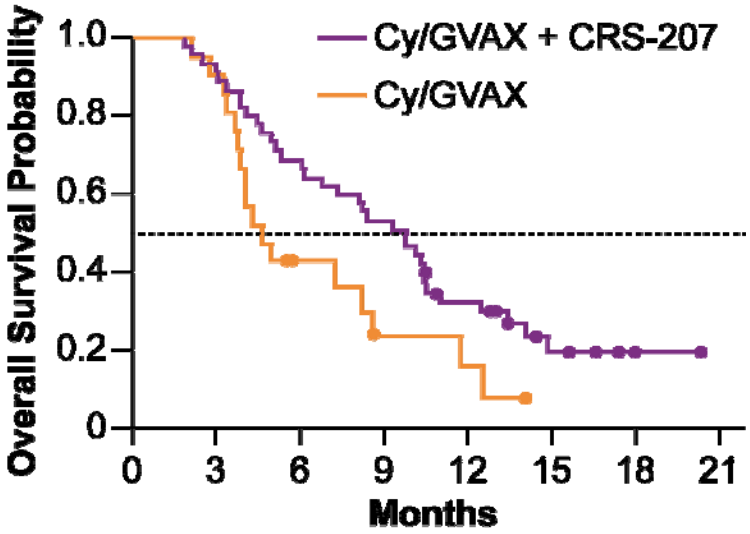
1. Le DT et al. *J Clin Oncol.* 2015;33:1325-1333.

Randomized phase 2 trial of GVAX +/- CRS-207 (pts receiving 2+ prior lines of chemotherapy)



Median OS, Full analysis set:
Cy/GVAX + CRS-207: 6.1 months
Cy/GVAX: 3.9 months

P = .02, HR = 0.59



Median OS, Per-protocol set (patients receiving at least one dose of CRS-207):
Cy/GVAX + CRS-207: 9.7 months
Cy/GVAX: 4.6 months

P = .02, HR = 0.53

- **Toxicities related to CRS-207:** transient fevers, rigors, lymphopenia

1. Le DT et al. *J Clin Oncol.* 2015;33:1325-1333.

Randomized phase 2 ECLIPSE trial (accrual complete)

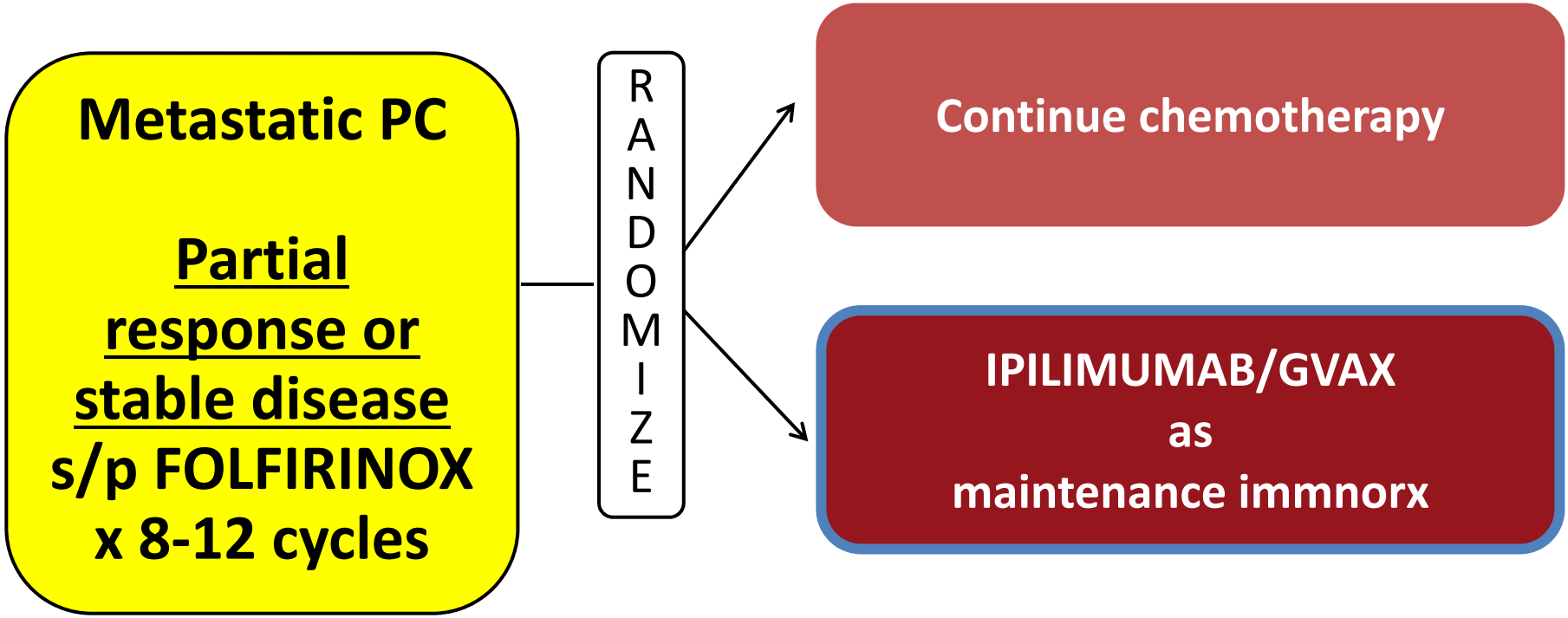
Successor studies looking at CRS-207 in combination with nivolumab +/- ipilimumab

Primary endpoint was not met[2]

	CRS-207 + GVAX	CRS-207	Chemotherapy
Median OS, mo	3.8	5.4	4.6

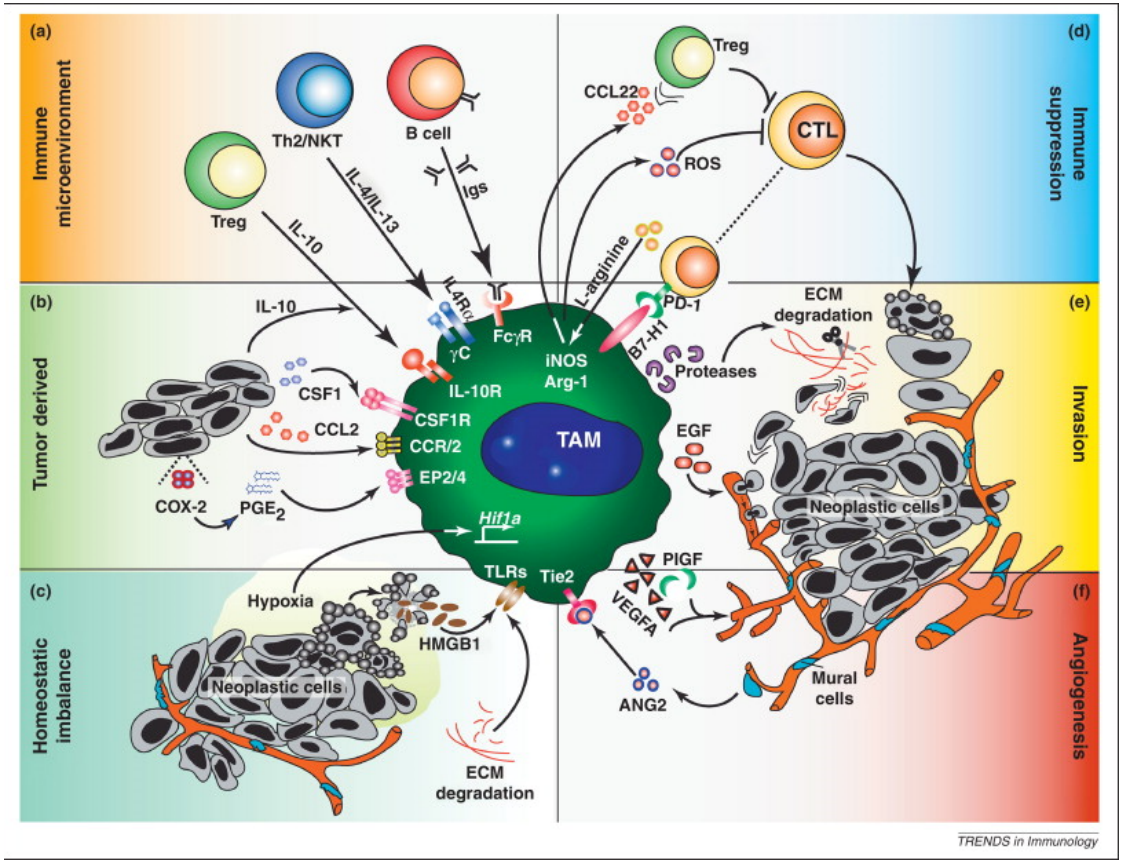
1. https://clinicaltrials.gov/ct2/show/NCT02004262. Accessed May 20. 2016.
2. http://investors.aduro.com/phoenix.zhtml?c=242043&p=irol-newsArticle&ID=2168543. Accessed May 20, 2016.

Randomized phase 2 trial
(Johns Hopkins/UCSF/Wash U collaboration)



https://clinicaltrials.gov/ct2/show/NCT01896869

Targeting tumor-associated macrophages (TAMs) in pancreatic cancer

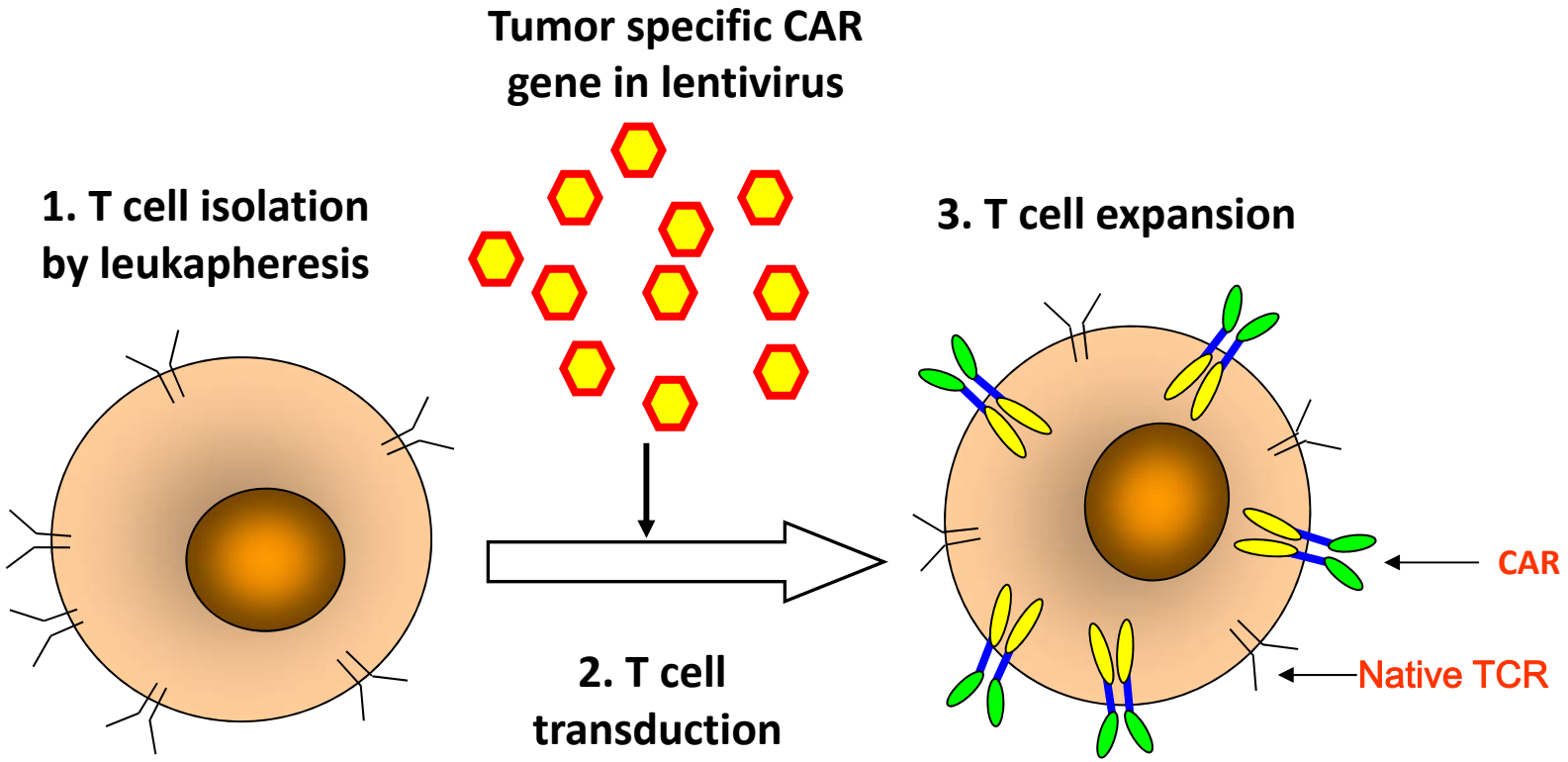


Ruffell et al, *Trends Immunol* 2012
Beatty et al, *Science* 2011
Sanford et al, *Clin Cancer Res* 2013
Nywening et al, *Lancet Oncol* 2016
Zhu et al, *Cancer Res* 2013

Therapeutic strategies:

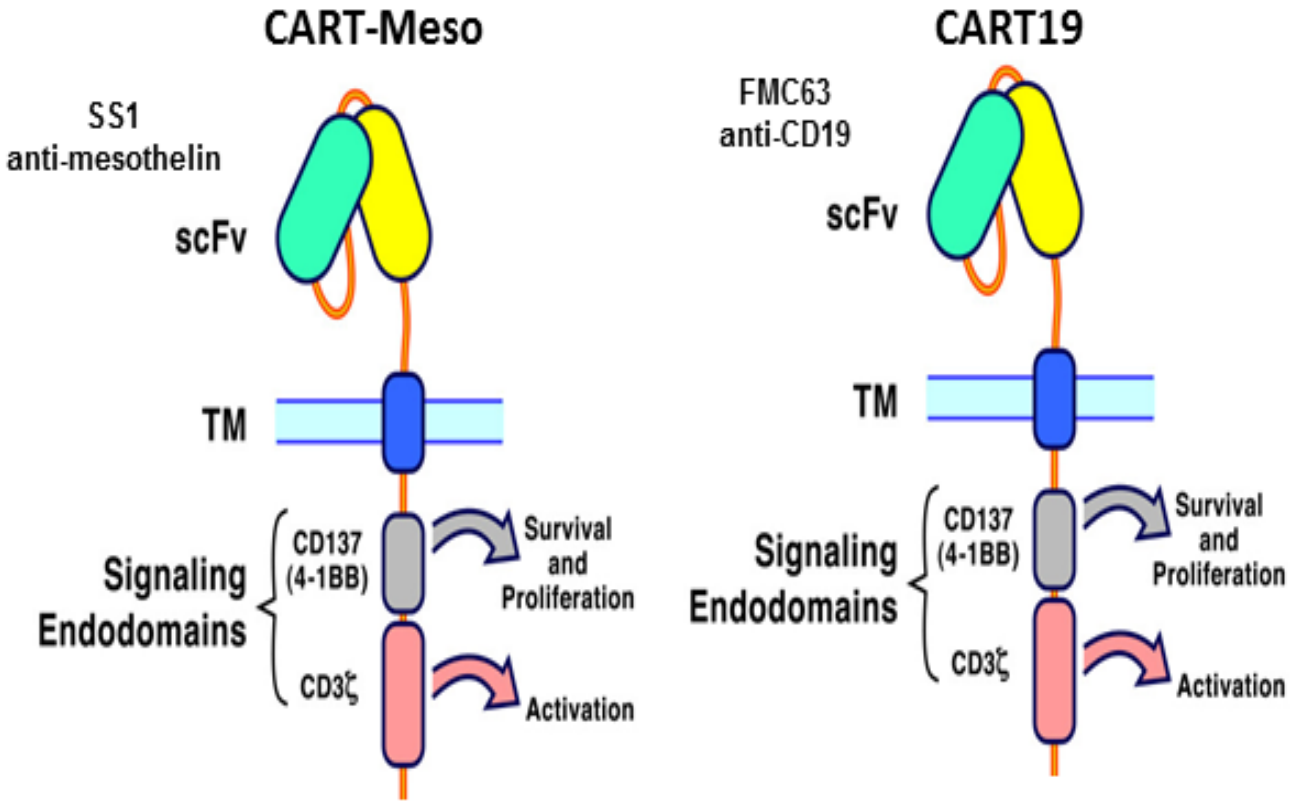
- **CD40 agonist antibodies**
  - *CD40 = member of TNF receptor superfamily*
- **CCR2 antagonists**
  - *CCR2 = receptor to chemokine CCL2*
- **CSF-1R antagonists**
  - *CSF-1/CSF-1R = colony stimulating factor axis*

Chimeric Antigen Receptor (CAR) T cells



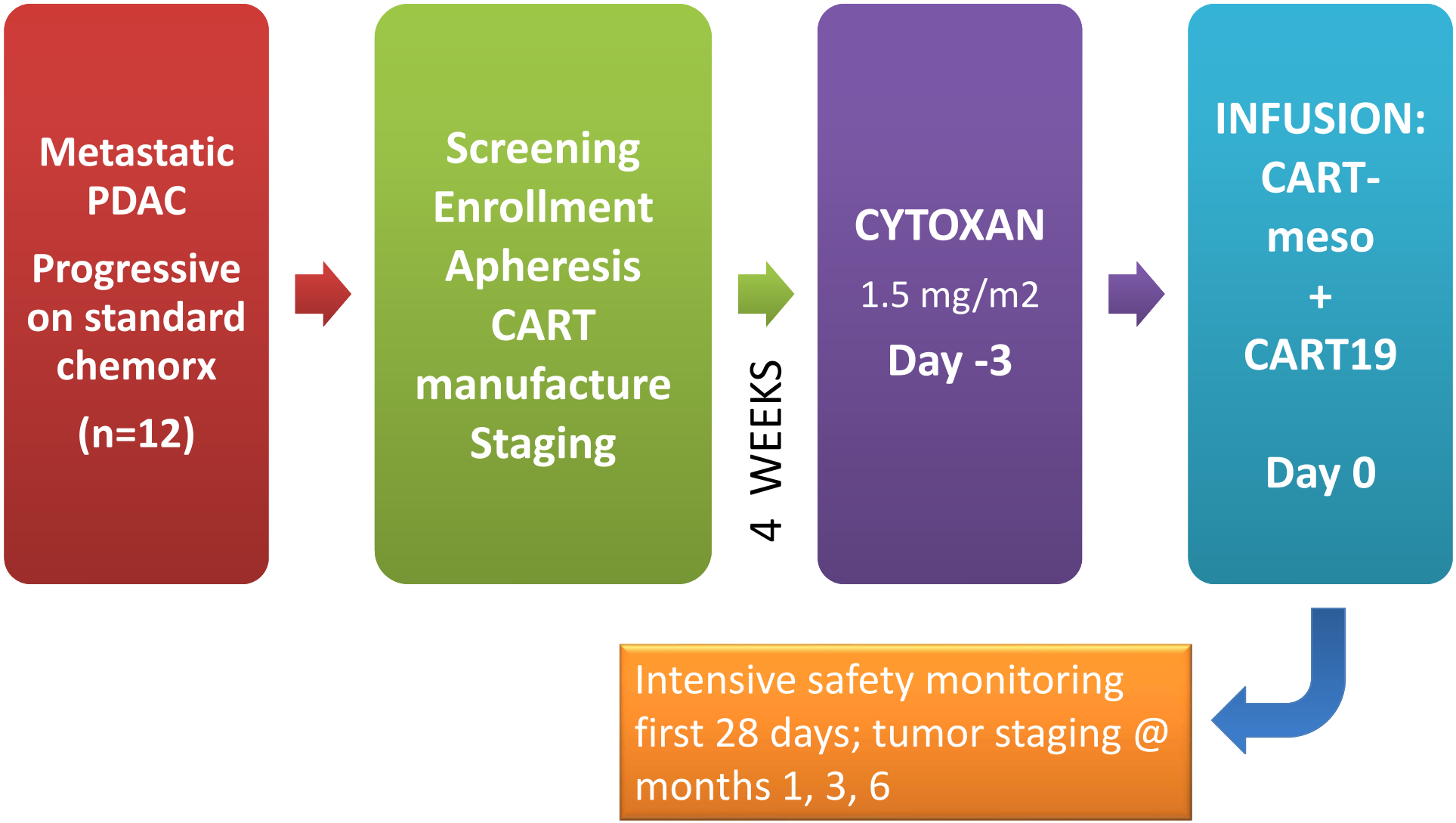
Courtesy of J. Lee.

Title: Pilot Study of Autologous T-cells Redirected to Mesothelin and CD19 with a Chimeric Antigen Receptor in Patients with Metastatic Pancreatic Cancer



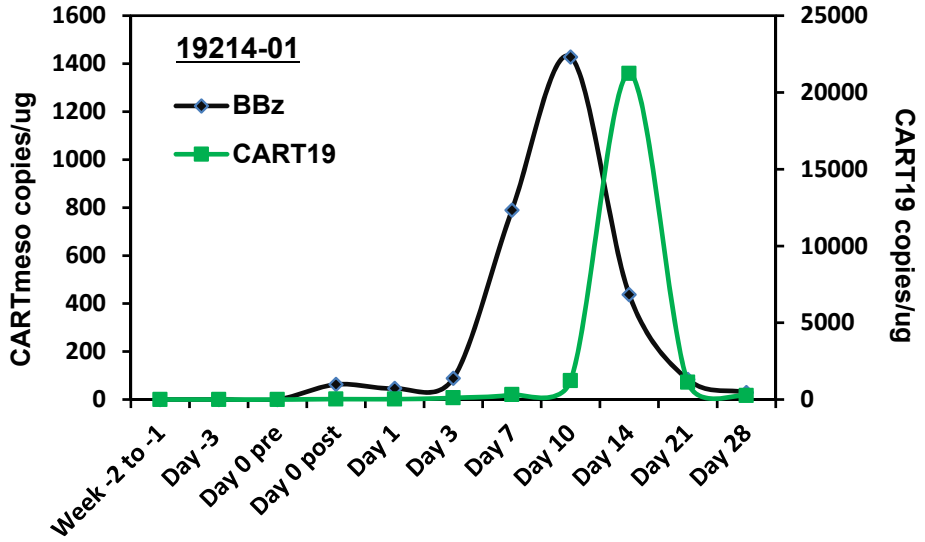
UCSF/U Penn collaboration; P.I., A. Ko.

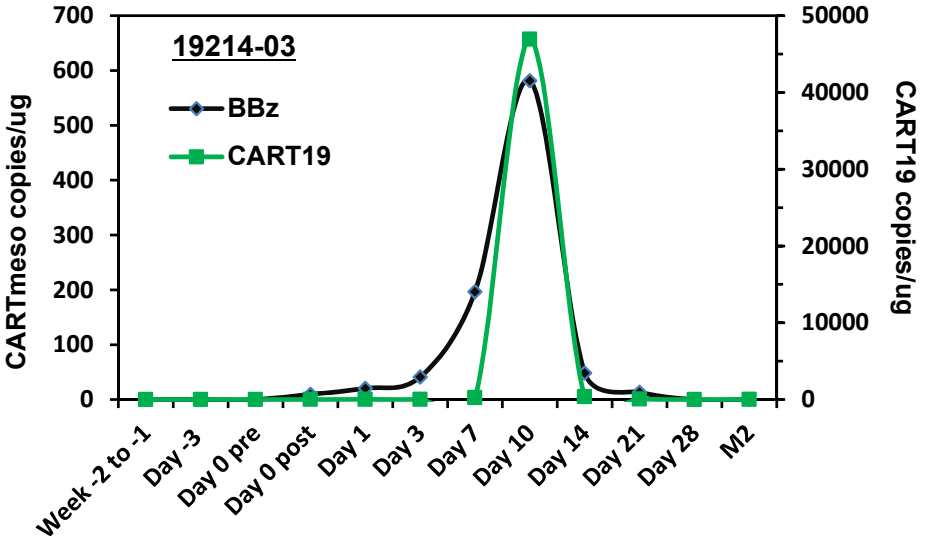
CAR-T protocol study schema

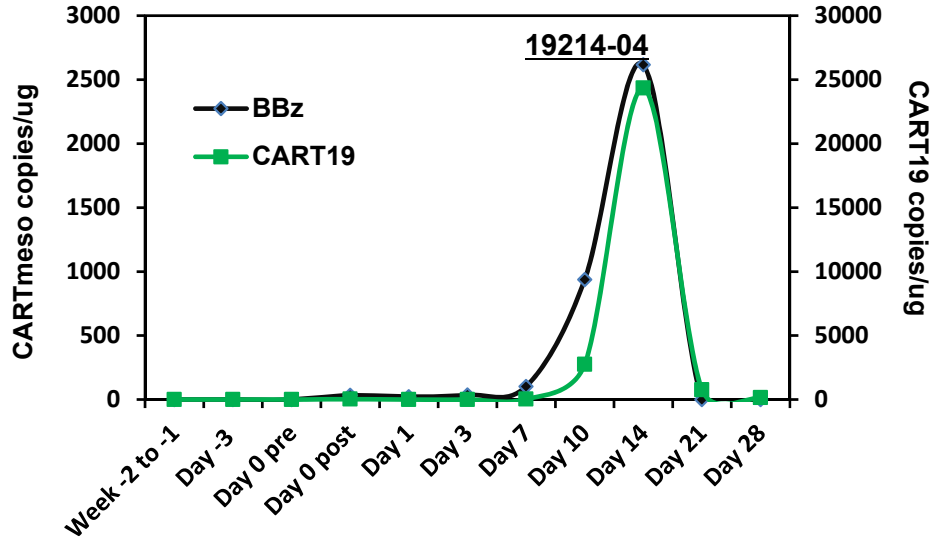


CART Expansion and Persistence in Blood

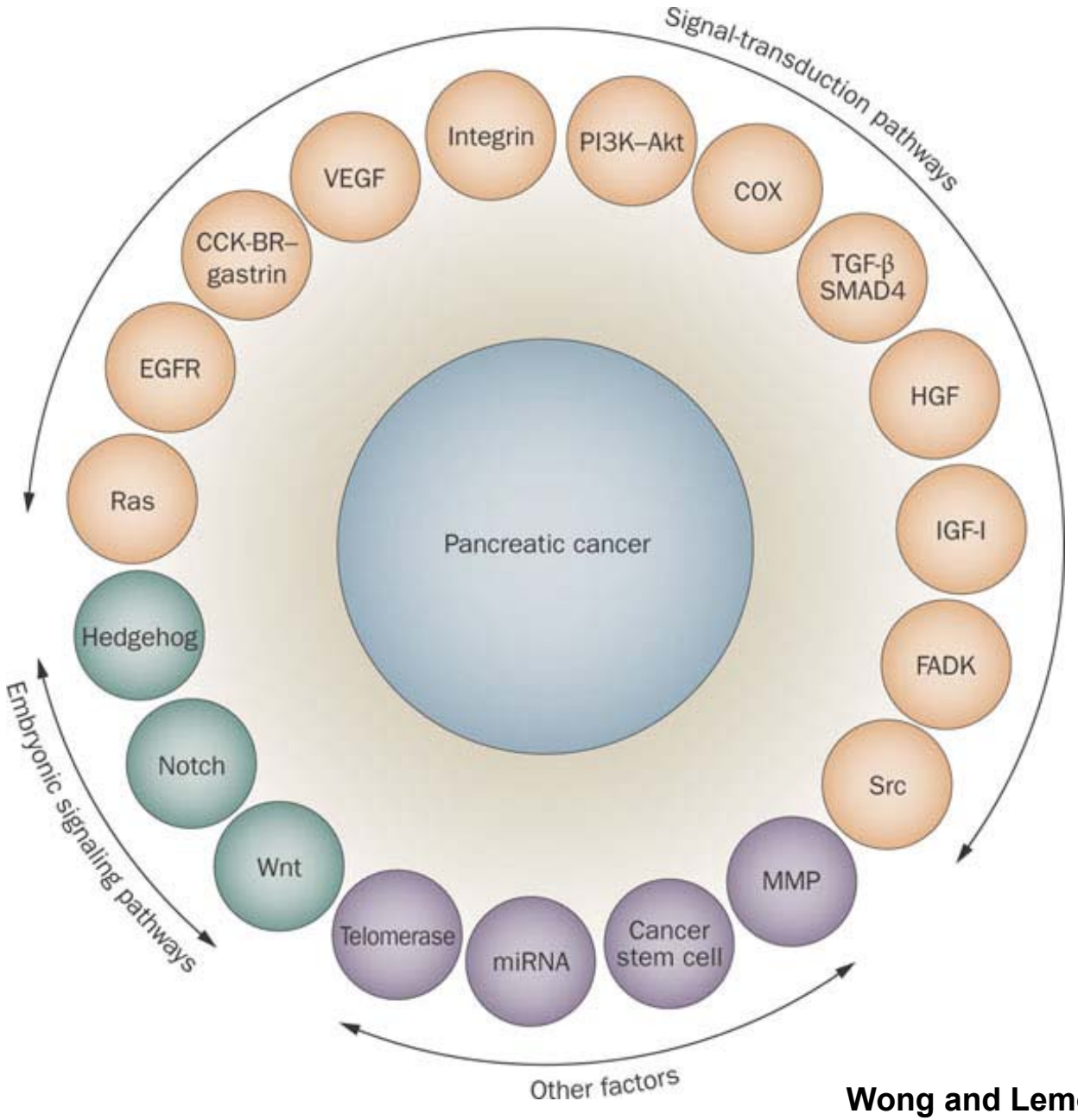
SS1.BBz and huCD19 Q-PCR







Halted enrollment after first 3 treated pts due to lack of persistence of CART cells and no clinical activity; planning development of successor study using fully humanized CART construct



Finally:

Can we validate any therapeutic targets and identify predictive biomarkers in pancreatic cancer?

Wong and Lemoine, *Nat Rev Gastro Hepatol*, 2009

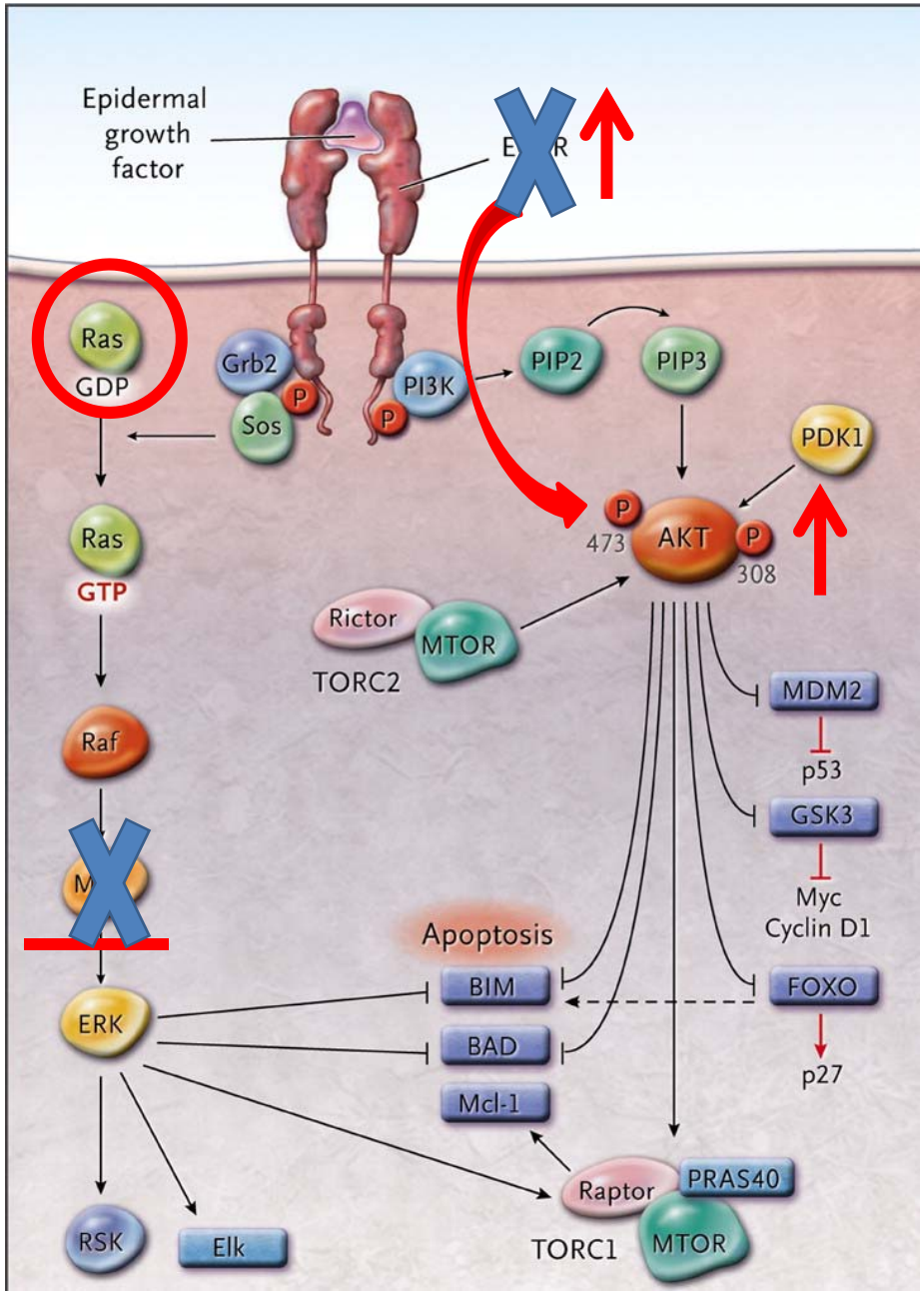
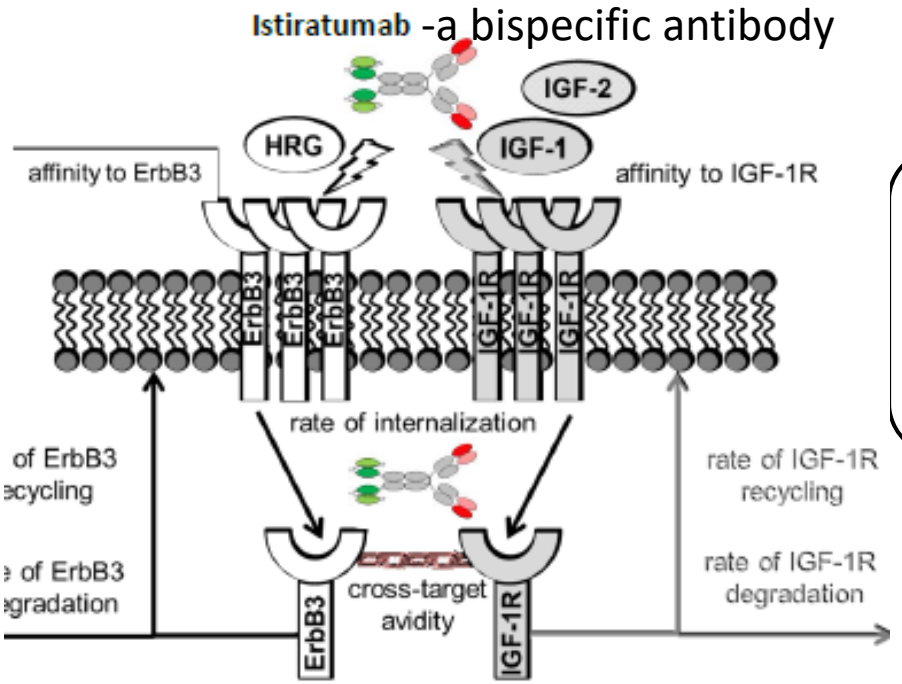


Figure adapted from DB Ryan, *N Eng J Med* 2010

- **K-Ras: is it truly "undruggable" (using competitive allosteric inhibitors)?**
- **"Whack-a-mole" – what happens when we go after a single target in pancreatic cancer?**
- **Combined blockade of multiple signaling nodes, e.g. dual MEK/EGFR inhibition** (AH Ko, *Clin Cancer Res* 2016)
  - 19/46 pts (41%) with S.D. > 6 weeks
  - Rate-limiting GI/skin toxicity in many pts

Randomized phase 2 study (CARRIE) of istiratumab for metastatic pancreatic cancer



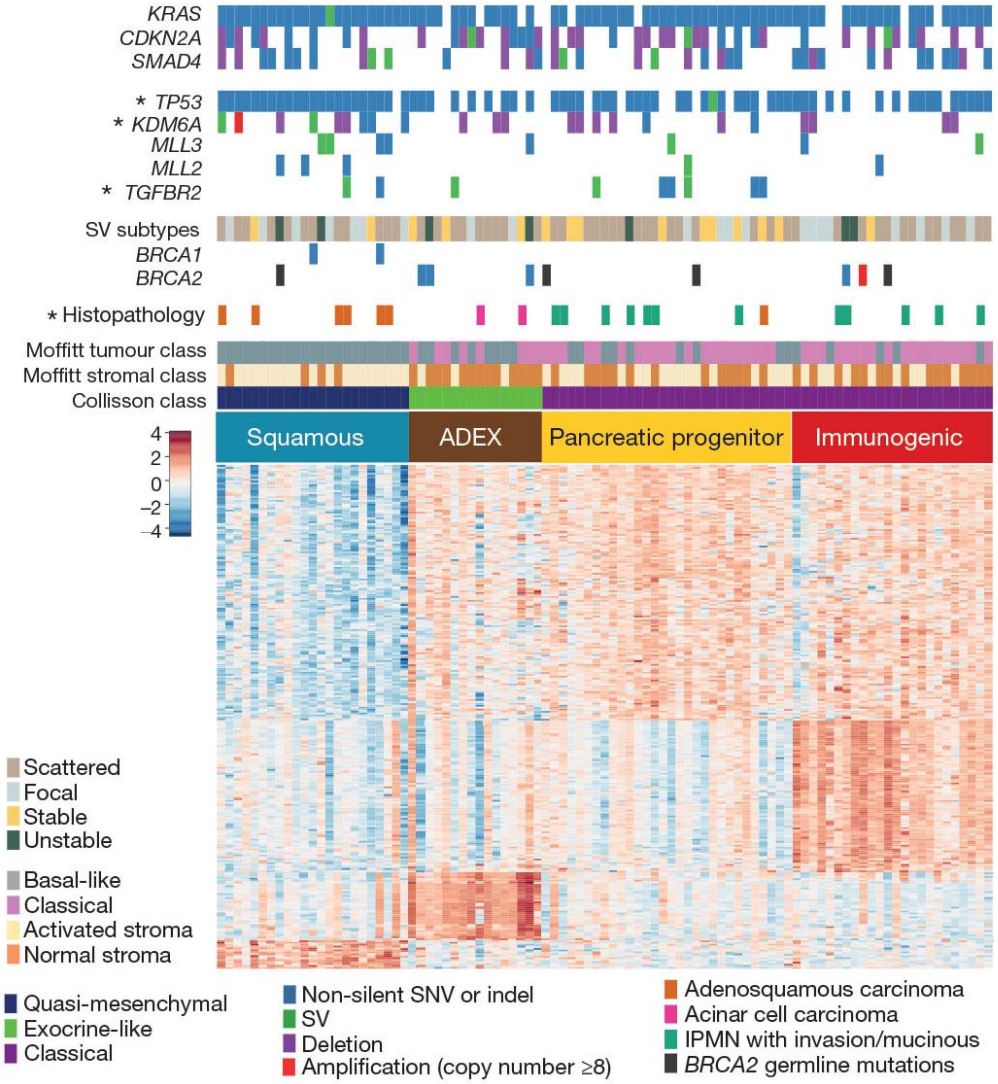
Metastatic PC
High serum free IGF-1 level
Screen 260 --> 146 eligible subjects

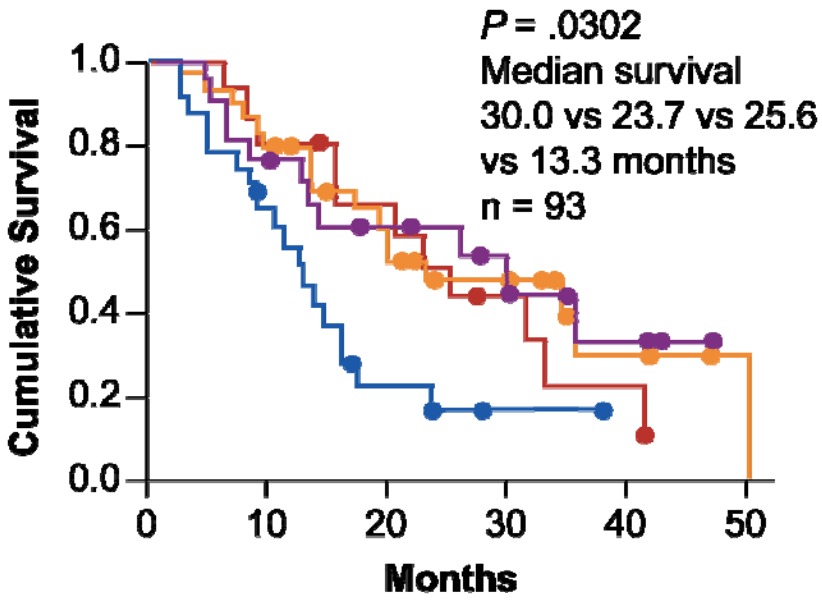
Istiratumab + nab-paclitaxel + gemcitabine

Placebo + nab-paclitaxel + gemcitabine

AH Ko, GI ASCO 2016; https://clinicaltrials.gov/ct2/show/NCT02399137. Accessed May 20, 2016.

Genomic analyses identify molecular subtypes of pancreatic cancer: Potential therapeutic implications?

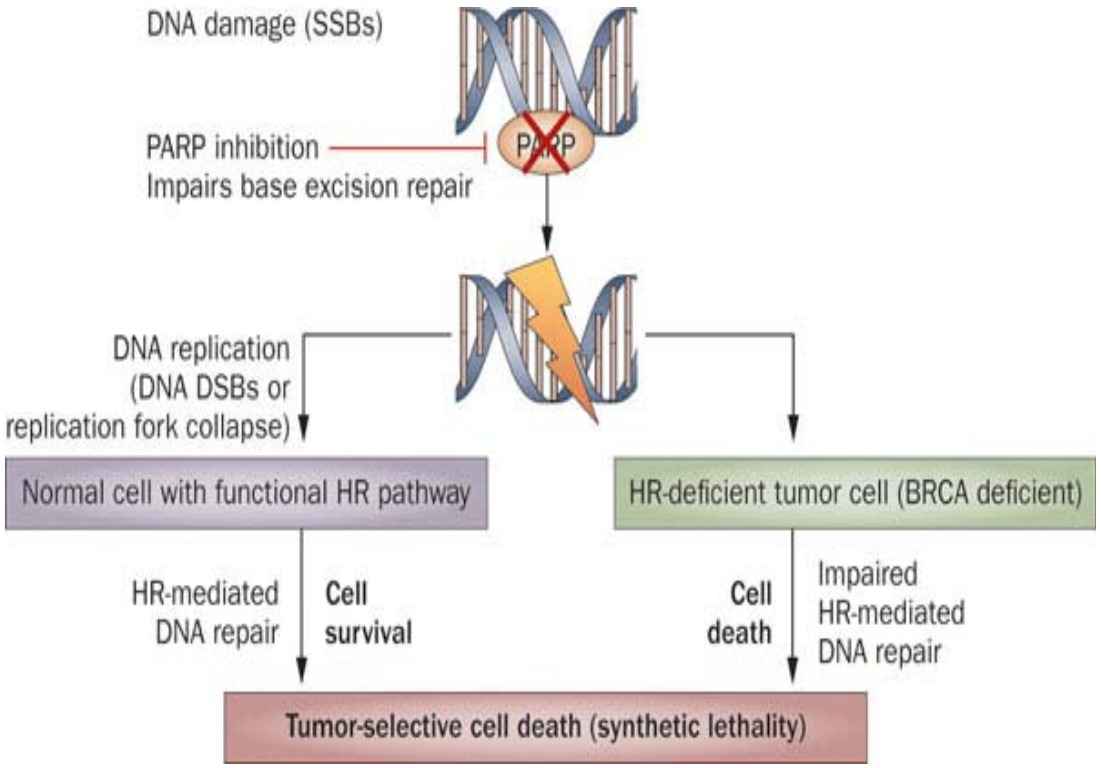




Bailey P et al. *Nature*. 2016;531:47-52.

PARP inhibitors in pancreatic cancer

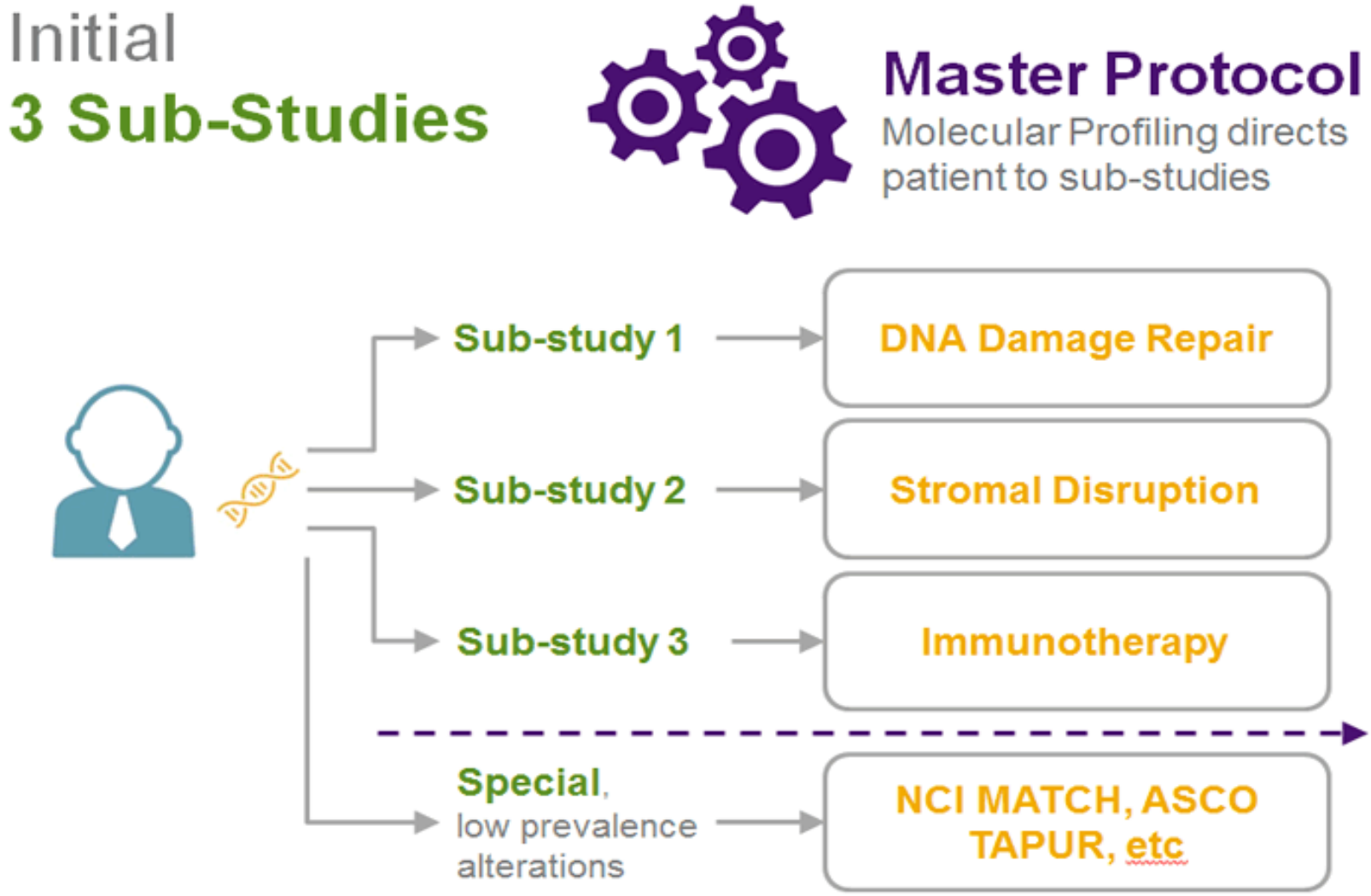
- Phase II trial of olaparib in patients with germline BRCA1/2 mutations and advanced solid tumors
  - Objective responses observed in **5 of 23 (21.7%)** patients with pancreatic cancer



- **POLO trial**: Placebo-controlled phase III trial of olaparib as maintenance rx (in pts w/germline BRCA-1/2-associated pancreatic cancer)

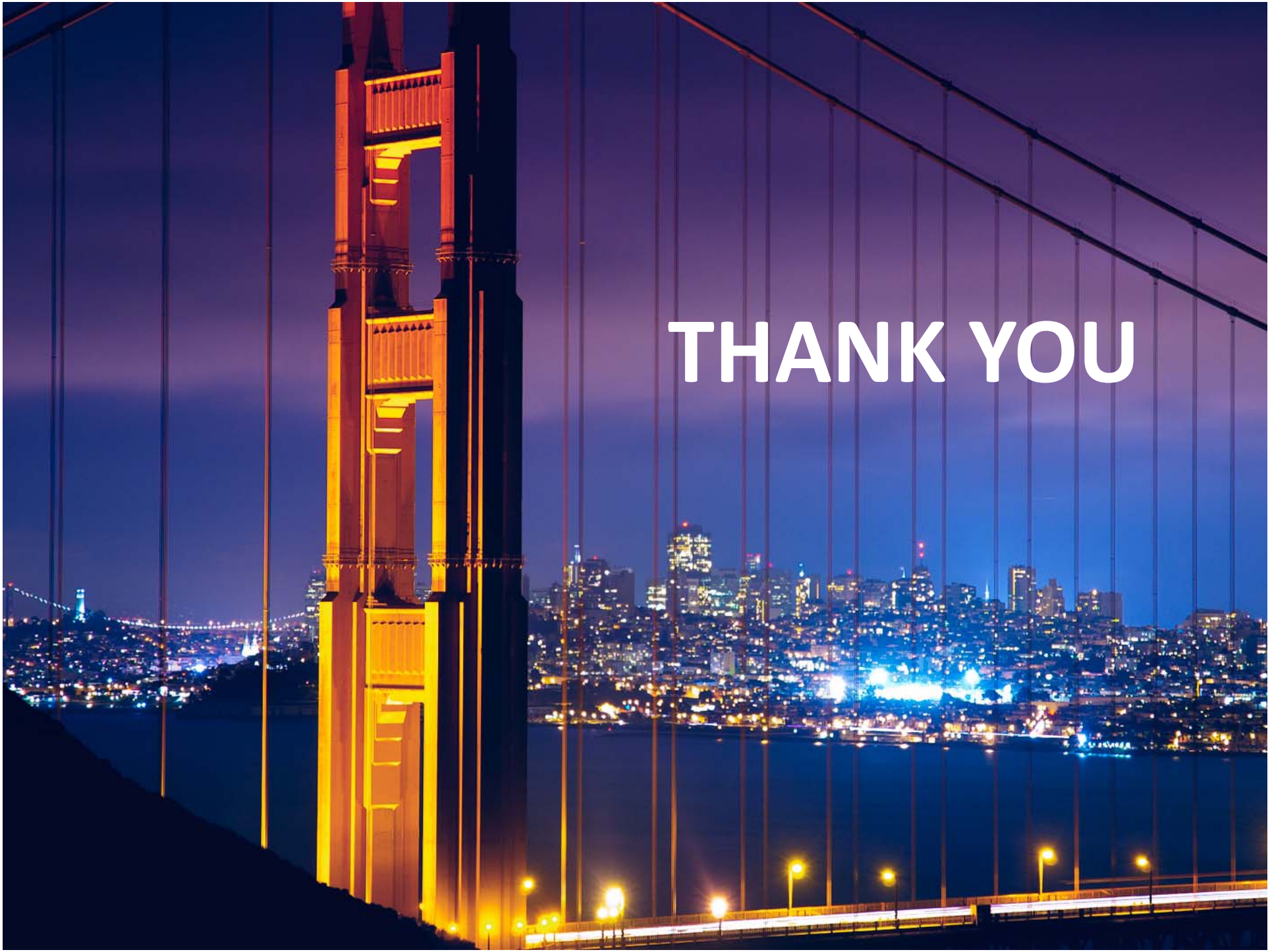
Kaufman B, et al. *J Clin Oncol*. 2015;33(3):244-50.
Kindler HL, et al. *J Clin Oncol*. 2015;33(suppl; abstr TPS4149).

PRECISION PROMISE (sponsored by Pancreatic Cancer Action Network) -- $35M initial investment



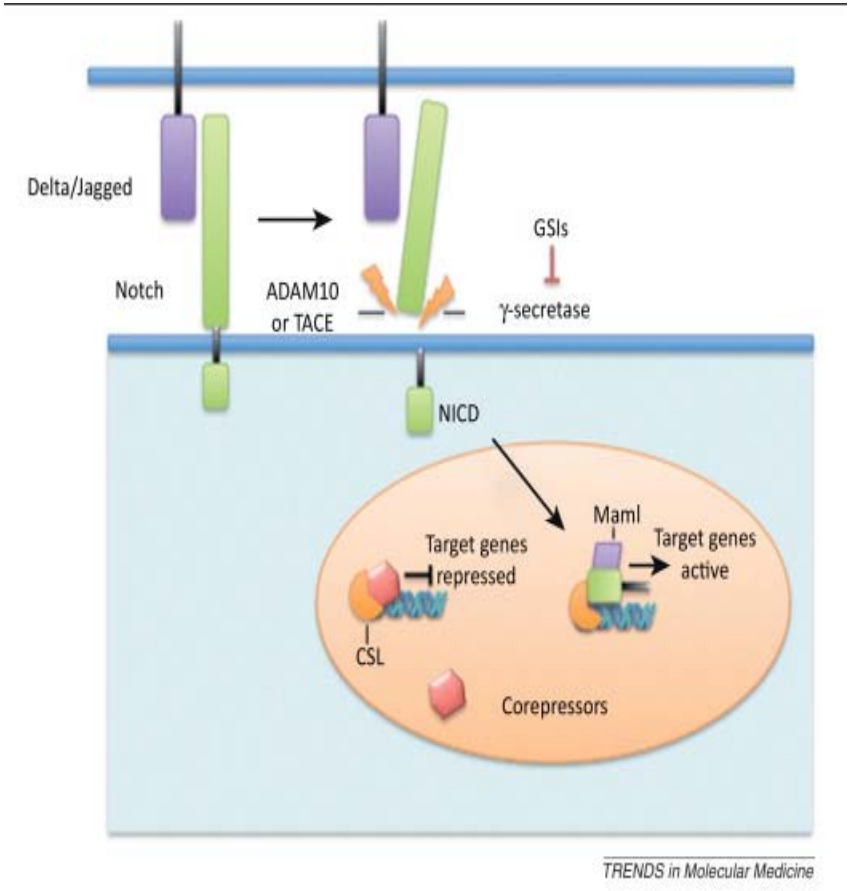
Conclusions

- **Cytotoxic agents remain the mainstay of treatment for advanced pancreatic cancer**
  - On a positive note: We are now able to offer more patients with metastatic pancreatic cancer multiple lines of therapy
- **Stromal microenvironment plays an important role in pancreatic tumor biology**
  - A variety of therapeutic strategies to modify/target the this stromal compartment are currently under investigation
- **Immune-based strategies have thus far shown only modest efficacy**
  - Novel combination approaches are needed
- **Identification of predictive biomarkers and actionable therapeutic targets are elusive, but remain a high priority**


THANK YOU

EXTRA SLIDES

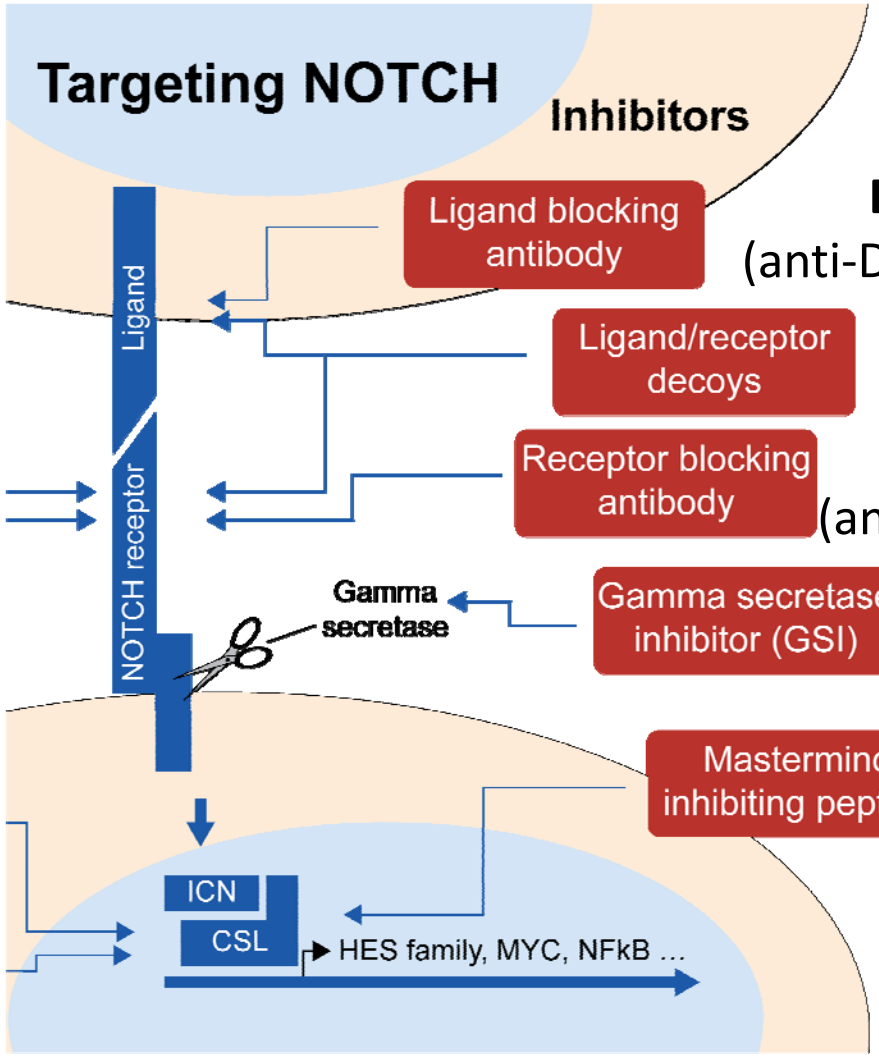
Notch signaling and pancreatic cancer



Avila and Kissel, Trends in Mol Medicine, 19:320-27.

- Mediates cell-to-cell communication in organ development, including pancreas
- Important in:
  - **Maintenance of stem cell populations**
  - Determination of cell fate decisions
  - Regulation of proliferation/apoptosis
  - Precursor lesion development (PanINs, etc.)
- Evidence for both oncogenic and tumor suppressive functions, depending on cellular context
- Functional interaction between Notch and Ras

Inhibitors of Notch signaling



Demcizumab
(anti-DLL4, OMP-21M18)

Tarextumab
(anti-Notch2/3, OMP-59R5)

1. Tejada FNH et al. *Front Pediatr*. 2014;2:54. doi:10.3389/fped.2014.00054.

Tarextumab and Demcizumab Trials

	ALPINE Trial[1] (Tarextumab)	YOSEMITE Trial[2] (Demcizumab)
Phase of study	Phase 1b/ randomized phase 2	Phase 1b/ randomized phase 2
Indication	First-line	First-line
Chemotherapy backbone	Gemcitabine/ nab-paclitaxel	Gemcitabine/ nab-paclitaxel
Planned sample size	154	201
Primary endpoint	PFS	

Closed in Jan 2016 after interim analysis indicated strong trend to lack of benefit

1. https://clinicaltrials.gov/ct2/show/NCT01647828. Access
2. https://clinicaltrials.gov/ct2/show/NCT02289898. Accessed May 20, 2016.