2018 World Pancreatic Cancer Coalition Meeting
Scientific Session and Panel Discussion
May 9, 2018

WORLD
PANCREATIC
CANCER
COALITION

Where We Began

- According to the WPCC Survey, the first organizations dedicated completely to pancreatic cancer were founded in 1997.
  - The Hirshberg Foundation for Pancreatic Cancer Research
  - The National Pancreas Foundation
- In 1999, pancreatic cancer received $17.3 million in government funding in the United States through the National Cancer Institute (NCI), which was less than half of 1% of its total budget.
- In 2000, the NCI convened a Progress Review Group on Pancreatic Cancer to set an agenda for pancreatic cancer research.

Where We Began Continued

- A report was released in 2001 which stated:
  - Pancreatic cancer is disproportionately underrepresented in both clinical and basic research compared to other cancer sites.
  - The pancreatic cancer research community is encouraged by the comprehensive and effective way that HIV/AIDS has been addressed in America. New dollars poured in to encourage investigators and institutions to create infrastructure and launch new research initiatives. Consequently, transmission and death rates decreased markedly.

Where We Are Now

- Twenty years later, of the 70+ organizations in the WPCC, there are more than 30 organizations funding pc research.

- **These groups have invested approximately $240 million in pancreatic cancer research.**

  ✓Research is starting to make an impact.

  ✓There are more options for patients.

  ✓Patients are living longer with a better quality of life.

  ✓**Breakthroughs are finally happening.**

The Lustgarten Foundation

- Founded in 1998.
- Our mission is to advance the scientific and medical research related to the diagnosis, treatment, cure and prevention of pancreatic cancer.
- Since inception, invested more than **$154 million** in research.
- Will commit an additional $25 million+ in research in 2018.
- 100% of every dollar raised goes directly to pancreatic cancer research.
- **Affiliated with Let's Win! Pancreatic Cancer Foundation**, a platform that enables patients, doctors, and researchers to share fast-breaking information on potentially life-saving pancreatic cancer treatments and trials.

The Pancreatic Cancer Collective

- Since 2012, the Lustgarten Foundation and Stand Up To Cancer (SU2C) have funded more than 170 investigators across 28 leading research centers in both the United States and United Kingdom.

- These collaborative teams have planned, started or completed **22 clinical trials**.

- The **Pancreatic Cancer Collective (pancreaticcancercollective.org)** launched in April 2018 to accelerate research for pancreatic cancer patients who desperately need better treatments:
  1) Inspire collaboration among people who haven't worked together
  2) Spread funding to new centers
  3) Leverage artificial intelligence approaches
  4) Find new treatments for pancreatic cancer
  5) Utilize the breadth and expertise of existing Lustgarten – SU2C teams and researchers

Breakthroughs

- **Immunology** – Keytruda® for MMRD patients
- **Early Detection** – CancerSeek
- **Personalized Medicine** -- Organoids and DNA Sequencing
- **Surgical Intervention** -- Taking More Patients to Surgery/ RO Resections

Keytruda

KEYTRUDA® (pembrolizumab) Injection 100 mg

- The FDA approved **Keytruda®** as the **first immunotherapy treatment** for advanced pancreatic cancer patients whose tumors are mismatch repair deficient. This deficiency alters their capacity to repair DNA, which is a factor in cancer development.

- It is estimated that approximately 1 in 50 advanced pancreatic cancer patients have tumors that are mismatch repair deficient, making them candidates for this type of therapy.

- Doctors hope this will be a cure for this small subset of patients.

Dr. Bert Vogelstein, Johns Hopkins and Dr. Luis Diaz, MSKCC

CancerSEEK

- A blood test that can detect the presence of pancreatic cancer as part of a panel of eight common cancers. Five of these cancers have no screening test.
- The test was done in patients with pancreatic cancer, mostly stage 2 pancreatic cancer. It needs to now be validated in patients without known cancer.
- The sensitivity of the detection method in pc was 72%.
  - Sensitivity is the ability of a test to correctly identify those with the disease (true positive).
- The specificity was greater than 99%.
  - Specificity is the ability of the test to correctly identify those without the disease (true negative).

This study lays the foundation for a single blood screening test for multiple cancers that could be offered as part of routine medical checks.

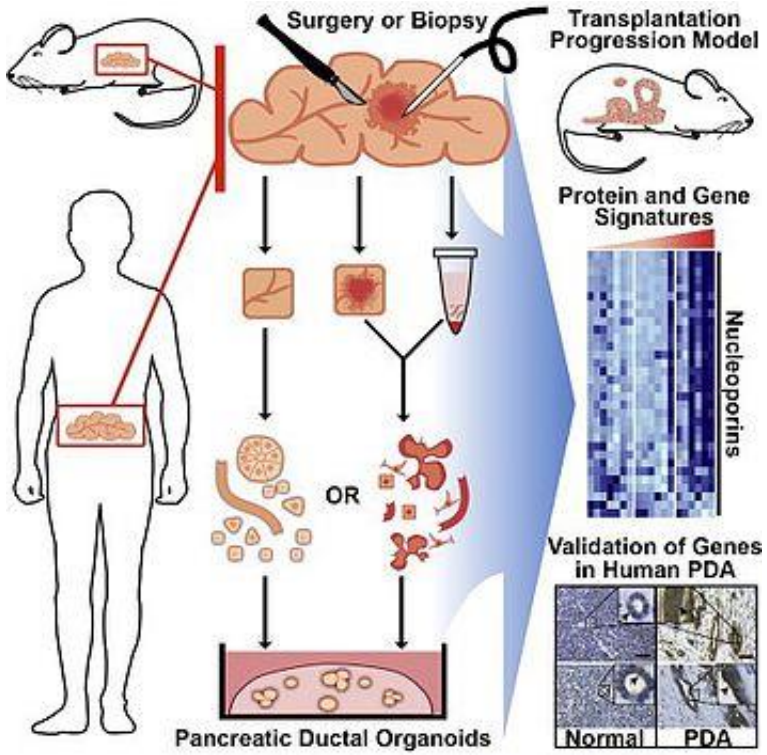
Dr. Bert Vogelstein, Johns Hopkins

Personalized Medicine

- **Personalized Medicine** is a type of medical care in which treatment is customized for an individual patient.

- Scientists and clinicians are using **organoids** and **DNA sequencing** to create personalized medicine for patients.

Organoids – A Key Tool in Personalized Medicine



- An organoid is a three-dimensional culture system that mimics organ structure and function.
- The organoids are derived from the pancreas of patients that undergo resection or biopsy of the pancreatic cancer.
- Organoids are used to test drug response with the aim of identifying the most effective treatment for each individual patient and potentially finding effective treatments in subsets of patients with specific similar mutations.

Dr. David Tuveson, Lustgarten Foundation Dedicated Lab, CSHL, NY

Organoid Profiling Identifies Common Responders to Chemotherapy in Pancreatic Cancer

- Current treatment selection for pancreatic cancer patients is often based on patient performance status. There is an unmet clinical need to define responsive subgroups to the 2 standards of care used now to inform treatment selection and to find alternative treatment options for patients who are resistant to the currently approved treatment regimens.

- **Organoids can predict if the patient will be sensitive to standard of care chemotherapy and which one** (Folfirinox vs Gem/Abraxane).

- Organoids resistant to all available options exhibited exceptional sensitivity to different targeted agents, providing alternative treatment options.

Dr. David Tuveson, Lustgarten Foundation Dedicated Lab, CSHL, NY

Personalized Medicine Clinical Application

Sequence of tumor
DNA and inherited
DNA

6-8 wks

Making treatment decision
(may include off label medication)

In 1/3 of patients, Dr. Wolpin finds genetic alterations that can be treated with a therapy that is either in clinical trials or used for another kind of cancer.

Dr. Wolpin also uses organoids to provide opportunities to go beyond DNA sequencing to identify new therapeutic approaches.

Dr. Brian Wolpin, DFCI

Taking More Patients to Surgery with Better Outcomes

- Enabling more patients to have surgery has the potential to dramatically improve long term survival, especially if we can accomplish R0 resections.

- **Almost half** of all pc patients have borderline resectable or locally advanced pc – many of these patients will be told they cannot have surgery.

- A clinical trial is opening for borderline resectable and locally advanced pancreatic cancer patients comparing those who receive neoadjuvant **chemotherapy vs. chemotherapy and losartan (a medication used for high blood pressure that is thought to open up the blood vessels) or chemotherapy, losartan and an immunotherapy followed by SBRT and surgery.**

- Initial data from this work show impressive increases in both the number of patients able to have surgery and improved outcomes for those patients who received treatment before surgery.

- The goal is an RO resection rate of greater than 65%.

Dr. David Ryan, Mass General Hospital

Advances are Happening!

Welcome Today's Scientific Panel

- **Brian Wolpin**, MD, MPH, Medical Oncologist and Translational Scientist at Dana-Farber Cancer Institute and Harvard Medical School
- **Allyson J. Ocean**, MD, Associate Professor of Clinical Medicine, Weill Cornell Medical College
- **Gayle Jameson**, MSN, ACNP-BC, AOCN Nurse Practitioner and Associate Clinical Investigator at HonorHealth Research Institute

Advances in the Prevention and Early Detection of Pancreatic Cancer

World Pancreatic Cancer Coalition Meeting

Brian M. Wolpin, MD, MPH
Dana-Farber Cancer Institute
Brigham and Women's Hospital
Harvard Medical School

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DANA-FARBER
CANCER INSTITUTE

Disclosures

- Research funding from:

CURE PANCREATIC CANCER
LUSTGARTEN FOUNDATION

DANA-FARBER CANCER INSTITUTE

Hale Center for Pancreatic Cancer Research

PANCREATIC CANCER ACTION NETWORK

STAND UP TO CANCER™

Celgene

NATIONAL® CANCER INSTITUTE

Reduce Mortality

- Prevention
- Screening and Early Detection
- Smarter and Better Therapies

Presentation and Prognosis

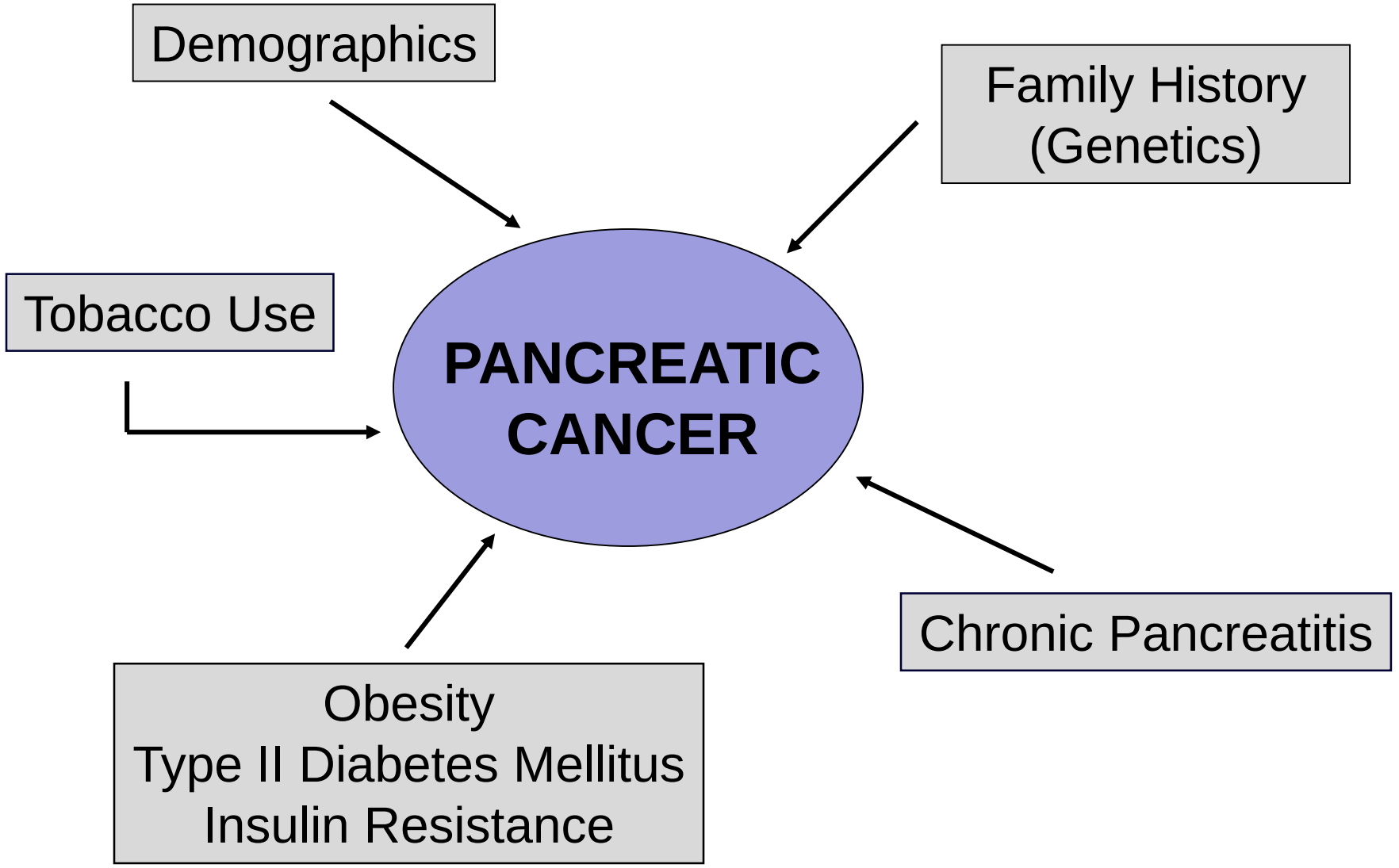
Stage	Presentation	Median OS	5-Year OS
Resectable local	15 – 20%	18 – 24 mo.	15 – 20%
Locally advanced	30 – 35%	10 – 12 mo.	< 5%
Metastatic	50 – 55%	6 – 8 mo.	0%

~80%

Early Detection Research

- Risk prediction models
- Blood tests
- Pancreatic juice, cystic fluid, and portal vein testing
- Imaging studies
- Machine learning approaches to detection

Predisposing Factors



Risk Models in Prospective Cohorts

	Base Model	+ Genetic Risk Score	+ Circulating Markers
Covariates	BMI Waist-hip ratio Physical activity Diabetes history Race/ethnicity Periodontal dz		
		wGRS	
			HbA1c Proinsulin IGFBP-1 Adiponectin 25(OH)D Interleukin-6 Total BCAAs
LR *P*-value	--	1.0×10^{-12}	4.0×10^{-4}
ROC AUC	0.596	0.660	0.692
% controls w ≥3-fold average risk	0	0.45	0.98

Pete Kraft (HSPH)
Jihye Kim

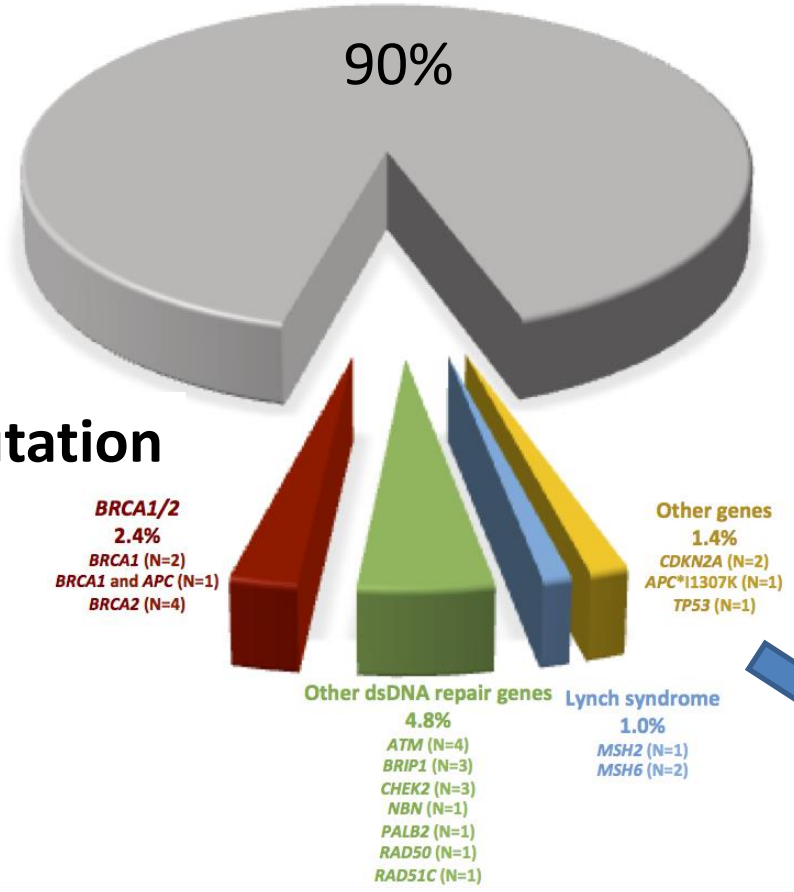
Chen Yuan (DFCI)
Ana Babic

Pari Pandharipande (MGH)

N=1,488
462 cases
1026 controls

Identify Inherited Mutations

No germline mutation



Germline mutation

~10%

300 pts with resected pancreatic cancer from Dana-Farber, Univ. of Rochester, and Stanford Univ.

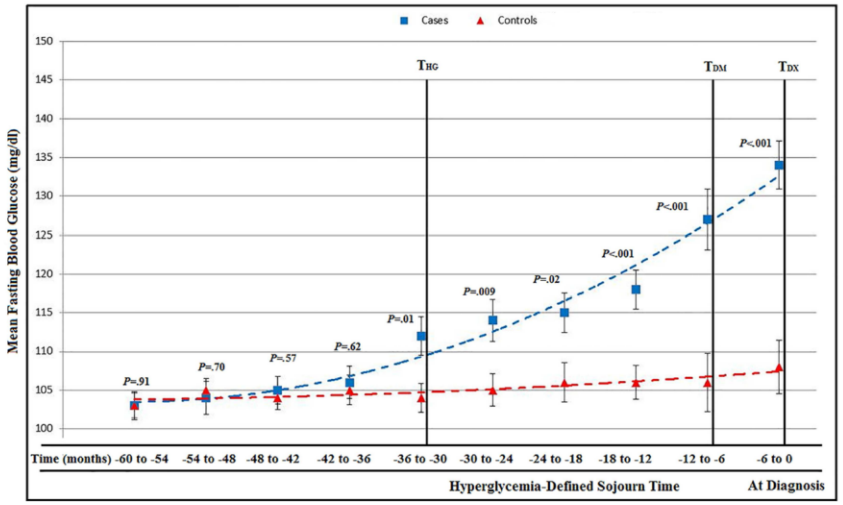
Cascade Testing

Yurgelun et al. *Genet Med* 2018;In press.

Interventions

- Prevention
  - Smoking cessation
  - Weight control
  - Diet and exercise
  - Chemoprevention studies
- Screening and Early Detection
  - Circulating biomarker studies
  - Screening protocols (e.g., CAPS)
- Smarter and Better Therapies
  - Anti-PD-1 Ab for MSI-H or MMR-D tumors
  - Platinum agents or PARPi for DDR deficient tumors

New Onset Diabetes (NOD) Cohorts



Time (months)	-60 to –54	-54 to –48	-48 to –42	-42 to –36	-36 to –30	-30 to –24	-24 to –18	-18 to –12	-12 to –6	-6 to 0
Cases	81	72	60	61	68	71	69	90	88	159
Controls	106	122	99	125	116	128	86	123	106	123

cases: $y = 0.3561x^2 - 0.6803x + 103.83$; $R^2 = 0.9743$ controls: $y = 0.0341x^2 + 0.025x + 103.75$; $R^2 = 0.7849$ For additional details see Supplementary Table 3

Sharma et al. *Gastroenterology.* 2018; Epub ahead of print.

0.5%-0.85% rate of PDAC over 3 years after diabetes diagnosis

NIH National Institutes of Health

PANCREATIC CANCER ACTION NETWORK

CPDPC Consortium:
Chronic Pancreatitis, Diabetes and Pancreatic Cancer Consortium

pancreatic cancer action

New Onset Diabetes

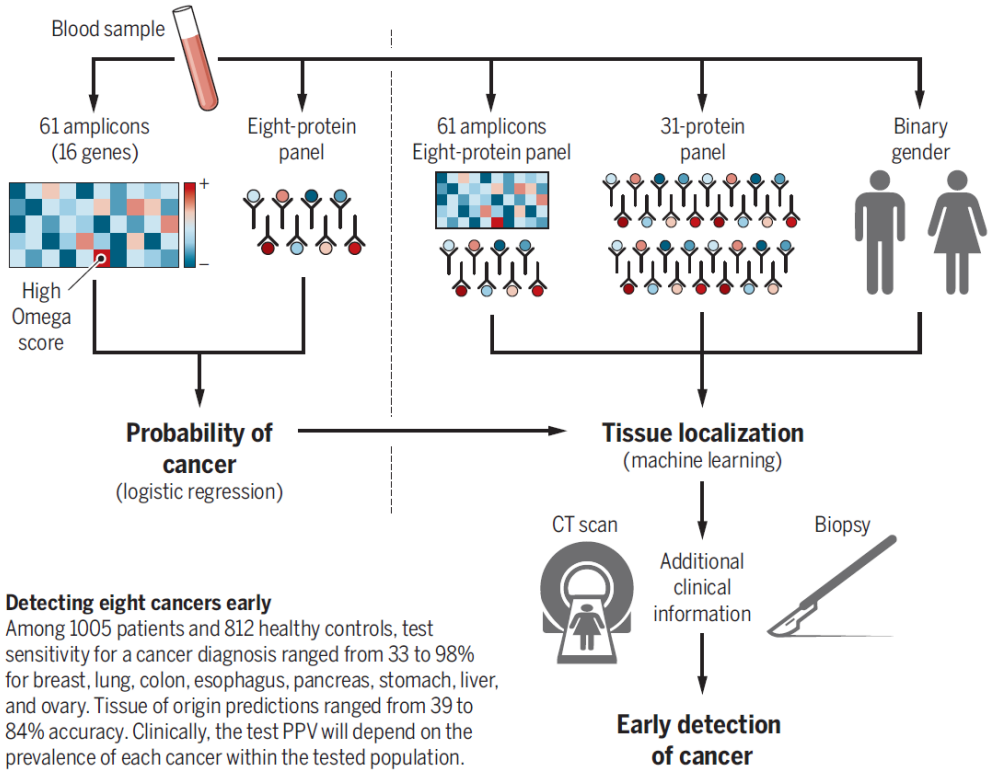
Early Detection Research

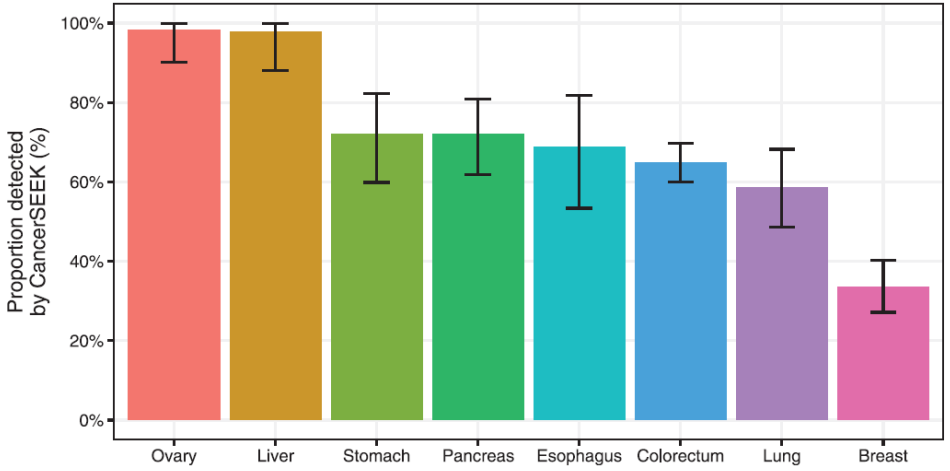
- Risk prediction models
- **Blood tests**
- **Pancreatic juice, cystic fluid, and portal vein testing**
- Imaging studies
- Machine learning approaches to detection

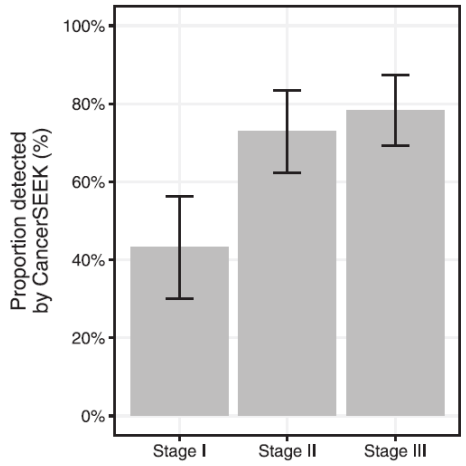
CancerSEEK Blood Test

Cohen et al. *Science*. 2018;359:926-30.
Kalinich et al. *Science*. 2018;359:866-7.

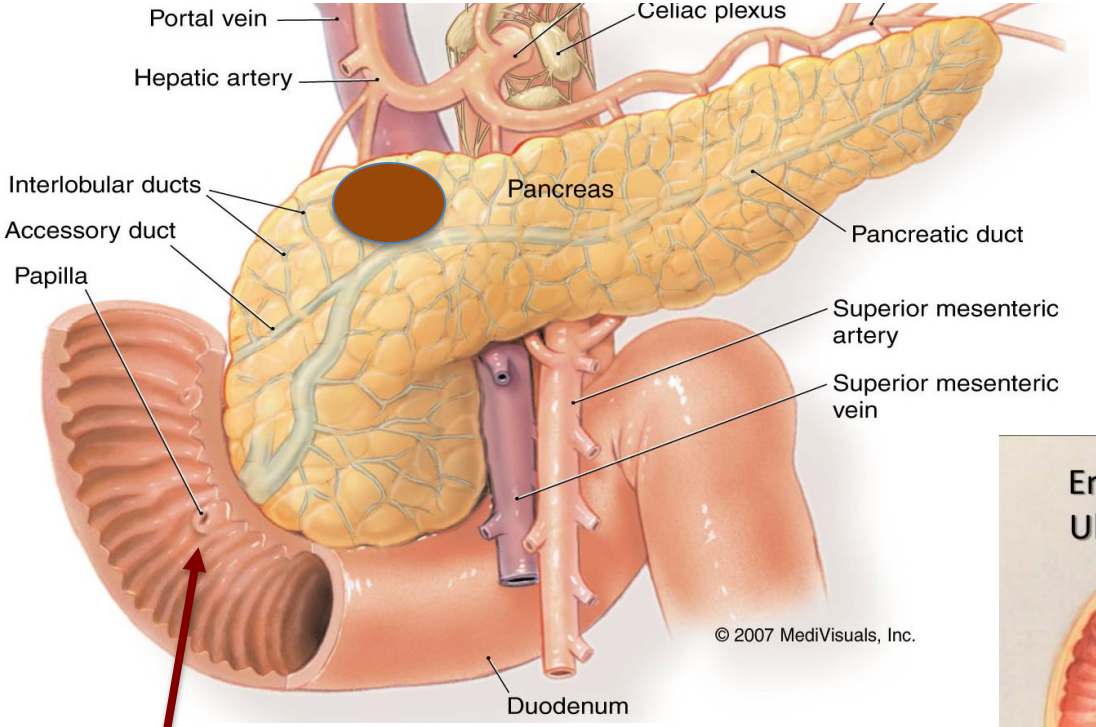
93 patients with pancreatic cancer:
Stage 1: 4 patients
Stage 2: 83 patients
Stage 3: 6 patients



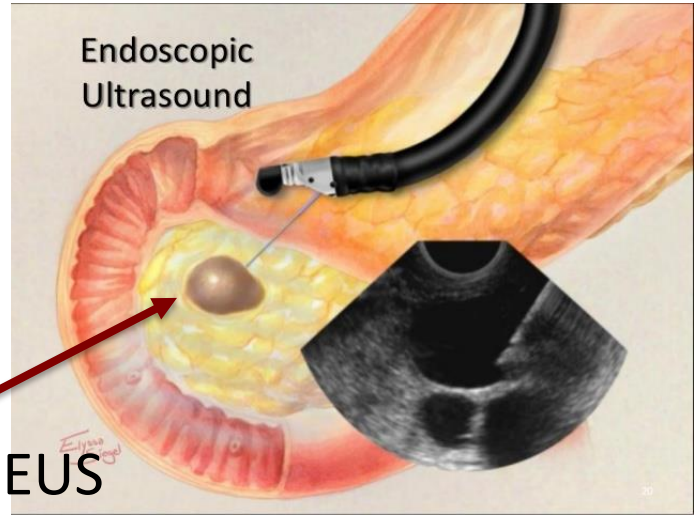




Getting closer to the source: Pancreatic juice and cystic fluid

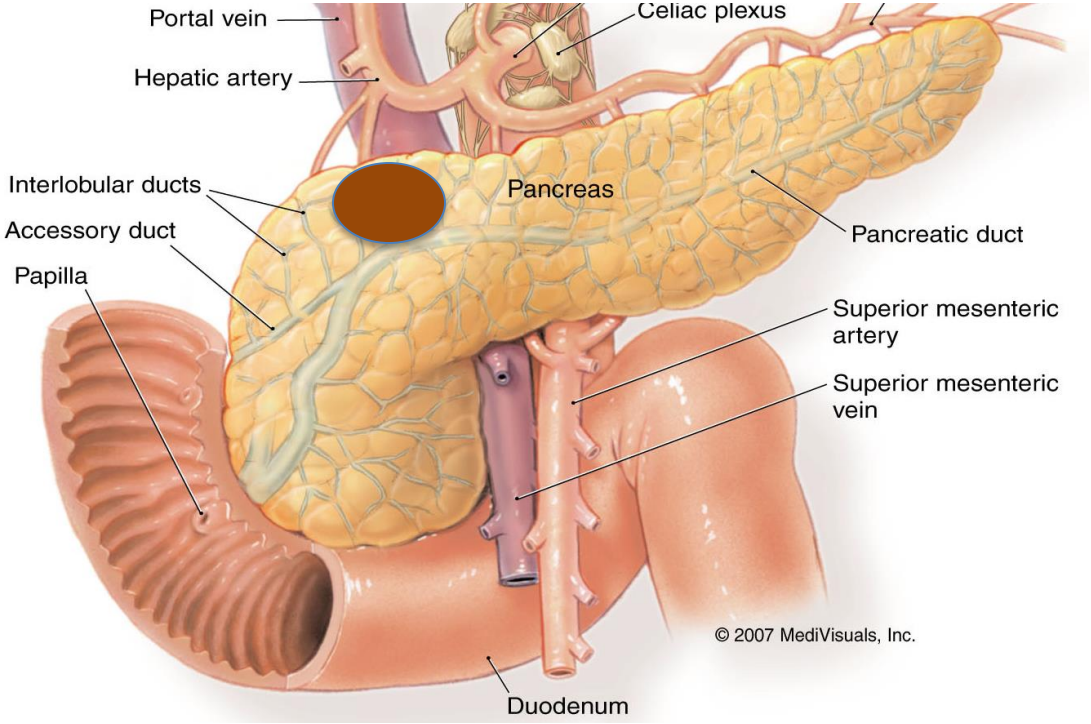


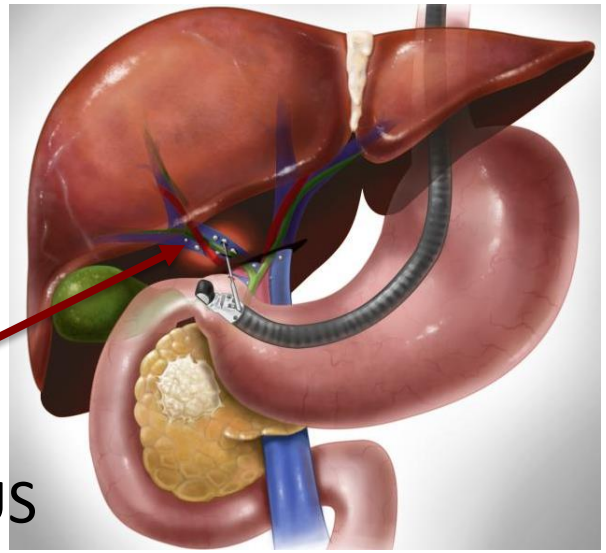
Pancreatic juice by ERCP



Cystic fluid by EUS

Getting closer to the source: Portal vein blood sampling



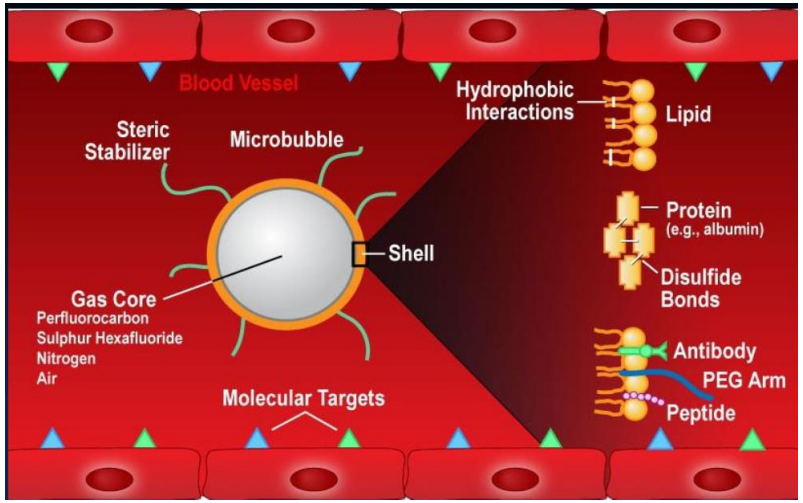


Portal vein blood by EUS

Early Detection Research

- Risk prediction models
- Blood tests
- Pancreatic juice, cystic fluid, and portal vein testing
- **Imaging studies**
- **Machine learning approaches to detection**

New Imaging Approaches



Abou-Elkacem et al. *Eur J Radiol*. 2015;84:1685-93.

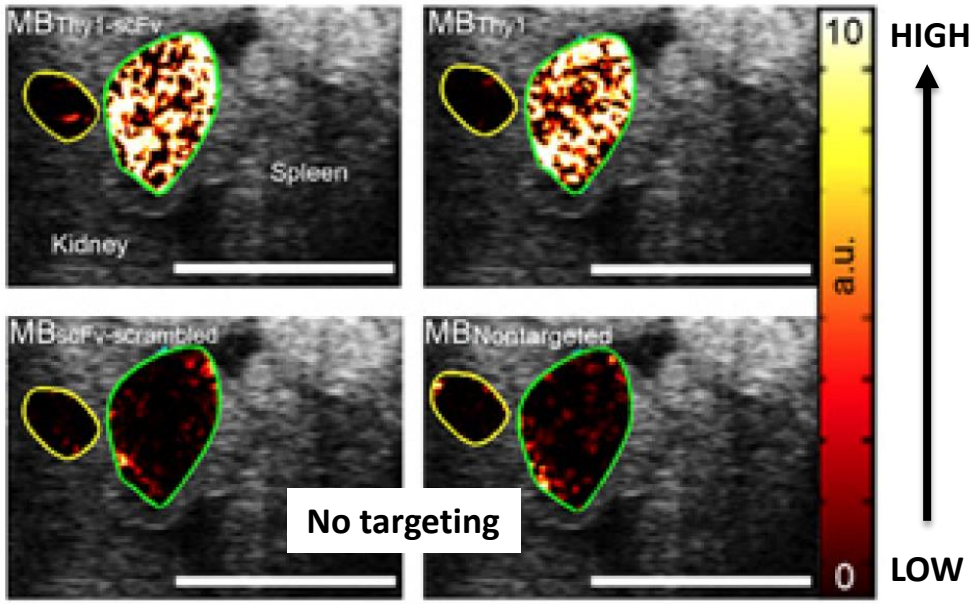
Thy1-Targeted Microbubbles for Ultrasound Molecular Imaging of Pancreatic Ductal Adenocarcinoma

Lotfi Abou-Elkacem[1], Huaijun Wang[1], Sayan M. Chowdhury[1], Richard H. Kimura[1], Sunitha V. Bachawal[1], Sanjiv S. Gambhir[1], Lu Tian[2], and Jürgen K. Willmann[1]

Abou-Elkacem et al. *Clin Cancer Res*. 2018;24:157-85.

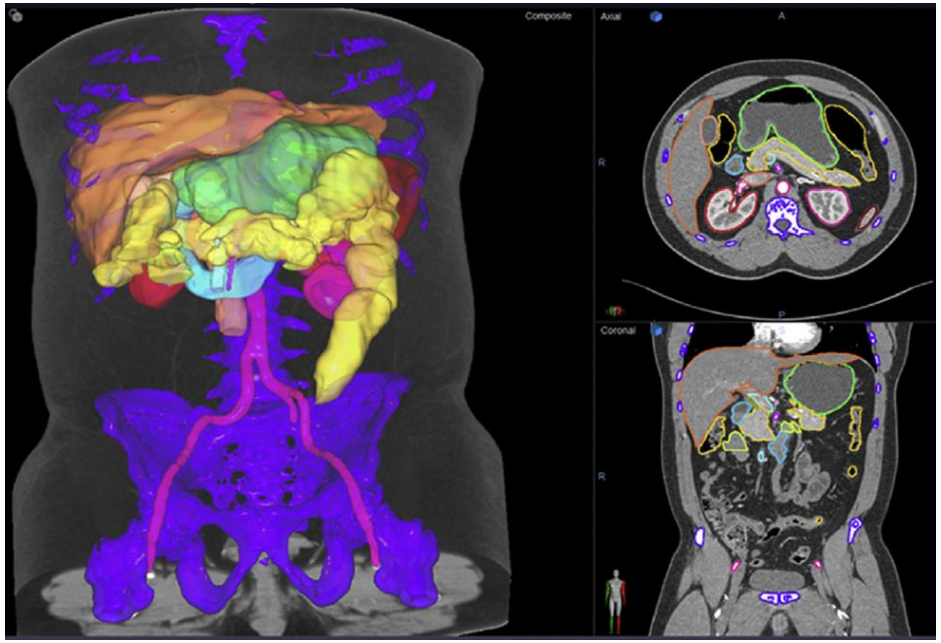
Normal pancreas

Pancreatic Tumor



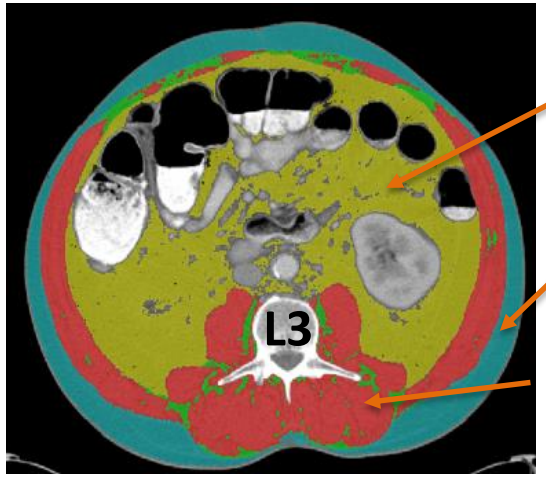
Transgenic mouse models

Harness the learning power of machines



Lugo-Fagundo et al. *Am Coll Radiol*. 2017;15:364-7.

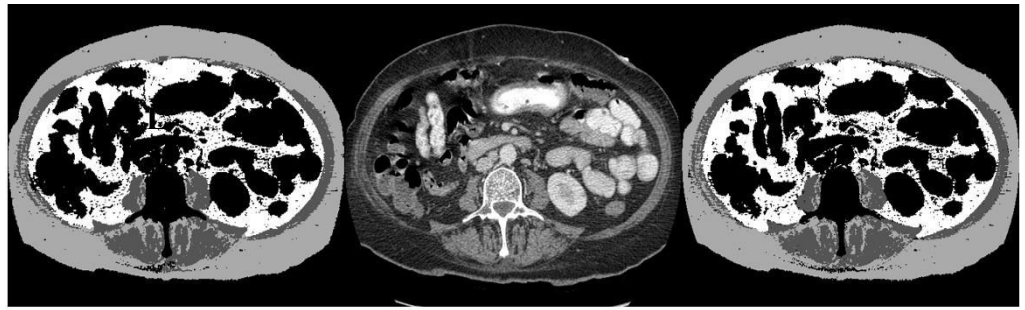
Elliot Fishman, MD



Visceral adipose

Subcutaneous adipose

Skeletal muscle



Automated Segmentation

Input CT Image

Manual Segmentation

Laura Danai, Ana Babic, Michael Rosenthal

Early Detection Research

- Risk prediction models
- Blood tests
- Pancreatic juice, cystic fluid, and portal vein testing
- Imaging studies
- Machine learning approaches to detection

Thank you

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Pancreatic Cancer Treatment Update

Allyson J. Ocean, M.D.
Associate Professor of Clinical Medicine
Weill Cornell Medical College
WPCC Annual Conference
May 8-10, 2018

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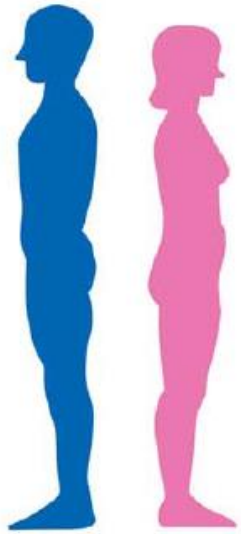
Pancreatic Cancer: The Fourth Leading Cause of Cancer-Related Death in the United States[1]

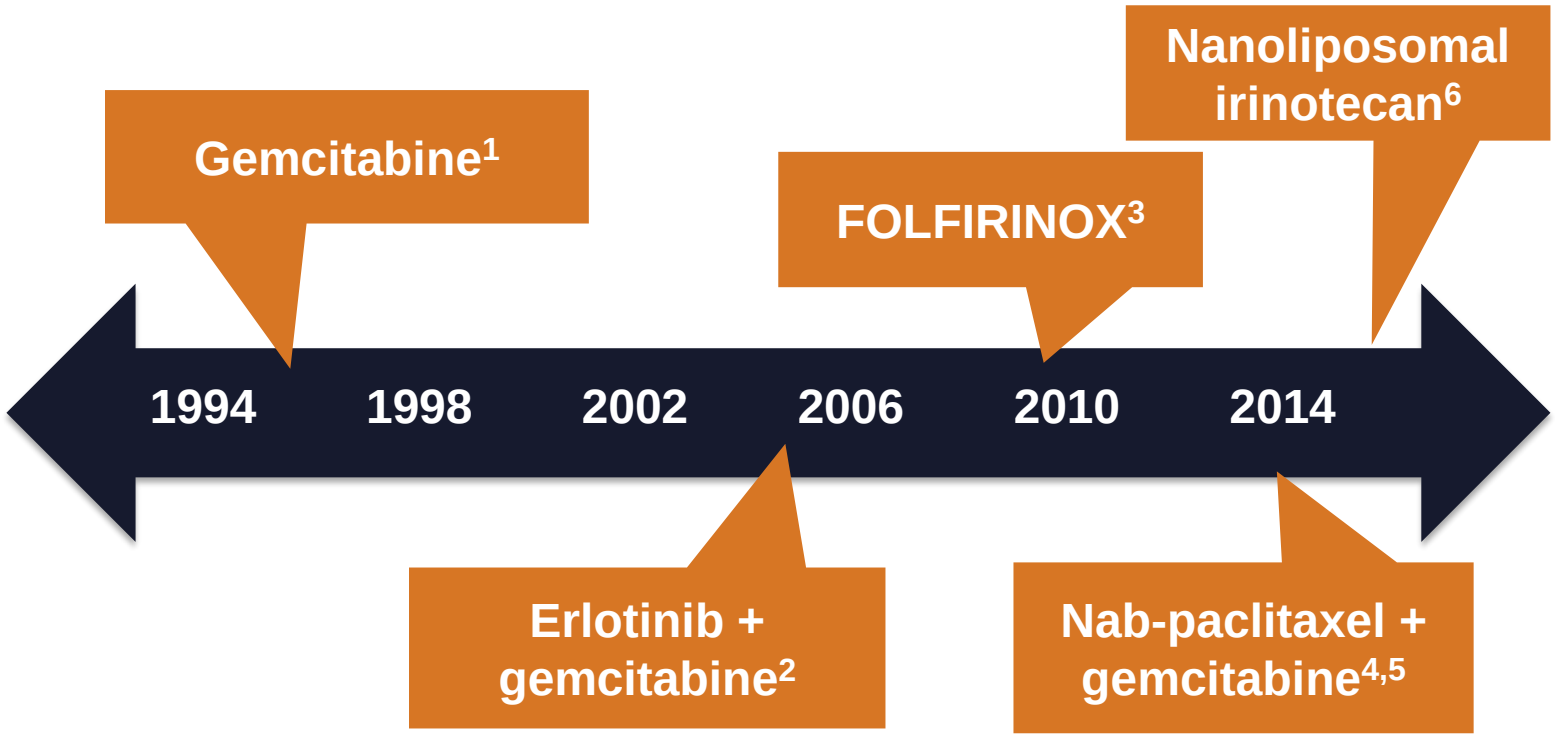
- An estimated 55,440 new cases and 44,330 deaths from pancreatic cancer in 2018
- While pancreatic cancer represents ~3% of estimated new cancer cases, deaths from pancreatic cancer represent ~7% of the total estimated number of cancer-related deaths in 2017

		Men		**Woman**		
Lung and bronchus	83,550	26%		Lung and bronchus	70,500	25%
Prostate	29,430	9%		Breast	40,920	14%
Colon and rectum	27,390	8%		Colon and rectum	23,420	8%
Pancreas	23,020	7%		Pancreas	21,310	7%
Liver and intrahepatic bile duct	20,540	6%		Ovary	14,070	5%



1. Siegel RL et al. *CA Cancer J Clin*. 2018 Jan 4. [Epub ahead of print]

Approved/Recommended Treatment Options for Pancreatic Cancer: A Timeline



1. Burris HA et al. *J Clin Oncol*. 1997;15:2403-2413. 2. Moore MJ et al. *J Clin Oncol.* 2007;25:1960-1966.
3. Conroy T et al. *N Engl J Med*. 2011;364:1817-1825. 4. Von Hoff DD et al. *N Engl J Med*. 2013;369:1691-1703.
5. Goldstein D et al. *J Natl Cancer Inst*. 2015;107:djv279. 6. Wang-Gillam A et al. *Lancet.* 2016;387:545-557.

Guideline Recommendations: Metastatic Disease[1,2]

Good Performance Status[a]	Poor Performance Status
• **Clinical trials** • **Preferred** – FOLFIRINOX (PS 0-1) – Gemcitabine + nab-paclitaxel (KPS ≥70) • Gemcitabine + erlotinib • Gemcitabine	• Gemcitabine[b] • Capecitabine[c] • Continuous 5-FU[c]

ASCO guidelines recommend gemcitabine alone for patients with PS = 2 or comorbidities; for PS ≥3 emphasis on supportive care measures

[a] All NCCN category 1 recommendations. [b] Category 2A recommendation. [c] Category 2B recommendation.

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. v3.2017. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 11, 2018.
2. Sohal DPS et al. *J Clin Oncol*. 2016;34:2784-2796.

Guideline Recommendations: Second-Line Therapy[1,2]

Prior Gemcitabine

Category 1

- 5-FU/LV + nal-IRI
  - ASCO recommends PS 0-1

Category 2A

- FOLFIRINOX
- Oxaliplatin/5-FU/LV
- FOLFOX
- Capecitabine/oxaliplatin
- Capecitabine
- 5-FU continuous

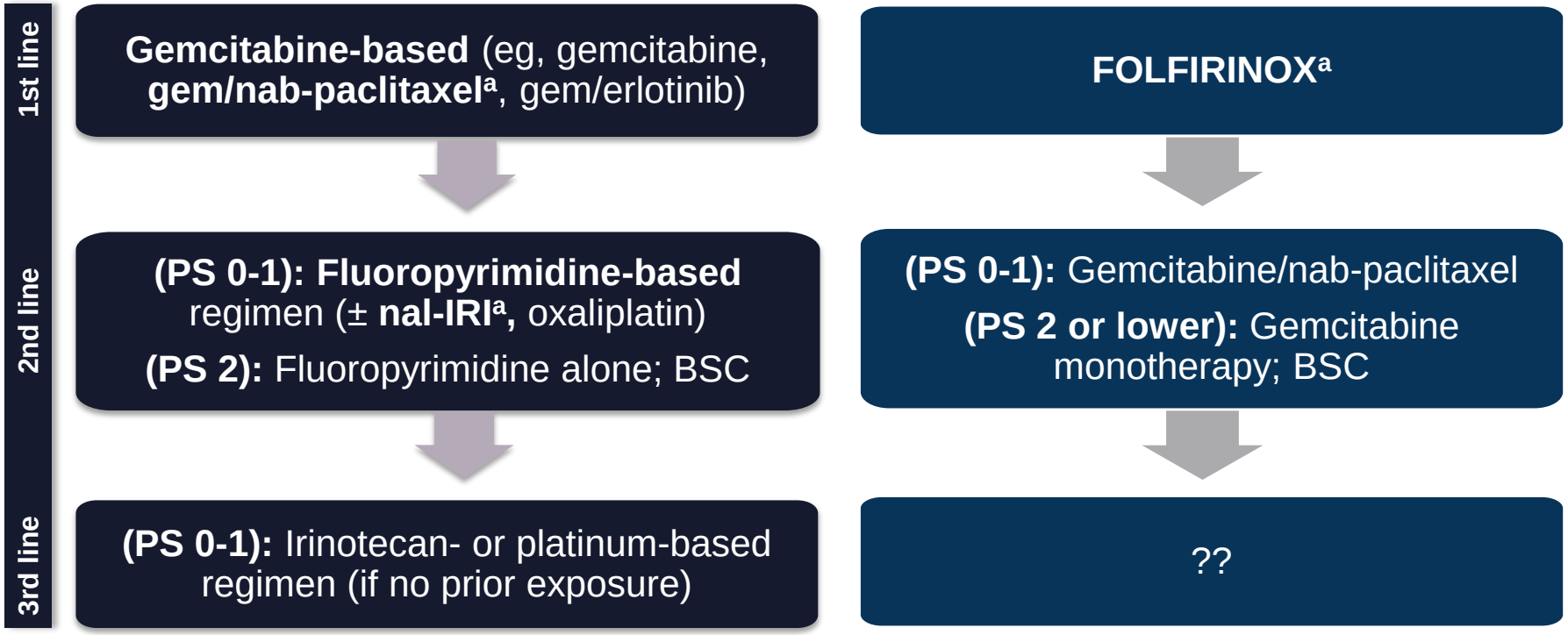
Prior Fluoropyrimidine

Category 2A

- Gemcitabine + nab-paclitaxel
- Gemcitabine
- Gemcitabine cisplatin
- Gemcitabine erlotinib
- 5-FU/LV + nal-IRI (no prior irinotecan)

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. v3.2017. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 11, 2018.
2. Sohal DPS et al. *J Clin Oncol*. 2016;34:2784-2796.

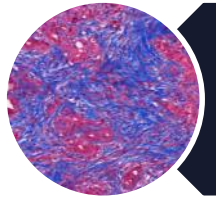
Practice Point: Current Approaches in Treatment Sequencing for Advanced Pancreatic Cancer



[a] Category 1 NCCN recommendation.[1]

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. v3.2017. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed January 11, 2018.

Novel Therapeutic Approaches to Pancreatic Cancer

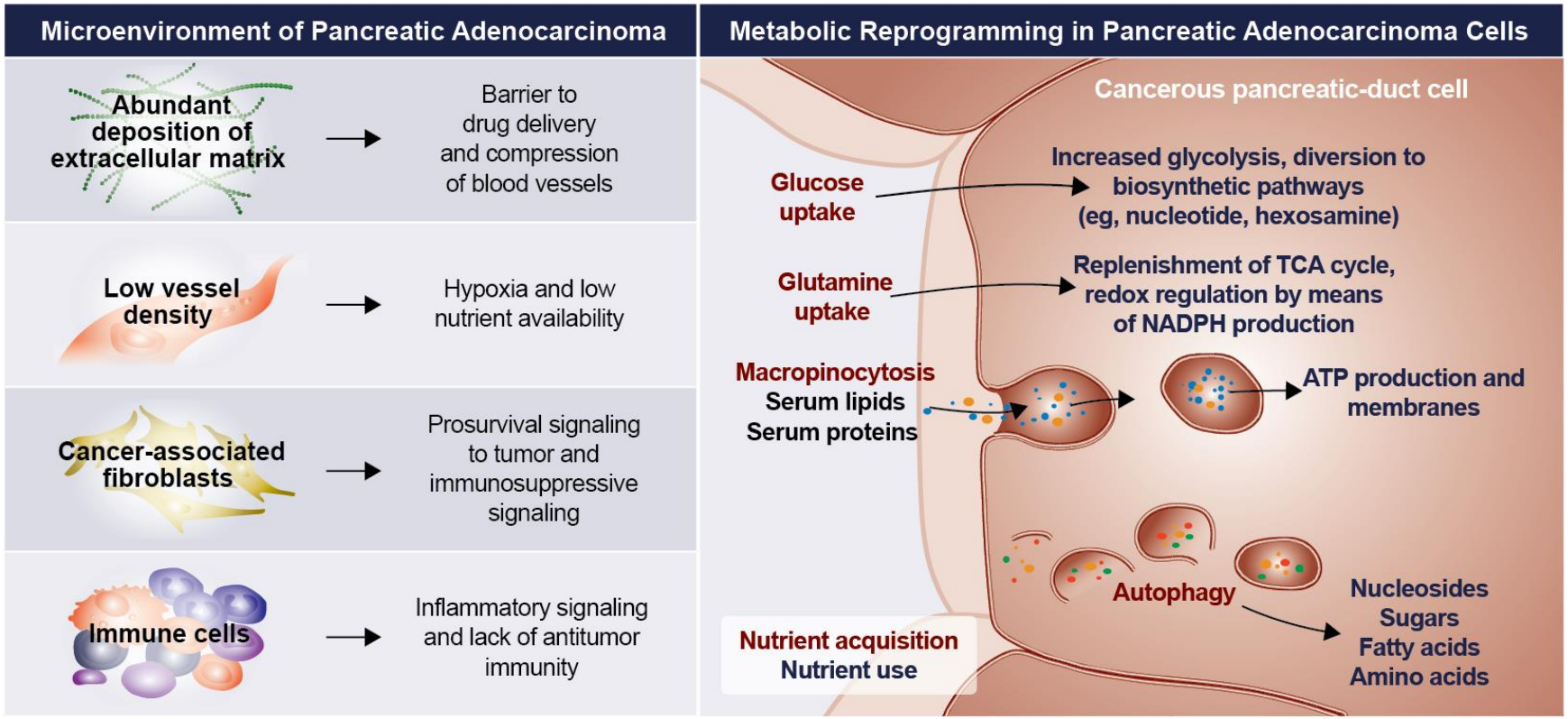


Stromal targeting

Precision medicine

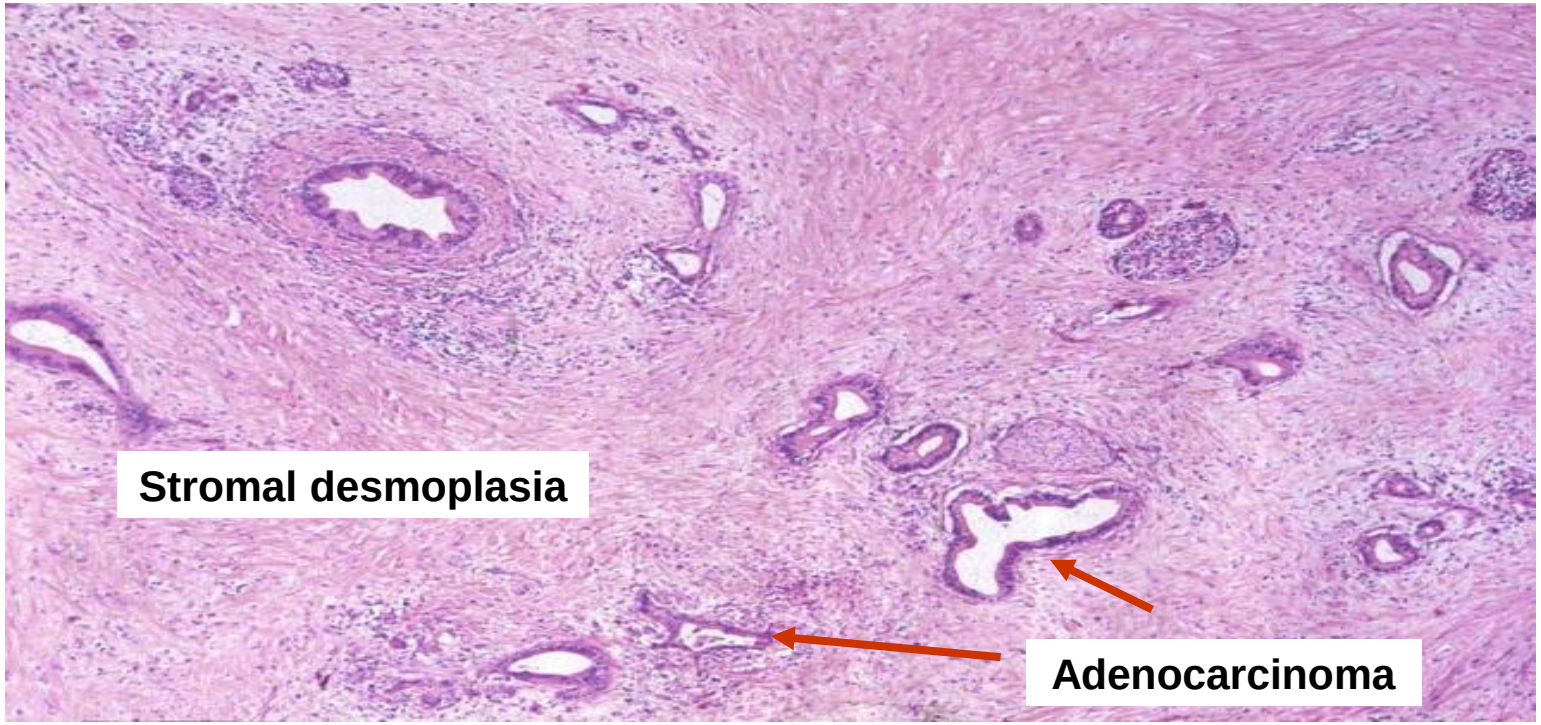
Immuno-oncology

Biologic Features of Pancreatic Cancer[1]

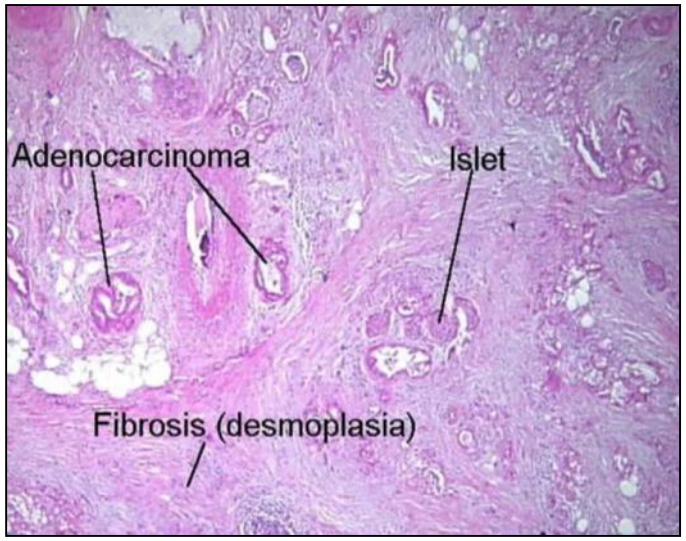


1. Ryan DP et al. *N Engl J Med.* 2014;371:1039-1049.

Pancreatic Cancer Stroma Impedes Drug Delivery

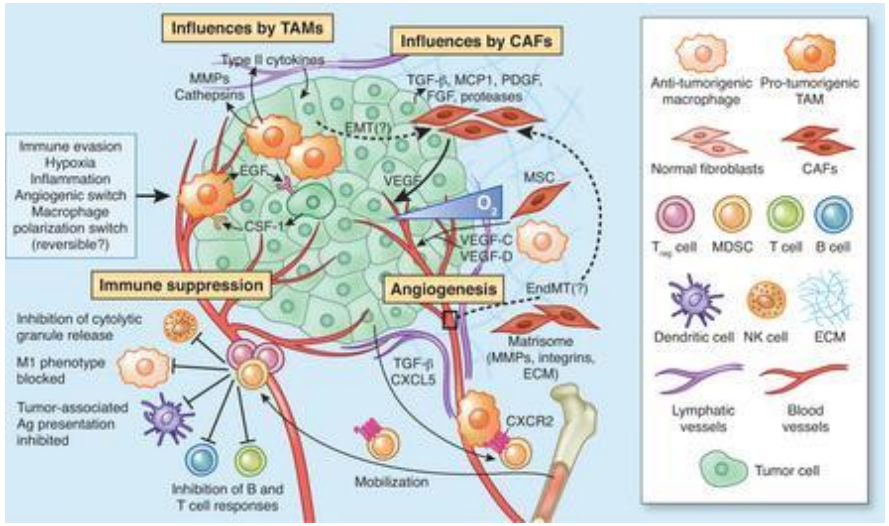


Targeting Tumor Stroma: A Promising Therapeutic Strategy?[1,a]



***Example*: PEGPH20 (recombinant hyaluronidase)**

- Breaks down hyaluronic acid present in tumor stroma
- Current phase 3 trial of gem/nab-paclitaxel +/- PEGPH20 (HALO-301)



[a] Courtesy of Eric Collisson, MD.

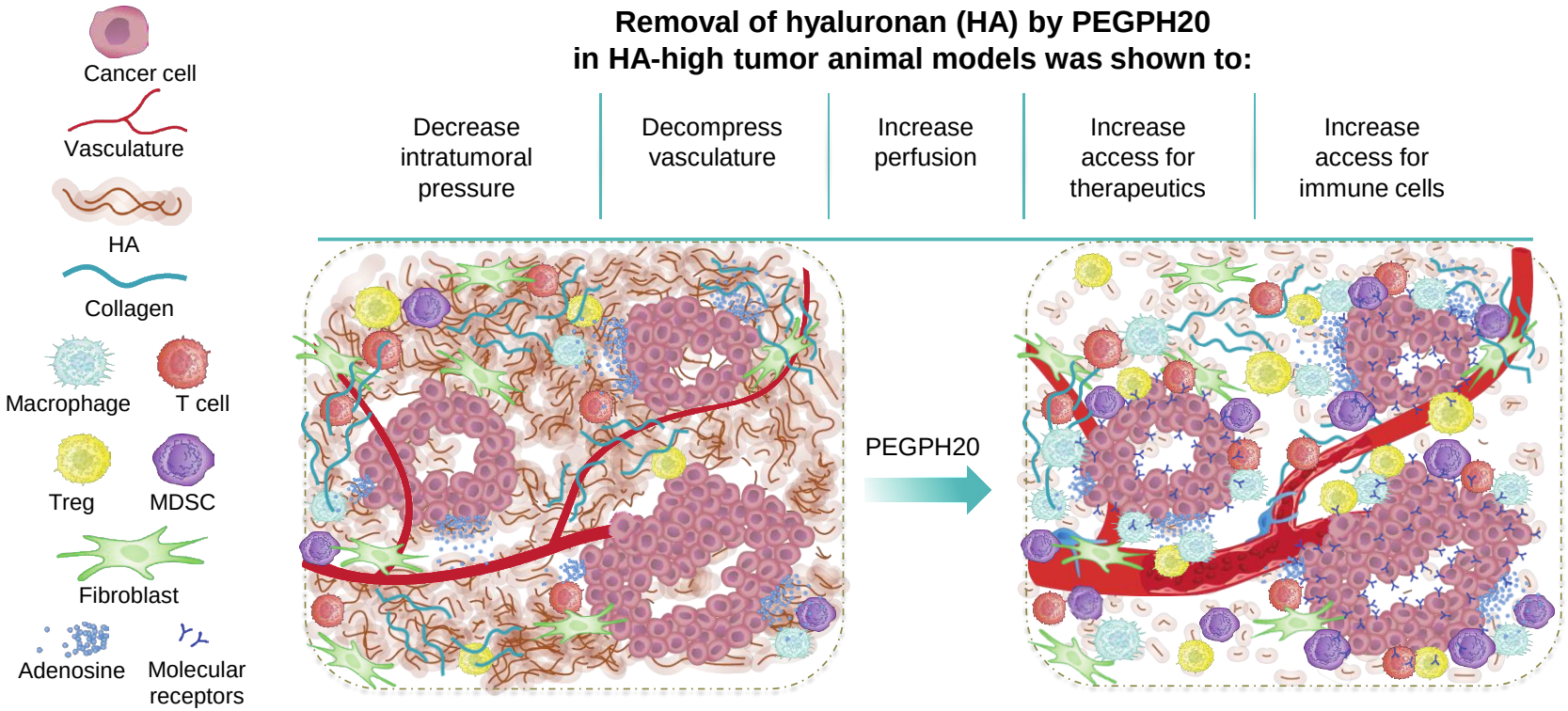
1. Quail DF, Joyce JA. *Nat Med*. 2013;19:1423-1437.

Stromal Modifying Agents[1-5]

- PEGylated recombinant hyaluronidase: PEGPH20
- Vitamin D analogs
- Bruton’s tyrosine kinase inhibitors
- CD40 mAb
- Hedgehog inhibitors

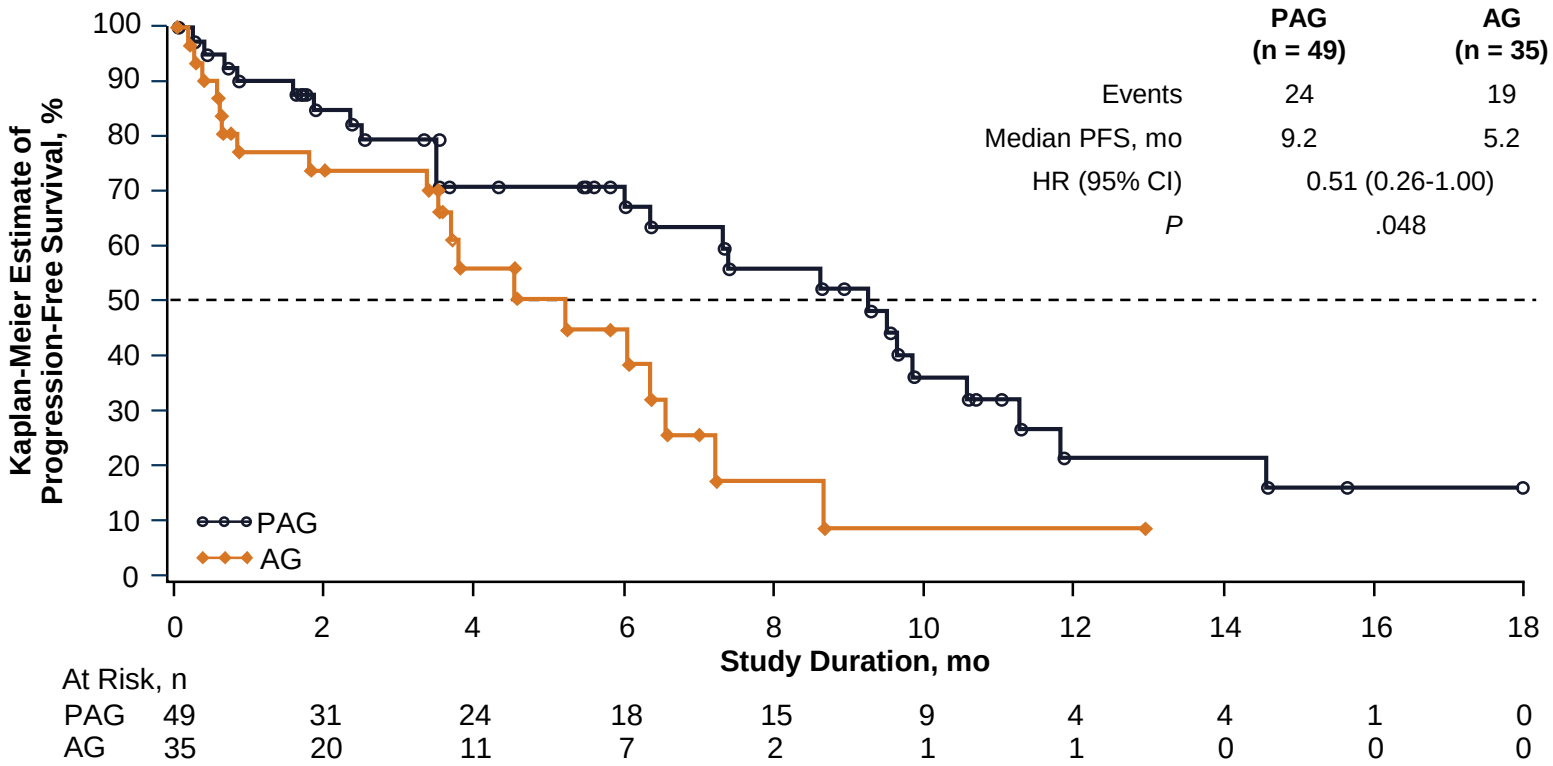
1. Olive KP et al. *Science*. 2009;324:1457-1461. 2. Provenzano PP et al. *Cancer Cell*. 2012;21:418-429. 3. Beatty GL et al. *Science*. 2011;331:1612-1616. 4. Sherman MH et al. *Cell*. 2014;159:80-93. 5. Alvarez R et al. *Br J Cancer*. 2013;109:926-933.

PEGPH20 Targets Hyaluronan in the Tumor Microenvironment[1]



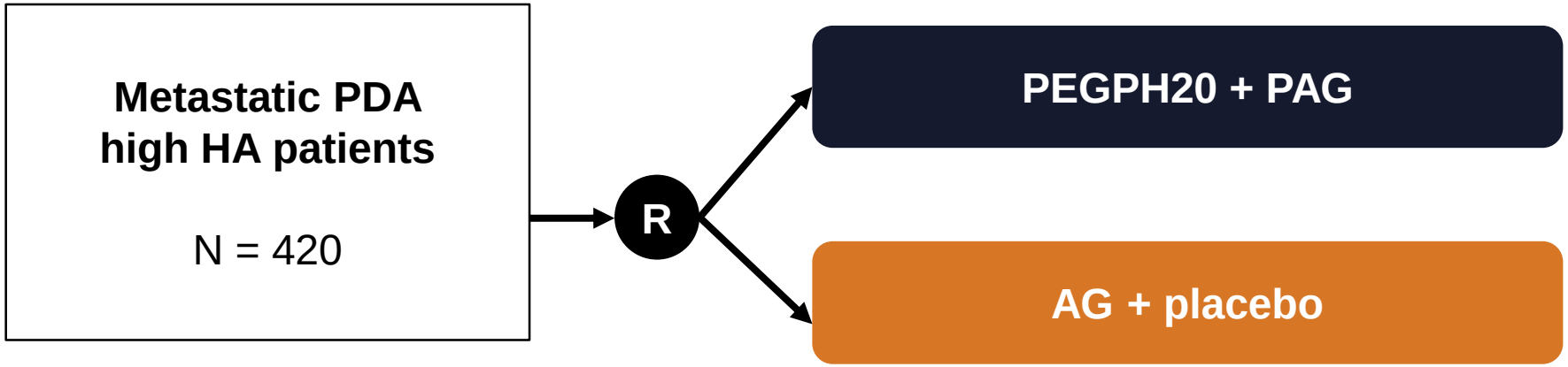
1. Hendifar A, Bullock A. Oncology & Hematology Review, 2017;13:107–111

Secondary Endpoint: PFS
HA-High (Combined Stages 1 and 2)[1]



1. Hingorani S et al. ASCO 2017. Abstract 4008.

Phase 3 HALO-301 Trial in Metastatic PDA[1]



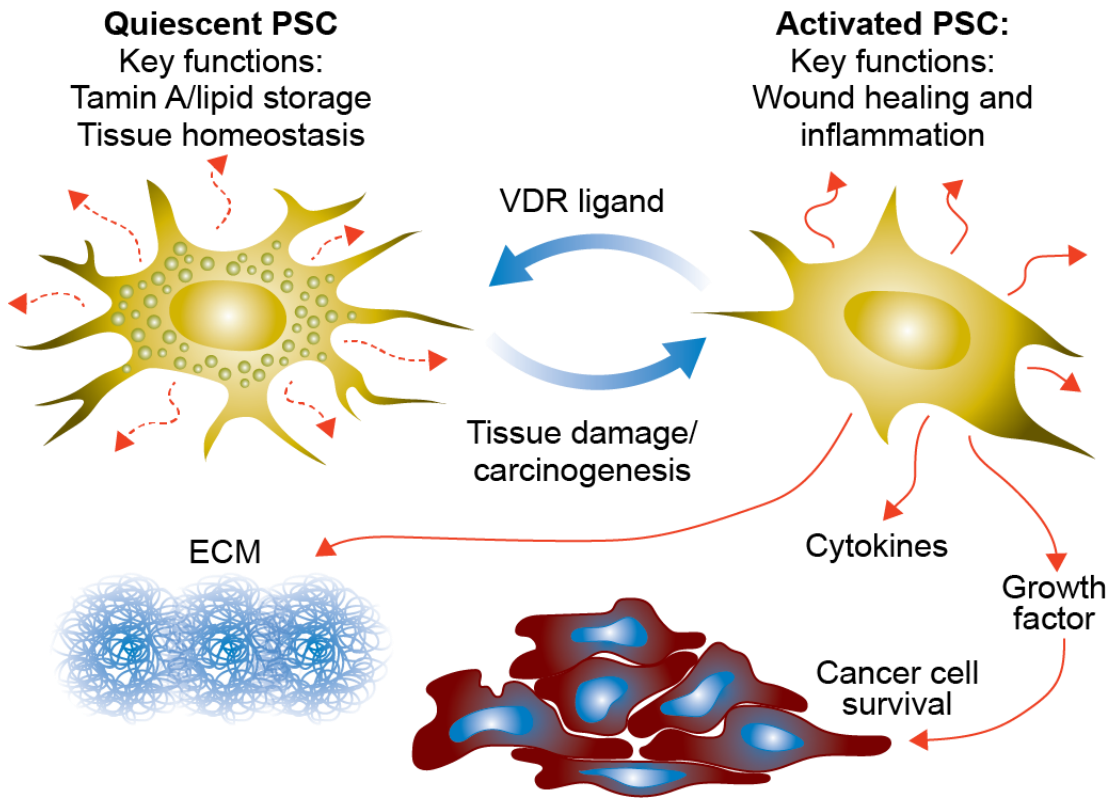
Primary endpoints: PFS, OS

- Randomized (2:1/PAG:AG), double-blind, placebo-controlled, and global
- Interim analysis when target number of PFS events reached
- PFS powered by HR of 0.59 (to detect 41% risk reduction for progression)
- First patient dosed in March 2016, study will include approximately 200 sites in 20 countries

1. https://clinicaltrials.gov/ct2/show/NCT02715804. Accessed January 16, 2018.

Vitamin D: “The Sunshine Vitamin”[1]

- VDR is expressed in stroma from human pancreatic cancer
- Calcipotriol reduces fibrosis and inflammation

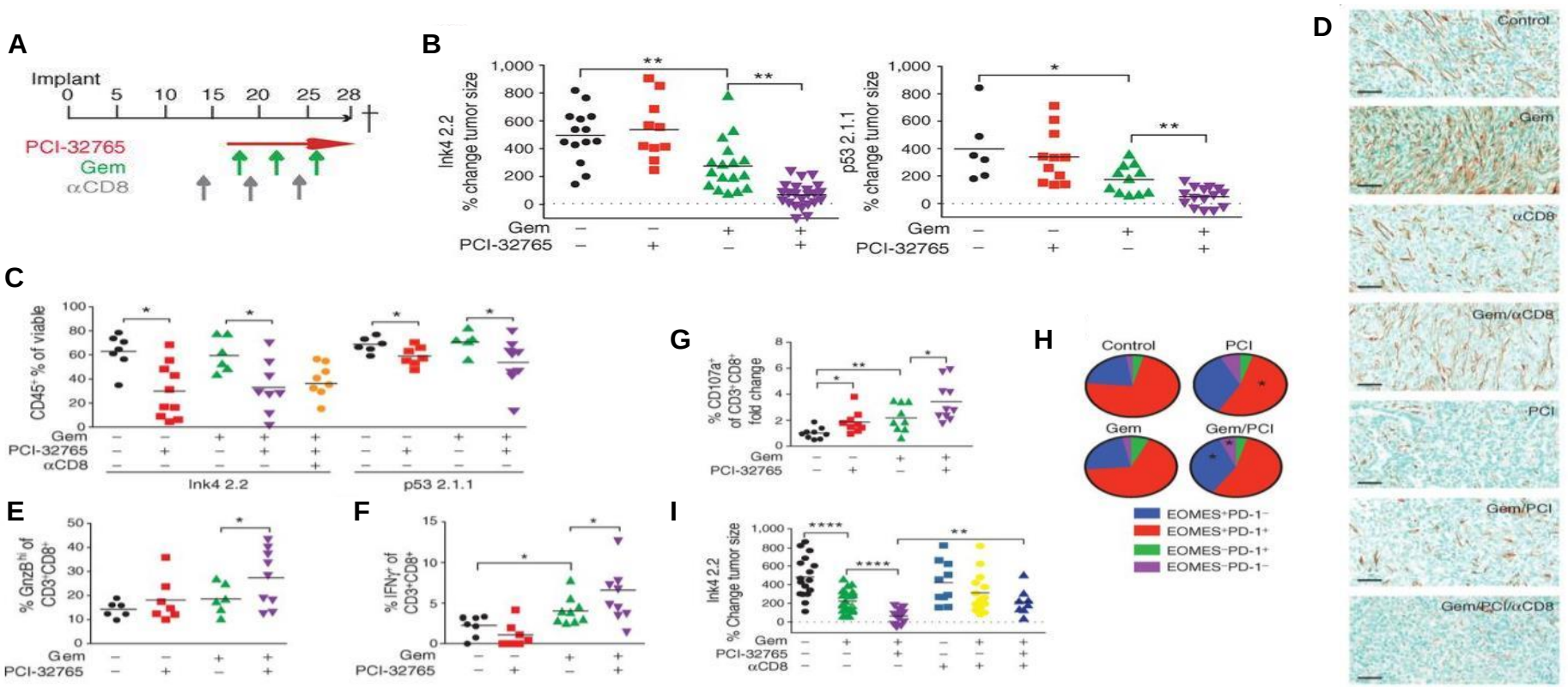


1. Sherman MH et al. *Cell*. 2014;159:80-93.

Paricalcitol (Synthetic Vitamin D)

- Poor clinical outcome in pancreatic ductal adenocarcinoma (PDA) is attributed to intrinsic chemoresistance and a growth-permissive tumor microenvironment.
- Conversion of quiescent to activated pancreatic stellate cells (PSCs) drives the severe stromal reaction that characterizes PDA.
- The vitamin D receptor (VDR) is expressed in stroma from human pancreatic tumors and that treatment with the VDR ligand calcipotriol markedly reduced markers of inflammation and fibrosis in pancreatitis and human tumor stroma.
- Evans et. al show that VDR acts as a master transcriptional regulator of PSCs to reprise the quiescent state, resulting in
  - induced stromal remodeling
  - increased intratumoral gemcitabine
  - reduced tumor volume, and a
  - 57% increase in survival compared to chemotherapy alone

BTK-Activated Signaling Regulates PDAC Tumorigenesis[1]



1. Gunderson AJ et al. *Cancer Discov.* 2016;6:270-285.

RESOLVE: Ibrutinib and *Nab*-Paclitaxel/Gemcitabine in the First-Line Treatment of Metastatic Pancreatic Cancer[1]

Phase 2/3, randomized, multicenter, double blind, placebo controlled trial

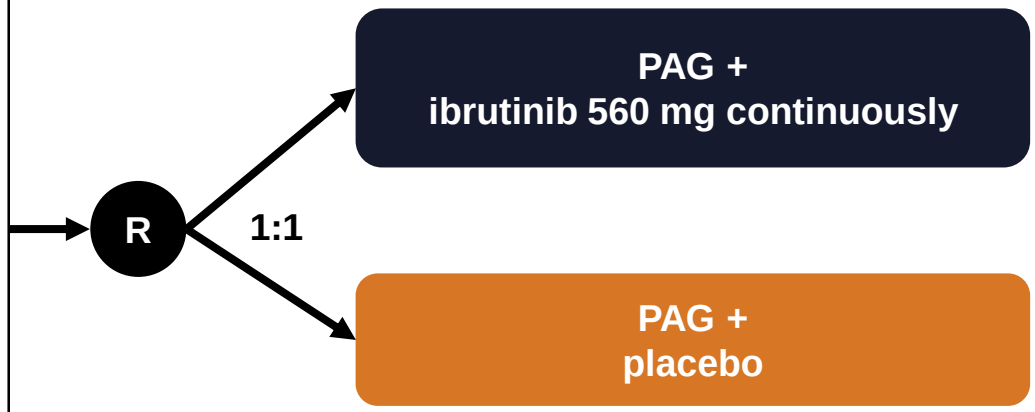
N = 420

Inclusion criteria

- Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas
- Stage IV disease diagnosed within 6 wk of randomization
- Adequate hematologic, hepatic, and renal function
- KPS ≥ 70

Exclusion criteria

- Prior treatment with BTK inhibitor, radiotherapy, cytotoxic chemotherapy, or radiotherapy in the adjuvant setting within 6 mo
- Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma
- Treatment with a strong CYP3A inhibitor



Primary endpoint: PFS
Secondary endpoints: OS, safety, and tolerability

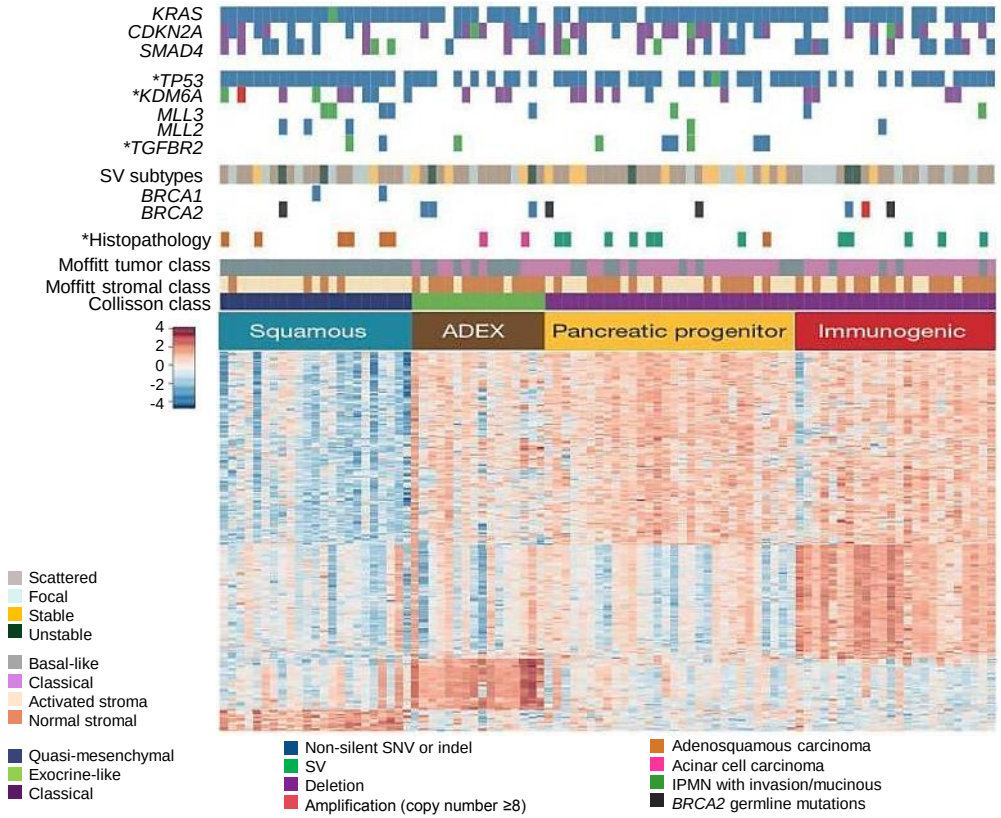
1. https://clinicaltrials.gov/ct2/show/NCT02436668. Accessed January 12, 2018.

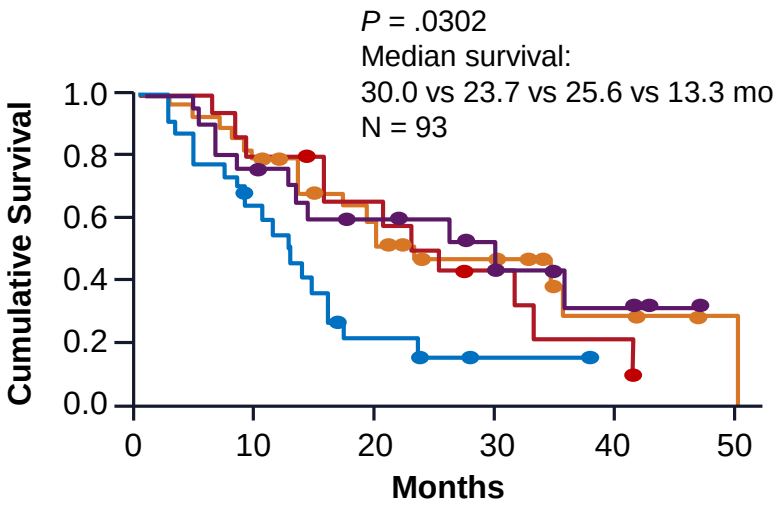
Targeted Therapy (Precision): A Definition

- Drugs targeted at pathways, processes, and physiology that are uniquely disrupted in cancer cells
  - Receptors
  - Genes
  - Angiogenesis
  - Stromal alterations
  - Metabolomic


TP53
KRAS
SMAD4
CDKN2A
PCDH15
ARID1A
SF3B1
MUC16
TGFBR2
MLL3
DNAH5
PREX2
HMCN1
CSMD1
LRP1B
RYR2
RYR3
ATM
DMD
PXDN
NALCN
ADAMTS20
DOCK2
SCN5A
FMN2
AFF2
ABCA12
NEB
MAP2K4
ZFHX4
ZIM2
CDH10
DLC1
AHNAK
EPC1
DPP6
XIRP2
ATP10A
SYNE1
ST6GAL2
THSD7A
MYH2
FBXW7
CREBBP
SMARCA4
www.pancreaticcancer.net.au

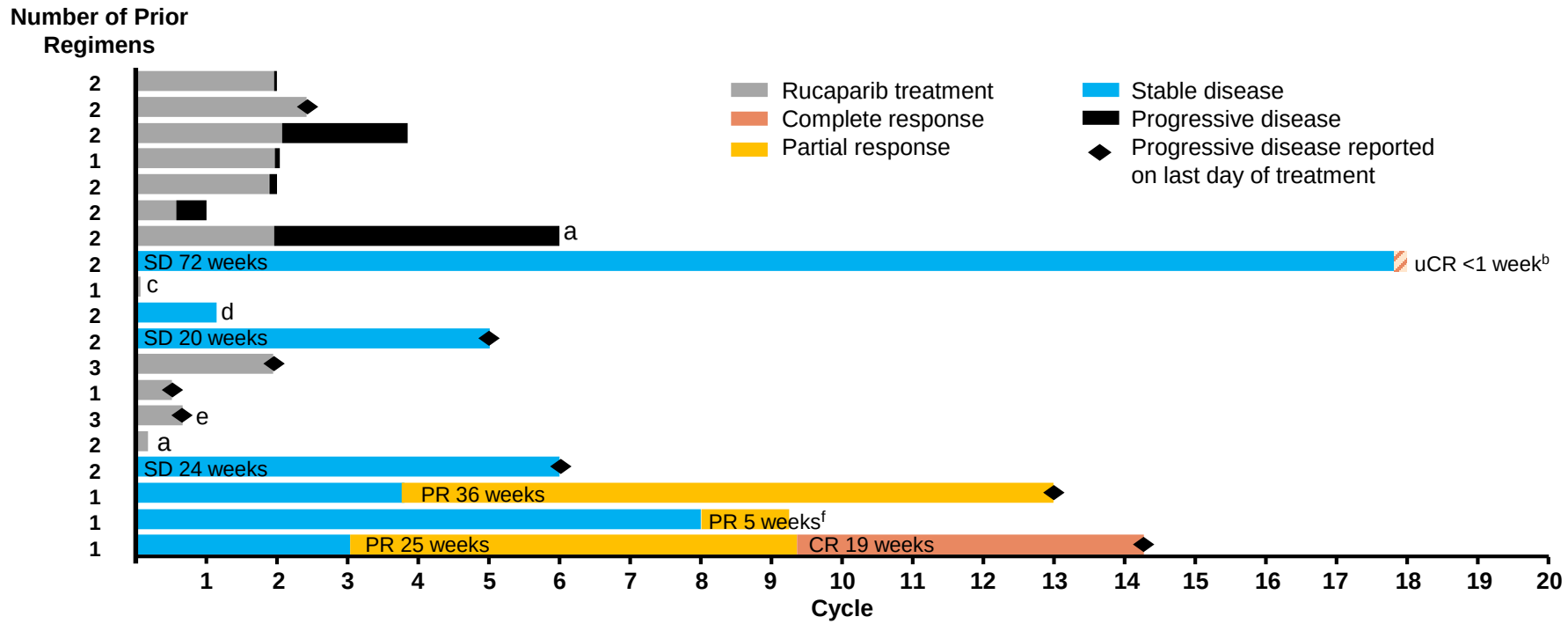
Genomic Analyses Identify Molecular Subtypes of Pancreatic Cancer: Potential Therapeutic Implications?[1]





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

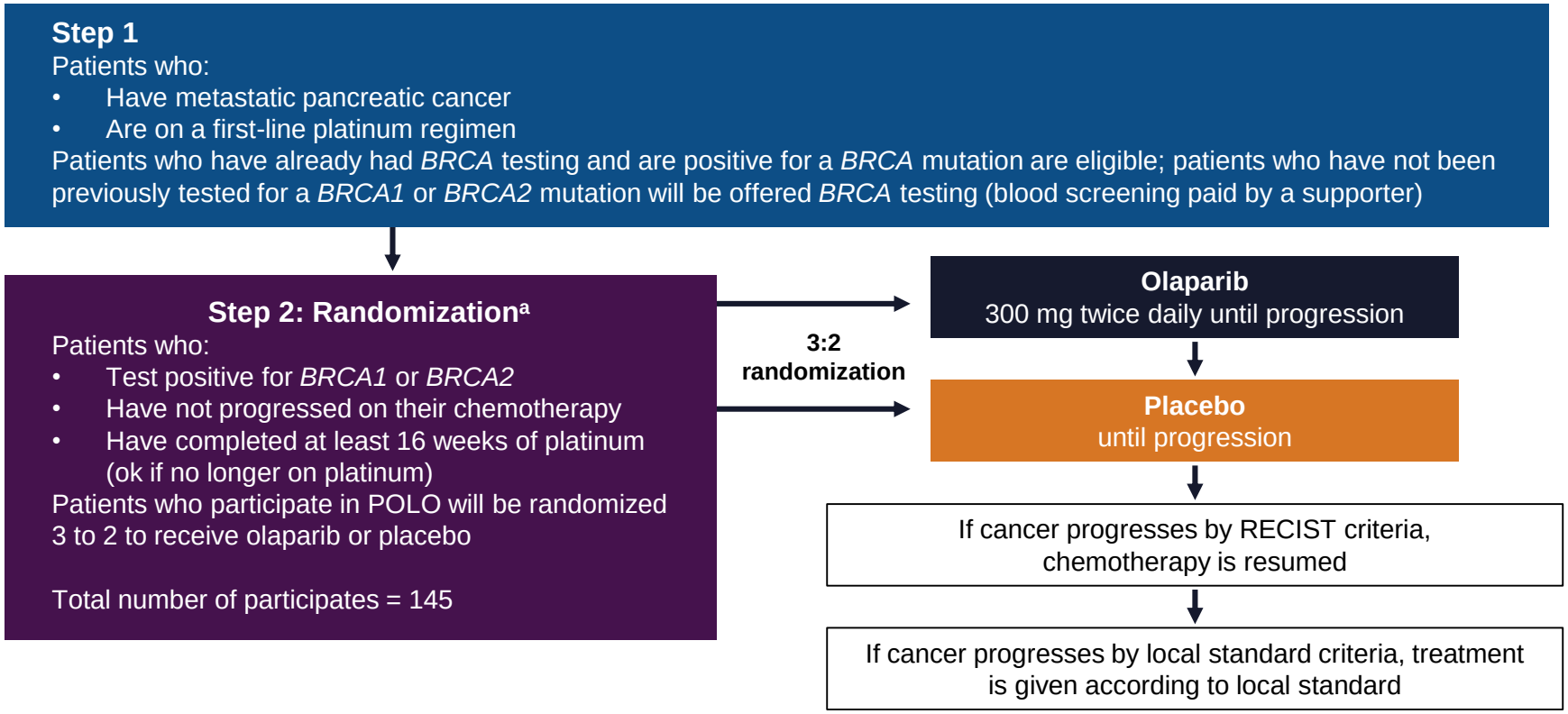
Treatment Duration With Rucaparib for Patients With Pancreatic Cancer and a *BRCA* Mutation (N = 19)[1]



[a] Patients discontinued treatment for other reason. [b] Study terminated; patient rolled over to an Individual Patient IND application. [c] Patient discontinued due to investigator decision. [d] Patient discontinued due to an AE and scan with stable disease performed after last treatment day. [e] Patient discontinued due to AE and progressive disease. [f] Patient withdrew consent; partial response confirmed with a scan after last treatment day.

1. Domcheck SM, et al. ASCO 2016. Abstract 4110.

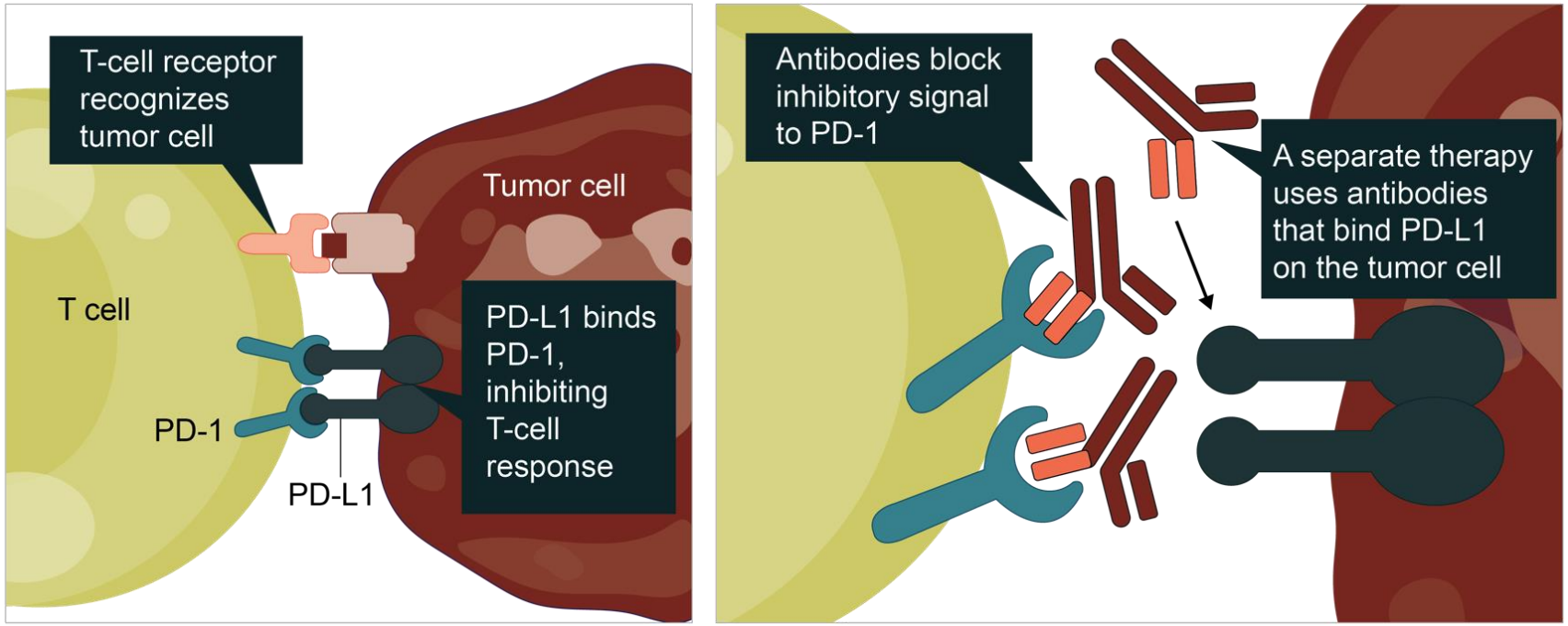
POLO: Olaparib in Metastatic BRCA-Mutant Pancreatic Cancer[1]



[a] If *BRCA1* or *BRCA2* positive, patients are inviting to join study.

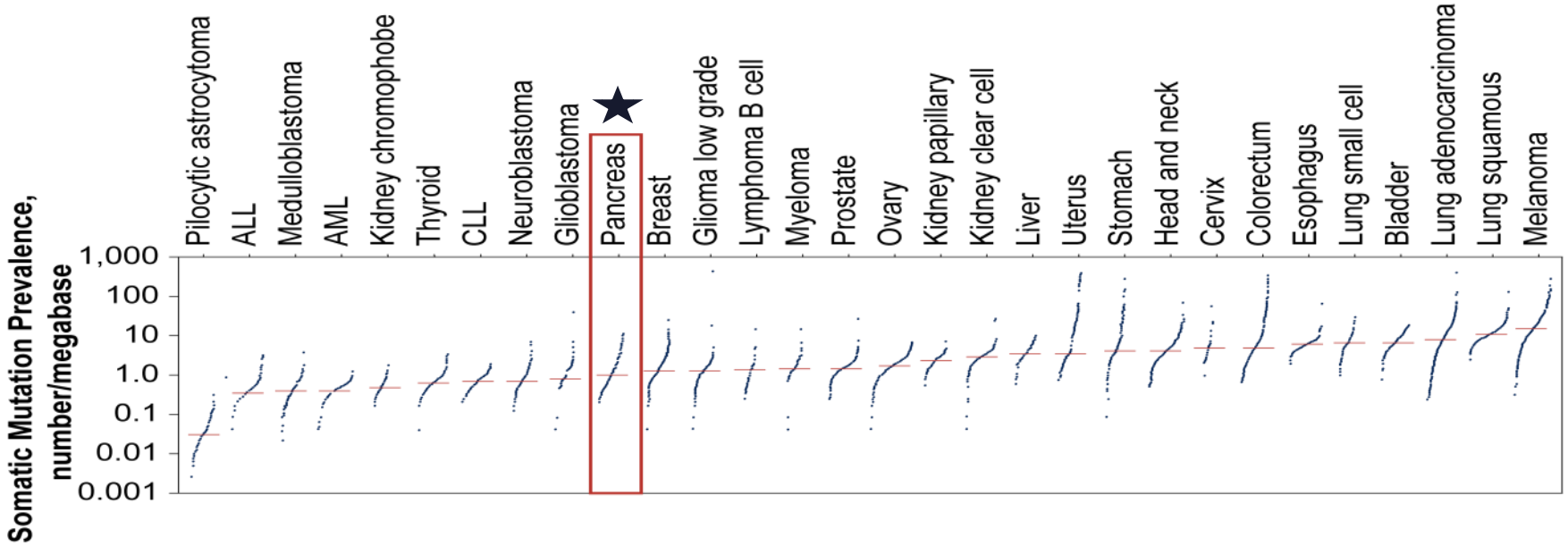
1. https://clinicaltrials.gov/ct2/show/NCT02184195. Accessed January 16, 2018.

Immuno-Oncology



Immunotherapy and Pancreatic Cancer[1-4]

- Limited infiltrating effector T cells seen in tumor specimens and modest mutational burden



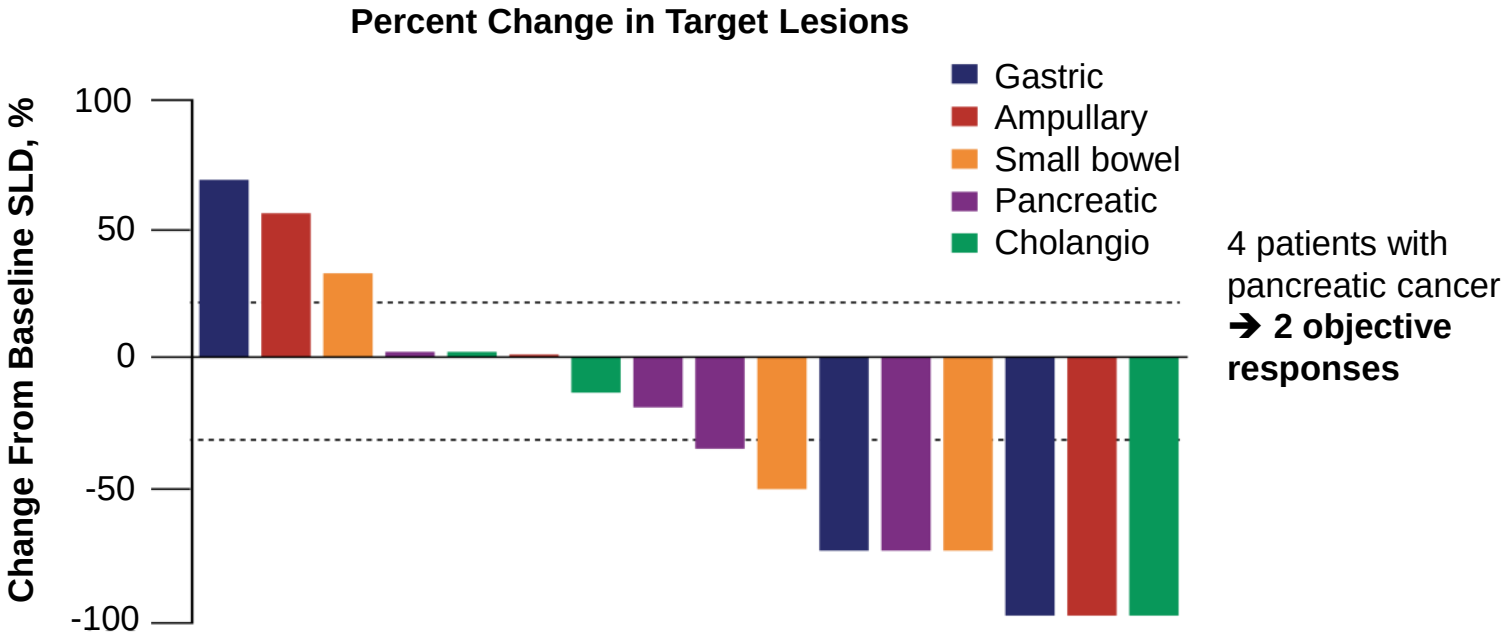
1. von Bernstorff W et al. *Clin Cancer Res*. 2001;7:925s-932s. 2. Clark CE et al. *Cancer Lett*. 2009;279:1-7.
3. Royal RE et al. *J Immunother*. 2010;33:828-833. 4. Alexandrov LB et al. *Nature*. 2013;500:415-421.

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	• Multiple ones under active investigation
CAR-T cells	• Pilot studies ongoing • Mesothelin represents frequent target

Immune Checkpoint Inhibitors in PDAC: Pembrolizumab[1]

- **KEYNOTE-028 study in advanced solid tumors with defective mismatch repair (dMMR/MSI-high); pembrolizumab 10 mg/kg every 2 weeks**



4 patients with pancreatic cancer
➔ **2 objective responses**

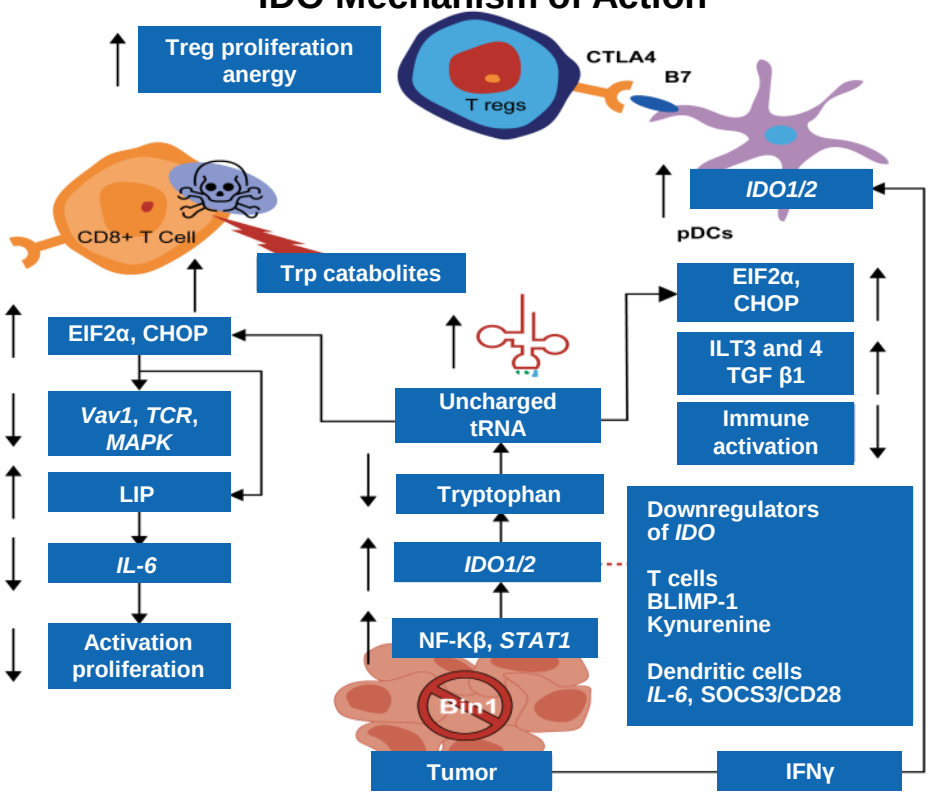
1. Le DT et al. ASCO 2016. Abstract 195.

Indoleamine 2, 3-Dioxygenase Pathway Inhibitors[1]

- IDO is a tryptophan-catabolizing enzyme and plays a key role in normal regulation of peripheral immune tolerance; in cancer, IDO facilitates evasion of immune-mediated destruction

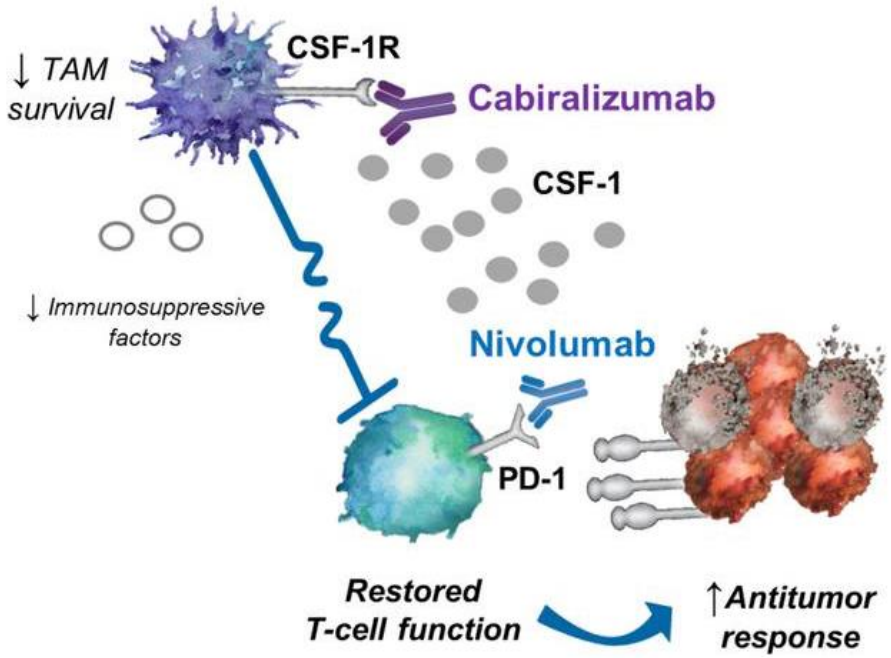
- Indoximod
  - Phase 1/2 study of indoximod + gemcitabine/*nab*-paclitaxel for metastatic PC reported at the 2016 ASCO GI meeting[1]
  - Interim results of the phase 2 portion were presented at the 2016 ASCO meeting[2]

IDO Mechanism of Action[3]



1. Bahary N et al. ASCO GI 2016. Abstract 452. 2. Bahary N et al. ASCO 2016. Abstract 3020.
3.Soliman H et al. *Cancer J*. 2010;16:354-359.

Rationale for Cabiralizumab in Combination With Nivolumab

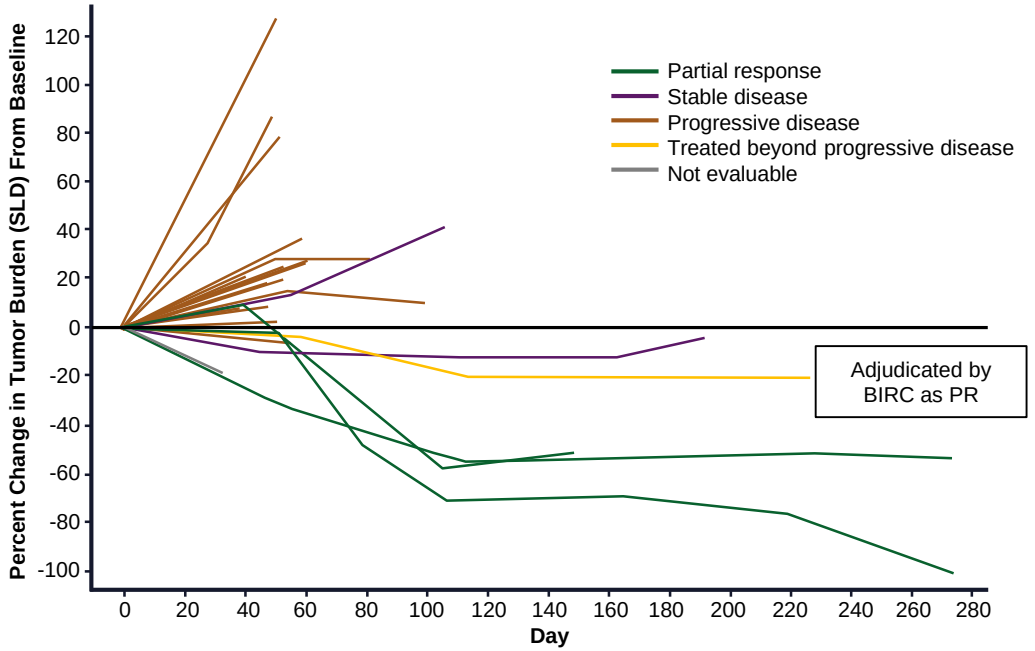


- TAMs inhibit antitumor T-cell activity in the tumor microenvironment[1,2]
  - In pancreatic and other cancers, high levels of TAMs are associated with poor prognosis[3-5]
  - Signaling through the CSF-1 receptor promotes the maintenance and function of TAMs[1,2]
- Cabiralizumab is a humanized IgG4 mAb that blocks *CSF-1R*[6] and depletes TAMs
- Preclinical data suggest that CSF-1R inhibition synergizes with PD-1 blockade to enhance antitumor activity[7]

1. Ries CH et al. *Cancer Cell*. 2014;25:846-859. 2. Cannarile M et al. *J Immunother Cancer*. 2017;5:53. 3. Hu H et al. *Tumour Biol*. 2016;37:8657-8664. 4. Kurahara H et al. *J Surg Reg*. 2011;167:e211-e219. 5. Goswami KK et al. *Cell Immunol*. 2017;316:1-10.
6. Bellovin D et al. *Cancer Res*. 2017;77(13 suppl): Abstract 1599. 7. Zhu Y et al. *Cancer Res*. 2014;74:5057-5069.

Deep and Durable Responses Observed Accompanied by Significant Reduction in Pancreatic Tumor Marker CA19-9

- Best change in tumor burden over time in efficacy-evaluable patients treated with cabiralizumab 4 mg/kg + nivolumab 3 mg/kg (n = 31)[a]



In this heavily pretreated population, durable clinical benefit was observed in **5 patients (16%)**

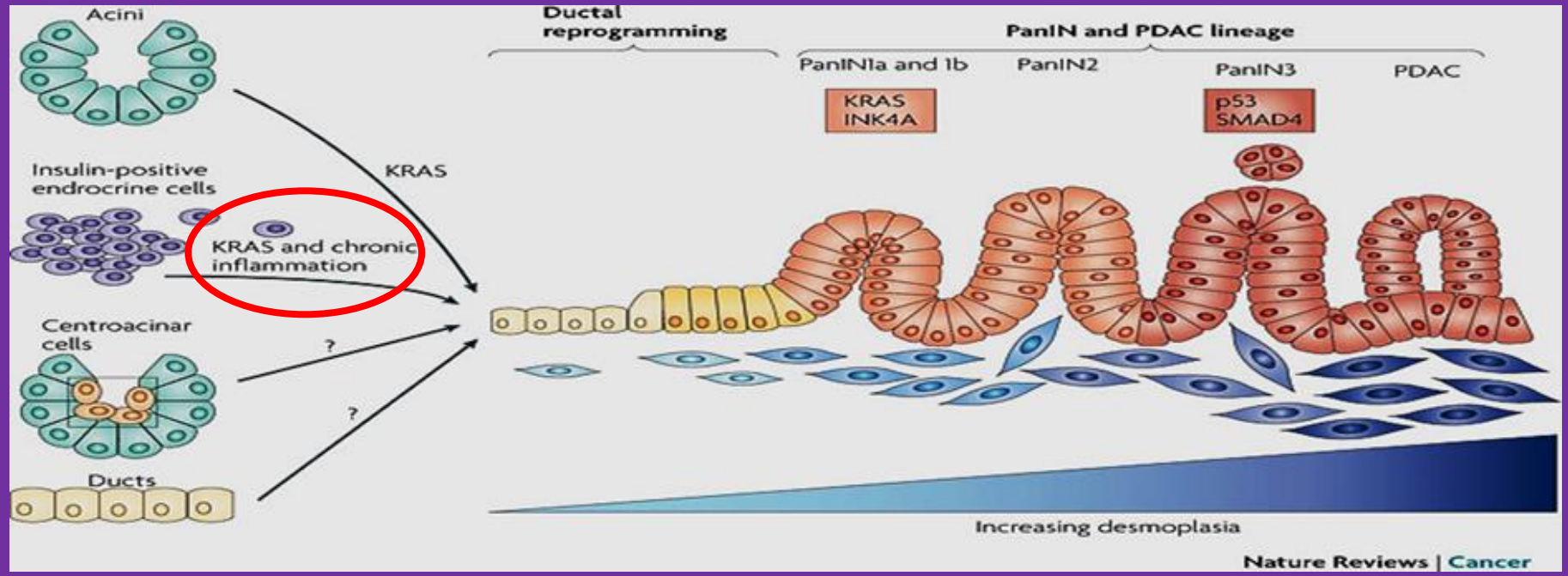
- All 5 had MSS disease, which historically has not shown benefit with anti–PD-1/L1 therapy[1,2]
- **Confirmed ORR = 10% (Updated confirmed ORR = 13%)**
- **Duration of treatment for responders = 275+, 168+, 258, and 247+ days**

Responses were accompanied by steep declines in levels of the pancreatic tumor marker CA19-9 over baseline

[a] Plot shows 31 efficacy-evaluable patients discontinued treatment early due to AEs before disease evaluation.

1. Overman M et al. *Ann Oncol*. 2016;27(suppl 6): Abstract 479P. 2. Le DT et al. *N Engl J Med*. 2015;372:2509-2520.

Mutated KRAS Initiates Pancreatic Carcinogenesis



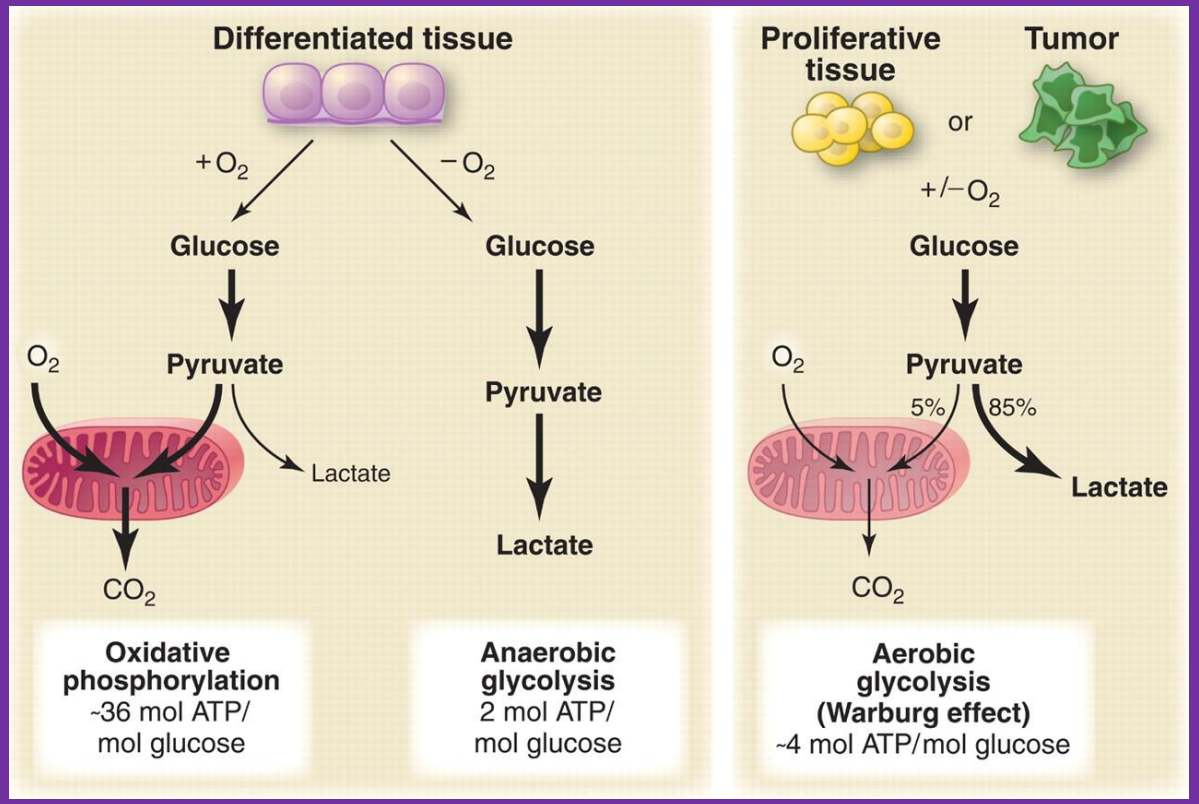
Morris JP 4th, et al. *Nat Rev Cancer*. 2010;10(10):683-695.

KRAS Mutation
Metabolic Reprograming

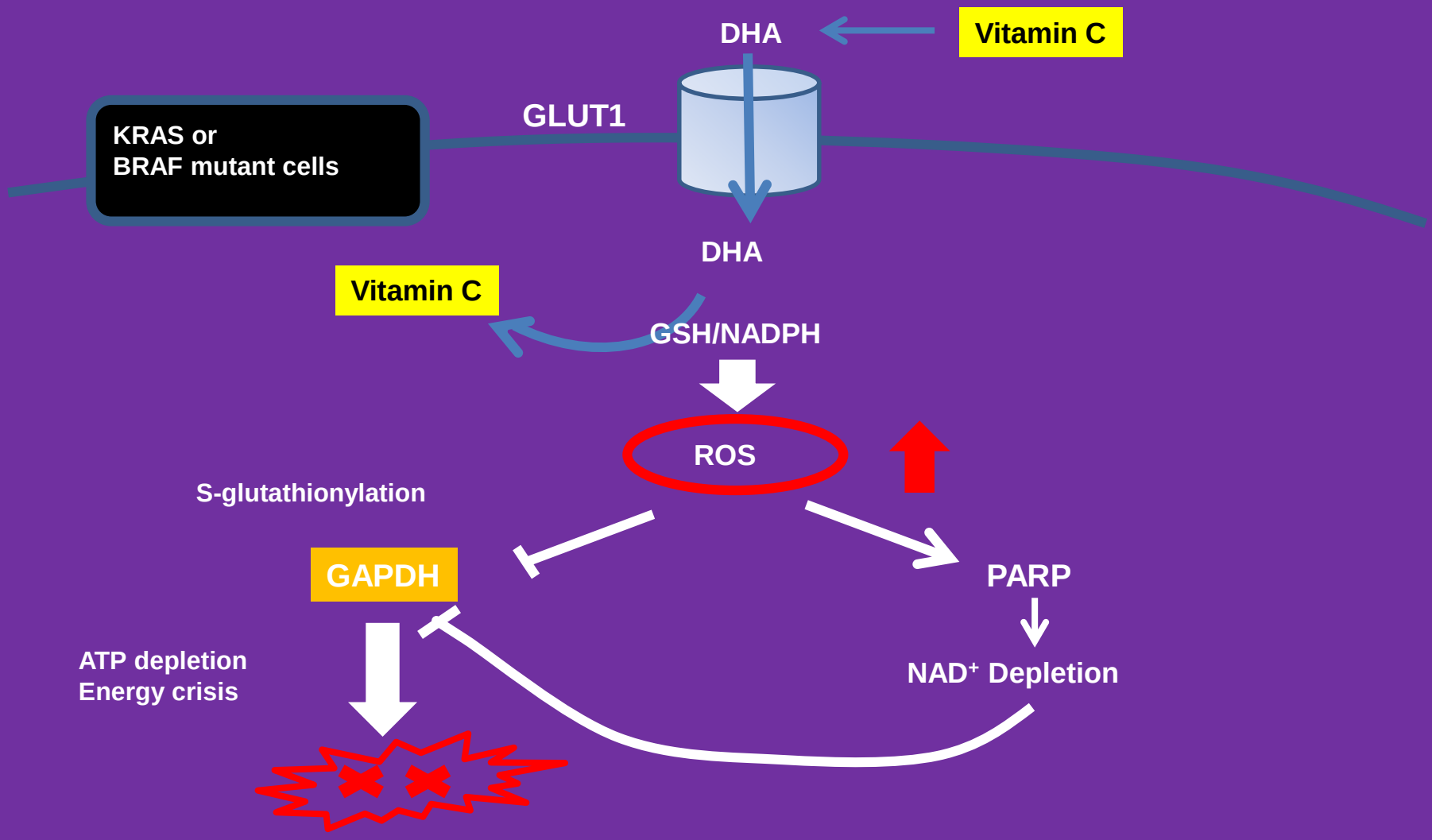
- Increased glucose uptake and metabolism (Warburg effect)
  - Increased GLUT1, HK1, HK2 expression
- Differential channeling of glucose intermediates
  - Hexosamine biosynthetic pathway
  - Non-oxidative pentose phosphate pathway
- Reprograming glutamine metabolism
- Increased autophagy
  - Mitophagy
- Increased macropinocytosis

Locasale JW, et al. *Cell*. 2012;149(3):656-670.

Schematic representation of the differences between oxidative phosphorylation, anaerobic glycolysis, and aerobic glycolysis (Warburg effect)



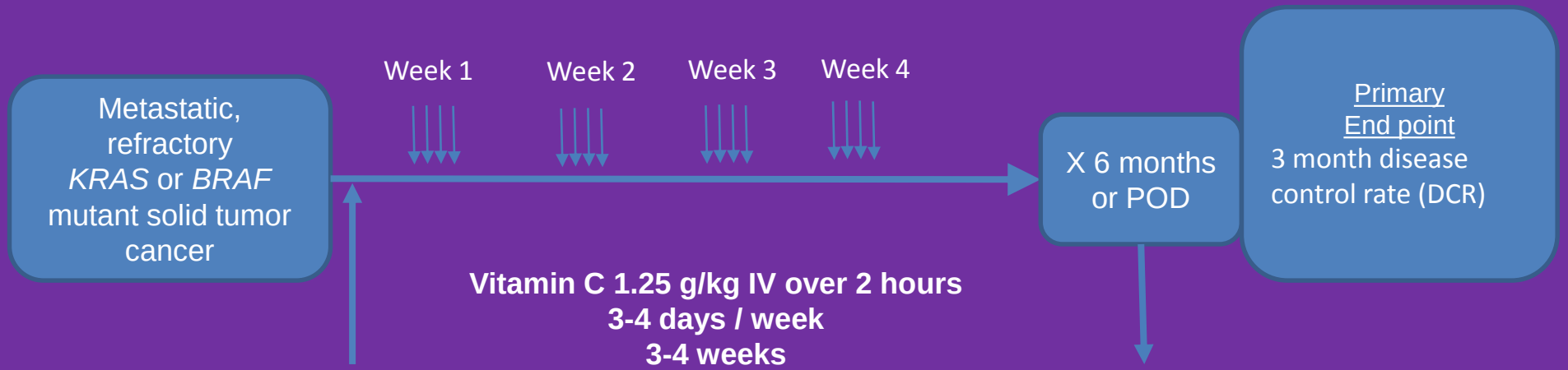
Matthew G. Vander Heiden et al. Science 2009;324:1029-1033


DHA
Vitamin C
KRAS or
BRAF mutant cells
GLUT1
DHA
Vitamin C
GSH/NADPH
ROS
S-glutathionylation
GAPDH
PARP
ATP depletion
Energy crisis
NAD+ Depletion

- Drug Molecule:

- Toxic to cancer cells 
- Extremely cheap 
- Very safe 
- Target molecule: **GAPDH**
- Mechanism of action: **Inhibiting Glycolysis**
- Responder ID: **KRAS or BRAF mutations**

WCMC Phase II Pilot Study: Cohort B



Biostats: 30% 3-month DCR vs. < 10%
90% power, one-sided alpha 0.1 requires 25 evaluable patients

Ongoing Research

- Organoids
  - Tuveson et al
  - CTCs to organoids
  - High throughput drug screen
- Role of radiation
  - SBRT
    - Neoadjuvant and adjuvant settings
  - Electroporation (IRE)
- New drugs
  - MEK inhibitors
  - Parp inhibitors
  - CDK inhibitors
  - SM-88 (tyrosine analog)
  - Anti-CA19-9 antibody
  - RX-3117
  - Grand Slam approach (chemotherapy, Vitamin D, Immunotherapy)

Technology

Gastrointestinal Oncology

Let's Win: Innovative Online Community Offers Guidance to Patients With Pancreatic Cancer and Their Families

By Caroline Helwick

Allyson J. Ocean, MD

Cindy Price Gavin

Let's Win is an online community for persons with pancreatic cancer (www.letswinpc.org), but it is far more than a typical support group. Let's Win propels interested users toward cutting-edge research, based on its founders' commitment that no patient with pancreatic cancer should settle on the standard-of-care treatment without seeking potentially better options.

The ASCO Post interviewed the co-founder of Let's Win, **Allyson J. Ocean, MD**, Chair of the Scientific Advisory Board, and **Cindy Price Gavin**, Founder, who is responsible for developing and actively promoting its clinical trial finder.

The two founders agreed that Let's Win offers a "unique niche," as Ms. Gavin put it, for patients and their families. "We think our site is the missing link," Dr. Ocean added. "We want to get the message out that patients can have hope through the science they will find on our site."

Visitors to Let's Win will find these sections: My Treatment, Promising Science, Clinical Trials, and Newsfeed. All sections allow readers to comment on what they find there. (Participants can comment on all sections except for the Newsfeed.)

> *"The problem with pancreatic research so far is that the amazing science being done is not getting to most patients on time."*
>
> —Allyson J. Ocean, MD

relations world and was in the prime of her life when she was diagnosed. She and her family were stunned. They knew they had to do something urgently, and they began to search for treatments. As what happens for most patients, she was initially told she didn't have much time and to 'get her affairs in order,'" Dr. Ocean said. "Anne said, 'No, I won't listen to this. I will seek out more information and more options.' And, since that time, her entire cancer journey has been a science experiment!"

> *"We encourage patients to think outside the box, not just to take what they are hearing on day 1 and run with it. Our core is to create an interactive patient and family forum that enables dialogue and informs patients about fast-breaking information on potentially life-saving treatments and trials."*
>
> —Cindy Price Gavin

Ms. Glauber became one of the first patients to have an organoid created in vitro of her tumor from a very small sample (via fine-needle aspirate), the results of a collaboration between Dr. Ocean and researchers at Cold Spring Harbor Laboratories. The researchers were able not only to interrogate her tumor genomically, but also to test thousands of compounds against the tumor and identify treatments that could be most effective.

and living well with her disease. "You would never know she's sick—all this from using standard drugs in a nonstandard way," Dr. Ocean commented.

Not Settling for Standard of Care

From Ms. Glauber's initial feelings of helplessness and confusion came the concept that would become Let's Win: Patients need to be empowered to seek out and to find the very best options for their cancer—not only those recommended in the guidelines but novel approaches that go beyond the standard of care, "which gives patients very limited long-term outcomes," Dr. Ocean noted.

Together, the oncologist and her patient created a network of supporters, formed the core group, and established its mission. Dr. Ocean and Ms. Glauber partnered with **Kerri Kaplan**, CEO of the Lustgarten Foundation, and **Willa Shalit**, entrepreneur and philanthropist, to create Let's Win. They recruited Ms. Gavin,

Supportive Care for Individuals Living with Pancreatic Cancer

Gayle S. Jameson, RN, MSN, ACNP-BC, AOCN

Nurse Practitioner, Associate Investigator

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Michael Gordon, MD

Frank Tsai, MD

Sunil Sharma, MD

Jasgit Sachdev, MD

Carol Guarnieri, NP

Courtney Snyder, NP

Jody Pelusi, NP

Slide courtesy of Gayle Jameson and Raji Chandrasekaran

Supportive Care
Symptom Prevention & Management

“The worst symptom you can have is cancer.”

Dr. Mark Green

Best Supportive Care

- The goal of **supportive care** is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment.
- Palliative Care

https://www.cancer.gov/publications/dictionaries/cancer-terms/def/supportive-care

Common Symptoms

General

- Fatigue
- Weight loss
- Malnutrition
- Pain
- Anxiety/Depression
- Insomnia
- Dehydration

Gastrointestinal

- Loss of appetite
- Nausea
- Bloating/Abdominal Pain
- Diarrhea
- Digestive Enzyme Insufficiency
- Jaundice

Other Associated Problems

- Diabetes
- Venous Thromboembolism
- Peripheral Neuropathy
  - May be diabetes or treatment related
- Ascites

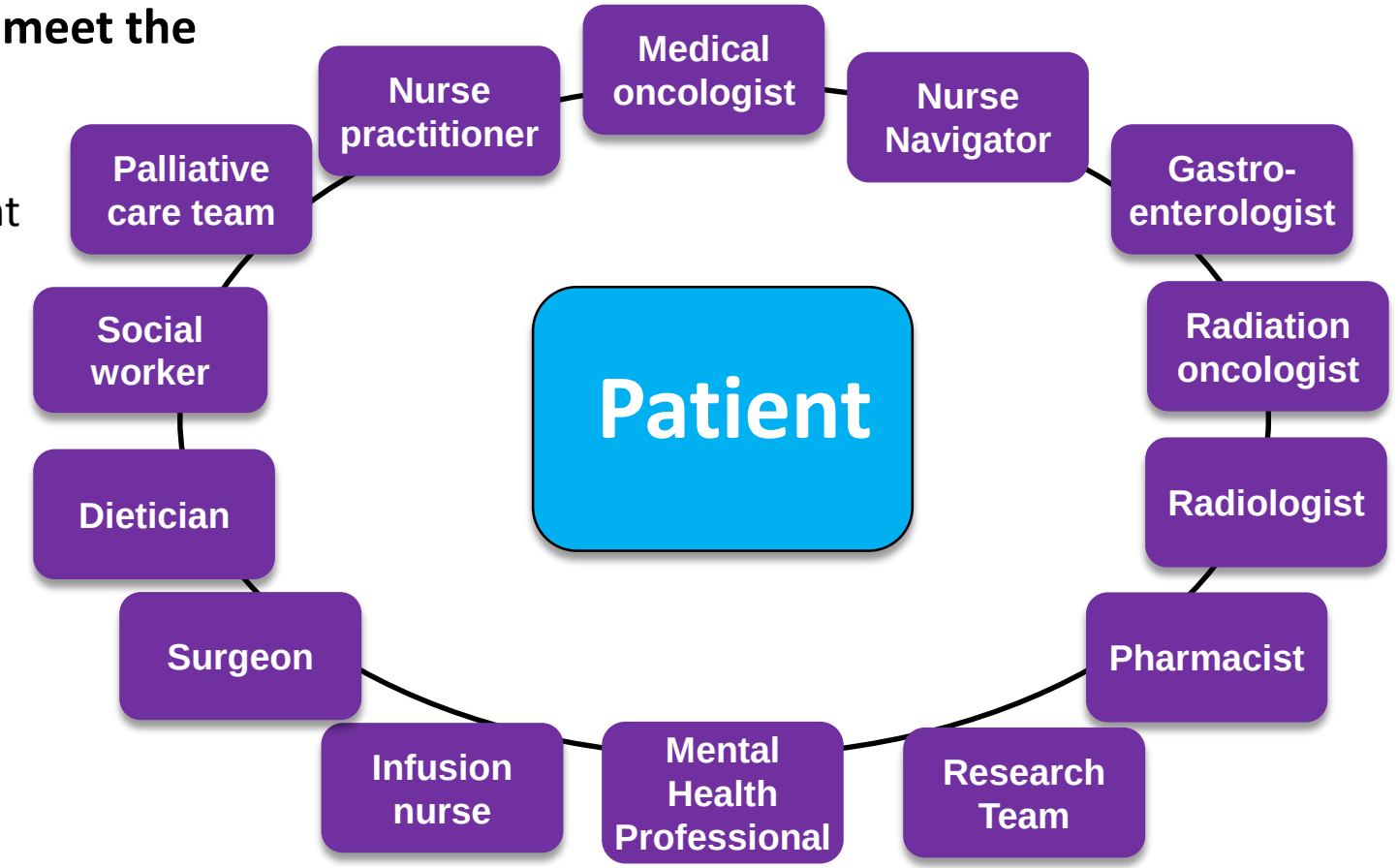
So how can we help patients live well with this disease?

Multidisciplinary Approach

Patient issues are very complex

Provide services to meet the following needs:

- Disease Management
- Physical
- Informational
- Emotional
- Spiritual
- Social



Cancer Related Fatigue (CRF)

CRF is a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning[1]

[1]National Comprehensive Cancer Network. NCCN.org Version 1.2016

Fatigue - What Can We Recommend?

***Important to rule out other causes; thyroid, adrenal dysfunction, narcotics, etc.**

Three Important Points

- **Good Nutrition**
- **Adequate Sleep**
- **Regular Exercise**

American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Survivors

Achieve and maintain a healthy weight.
- If overweight or obese, limit consumption of high-calorie foods and beverages and increase physical activity to promote weight loss.

Engage in regular physical activity
- Avoid inactivity and return to normal daily activities as soon as possible following diagnosis.
- Aim to exercise at least 150 minutes per week.
- Include strength training exercises at least 2 days per week.

Achieve a dietary pattern that is high in vegetables, fruits, and whole grains.
- Follow the American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention.

Correct the Myth
that More Rest is Good

Pancreatic Exocrine Insufficiency

Symptoms can be disabling and impact nutrition:
- bloating, excessive gas, abdominal pain, diarrhea – especially after meals

Symptoms may not be recognized as enzyme
Patients are frequently not treated or are under-dosed

Treat with oral Pancrealipase
- FDA has 3 approved products
- Tolerated well
- Instruct to take with first bite food
- May be “financially toxic” and not affordable

GI Symptoms

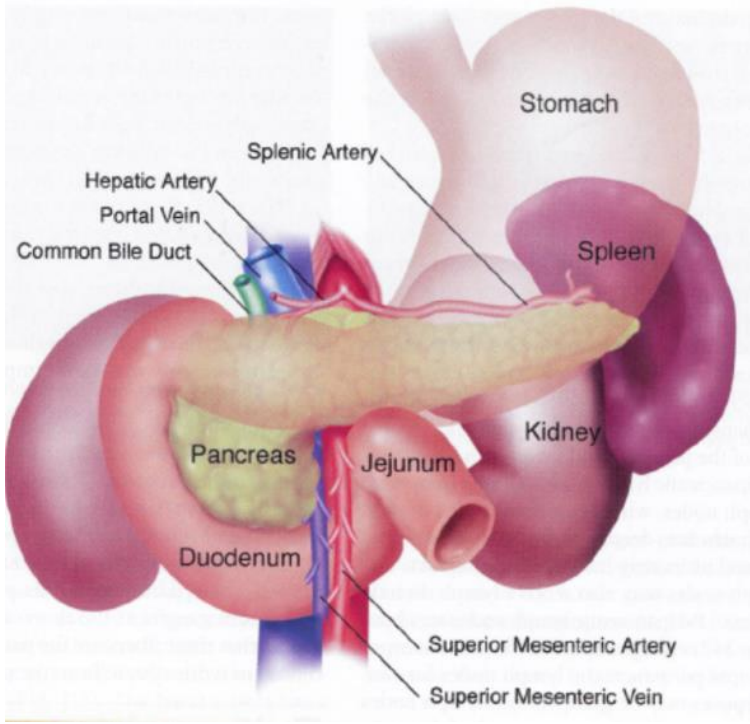
Nausea/vomiting

Determine cause

- Disease
- Chemotherapy
- Delayed gastric emptying
- Gastric outlet obstruction

Antiemetics, pro-motility agents

IV Hydration



Anorexia/cachexia

- Nutrition consult at time of dx
- Appetite stimulants
- Exercise for muscle strengthening

https://www.nccn.org/patients/resources/life_with_cancer/managing_symptoms/fatigue.aspx. Accessed April 9, 2018.
Mustian KM et al. *JAMA Oncol*. 2017; 3:961-968.

Pain

- Location depends on tumor site (head vs tail)
- Best treatment is to decrease tumor
- Narcotics: short and long acting
- NSAIDS
- Pain specialist
- Intrathecal pumps
- Celiac plexus block
- Palliative radiation or chemoradiation

Anxiety/Depression

Pancreatic cancer is believed to have one of the highest rates of concomitant depressive disorders[1]

- Discuss mood often with patients and family
- Assess for suicide risk
- Referrals to psychology or psychiatry, social services
- Pastoral Care
- Complementary Therapies
  - Yoga, Tai Chi, Massage, etc.
- Consider antidepressant meds

1. Akizuki N et al. *Jpn J Clin Oncol*. 2016;46:71-77.

Chemotherapy Induced Peripheral Neuropathy (CIPN)

- Despite 25+ years of study, CIPN remains essentially an untreatable toxicity of many chemotherapy agents
- Clearly affects quality of life and quantity of life by limiting effective treatments
- No well accepted evidence – based prevention interventions to date
- Interventions have been “borrowed” from the diabetic literature – not proven in CIPN; unknown if may interfere with chemotherapy effect
- New strategies for prevention and treatment are needed

Example of a non-pharmaceutical trial to address a common disabling treatment related problem

CIPN Prevention Trial

A Pilot Randomized Feasibility Trial Comparing an Investigational Hand Therapy Intervention to a Traditional Occupational Therapy Intervention to Prevent Chemotherapy-Induced Peripheral Neuropathy of the Hands in Patients Receiving Albumin-Bound Paclitaxel plus Gemcitabine Containing Combination Chemotherapy

Principal Investigator:
Gayle Jameson, MSN,ACNP-BC, AOCN

Medical Consultant:
Daniel Von Hoff, MD, FACP

Sponsored by Celgene
Site: HonorHealth Research Institute
Scottsdale, AZ

Research

Great need for clinical trials addressing symptom prevention and management

Goals – improve QOL for patient and family, decrease symptom burden

Hot Topics in cancer related symptom research[1]

- Pain: 164 studies
- Fatigue: 80 studies
- Caregivers: 50 studies
- Neuropathy: 27 studies
- Cachexia – 20 studies

[1]https://clinicaltrials.gov, retrieved 4/30/18

Let’s not forget the Family

- Involve family members only as requested by the patient
- Respect boundaries
- Caretaker support & counseling
- Involve specialists in supporting children

Pancreatic Cancer is Not an Impossible Enemy

Slide courtesy of Daniel Von Hoff

Thank you