Pancreatic cancer

TRACO-2022

Pancreatic Cancer: From Bench to Bedside

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Cancer incidence and mortality

Pancreatic Cancer Incidence and Mortality

Estimated Deaths

Siegel R et. al., *CA Cancer J Clin*, 2022

Males				Females		
Lung & bronchus	68,820	21%		Lung & bronchus	61,360	21%
Prostate	34,500	11%		Breast	43,250	15%
Colon & rectum	28,400	9%		Colon & rectum	24,180	8%
Pancreas	25,970	8%		Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%		Ovary	12,810	4%
Leukemia	14,020	4%		Uterine corpus	12,550	4%
Esophagus	13,250	4%		Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%		Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%		Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%		Brain & other nervous system	7,570	3%
All Sites	**322,090**	**100%**		**All Sites**	**287,270**	**100%**

- **3rd leading cause of cancer death in the United States**
- **Median 5-year survival is 11.5%**
- **Estimated 62,210 new diagnoses and 49,830 deaths in 2022**
- **Incidence is increasing**

Risk factors

Risk Factors

Ryan, Hong and Bardeesy, *NEJM*, 2014

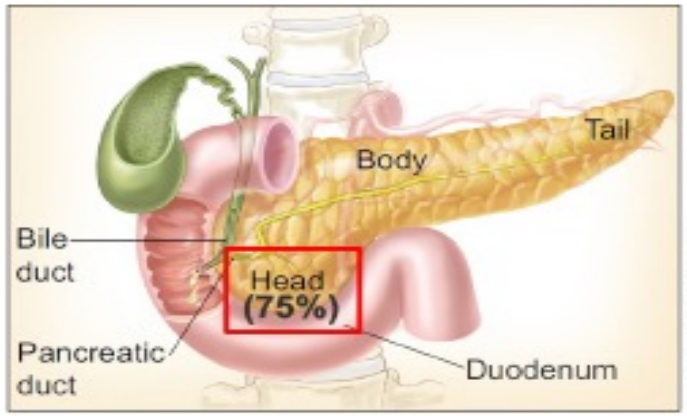
Table 1. Risk Factors and Inherited Syndromes Associated with Pancreatic Cancer.*

Variable	Approximate Risk
Risk factor	
Smoking[3]	2–3
Long-standing diabetes mellitus[4]	2
Nonhereditary and chronic pancreatitis[5]	2–6
Obesity, inactivity, or both[6]	2
Non–O blood group[7]	1–2
Genetic syndrome and associated gene or genes — %	
Hereditary pancreatitis (*PRSS1, SPINK1*)[8]	50
Familial atypical multiple mole and melanoma syndrome (*p16*)[9]	10–20
Hereditary breast and ovarian cancer syndromes (*BRCA1, BRCA2, PALB2*)[10,11]	1–2
Peutz–Jeghers syndrome (*STK11* [*LKB1*])[12]	30–40
Hereditary nonpolyposis colon cancer (Lynch syndrome) (*MLH1, MSH2, MSH6*)[13]	4
Ataxia–telangiectasia (*ATM*)[14]	Unknown
Li–Fraumeni syndrome (P53)[15]	Unknown

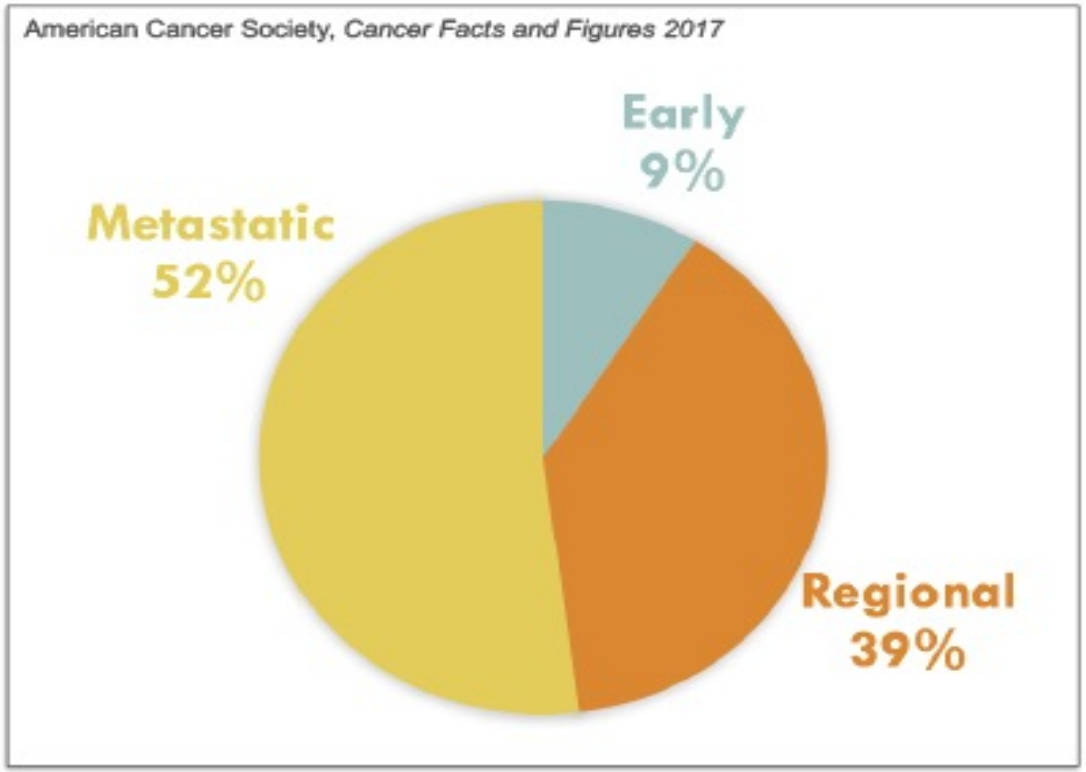
* Values associated with risk factors are expressed as relative risks, and values associated with genetic syndromes are expressed as lifetime risks, as compared with the risk in the general population.

Pancreatic cancer types and stage

Pancreatic Cancer: Types and Stage at Diagnosis

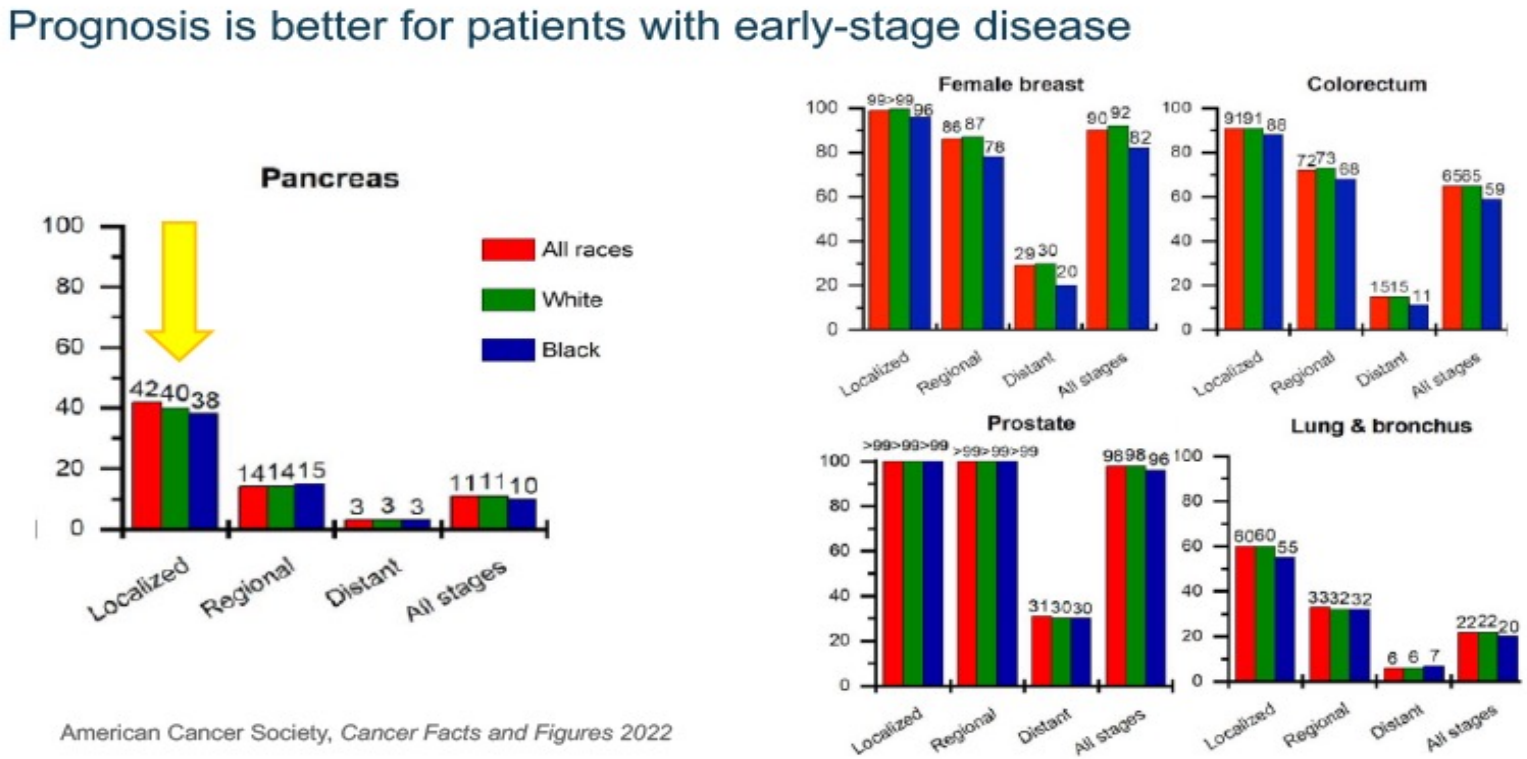


- **Adenocarcinoma (~90%)**
- Neuroendocrine (<5%)
- Rare exocrine tumors



Cancer of the Pancreas, NIH Publication No. 10-1560, 2010

Prognosis and stage

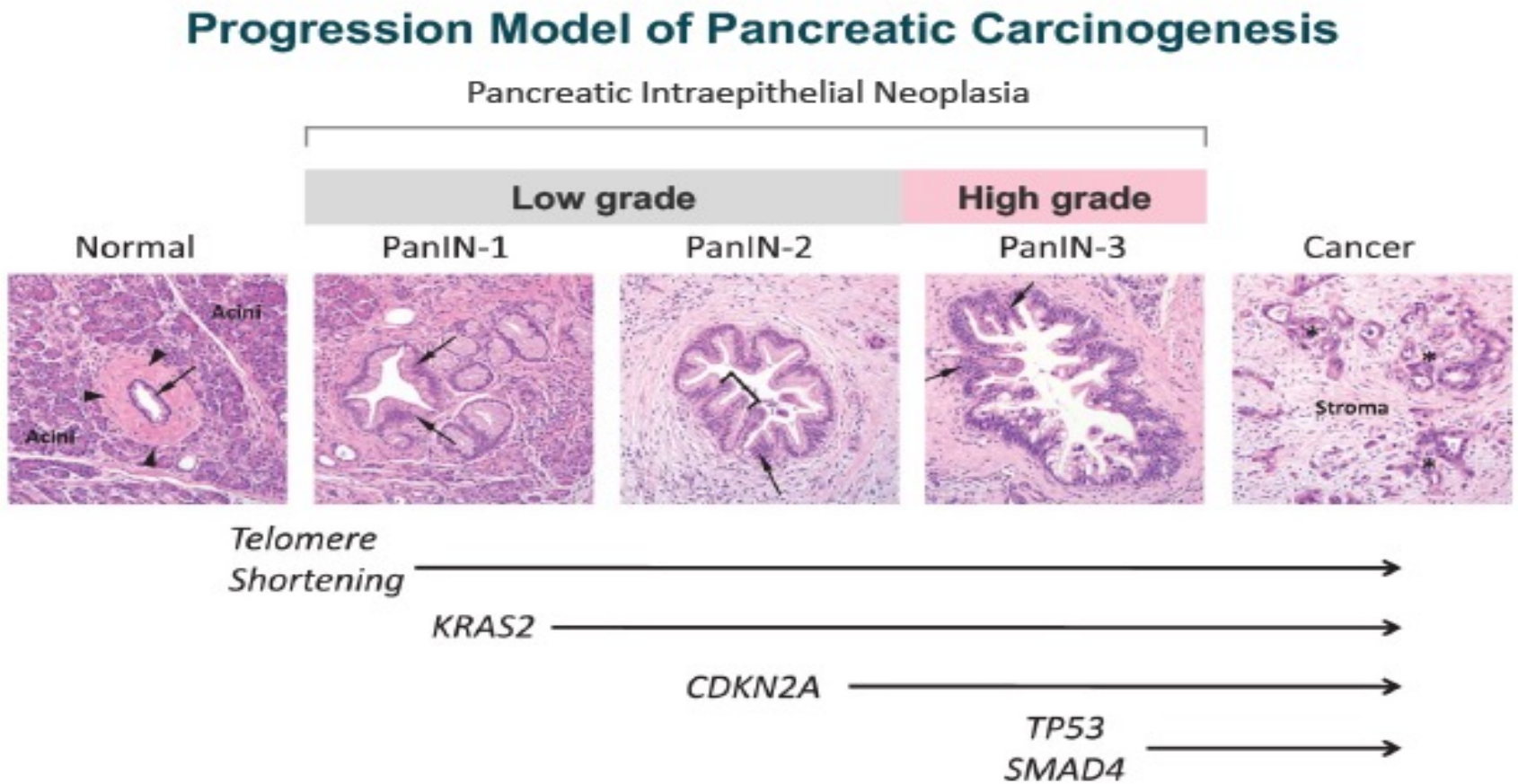


Lack of early detection

Why can't we detect pancreatic cancer earlier?

- Early symptoms are non-specific
- Current imaging methods rarely detect small lesions
- Difficulty in identifying specific biomarkers
  - Pancreatic Cancer is relatively rare (12.1/ 100,000 persons)
  - Test with 100% sensitivity and 99% specificity => 83 false positive for every real case
- Retroperitoneal positioning of the pancreas makes biopsy difficult
- Risk vs. benefit of removing suspicious pre-cursor lesions

Progression



Iacobuzio-Donahue et al., *Gut*, 2012

High-risk populations

Screening in High-Risk Populations

- Families with known genetic mutations that predispose to pancreatic cancer
- Persons with multiple close relatives who developed pancreatic cancer
- Over age 50 with newly diagnosed diabetes
- Chronic pancreatitis

Surveillance protocol

Annual surveillance with EUS and/or MRI/MRCP, often alternating between the two methods (surveillance interval was modified when concerning lesions were detected)

Dbouk et al, *Clin. Canc. Res.*, 2022

Familial disease

Progress in Screening Patients with Familial Disease- CAPS

HRIs

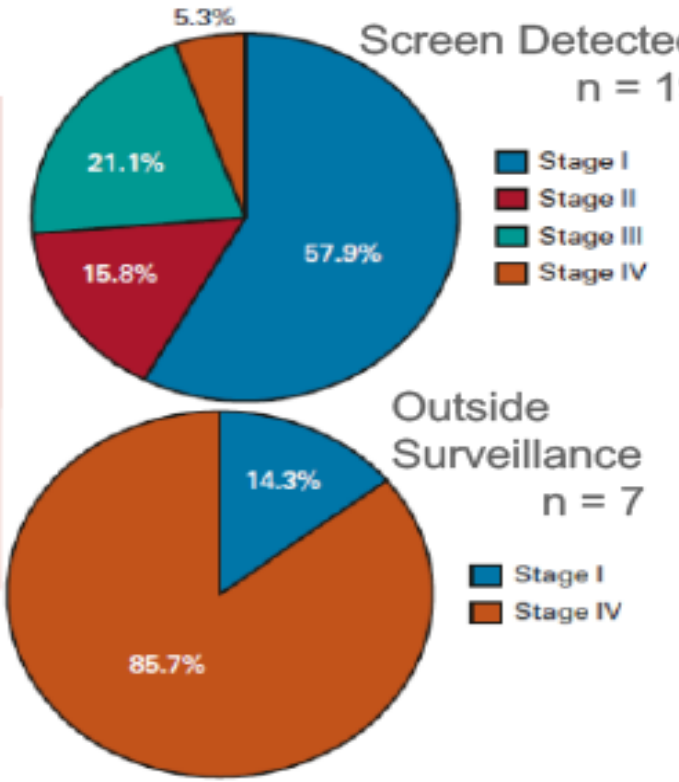
Hereditary syndromes or germline variant carriers:

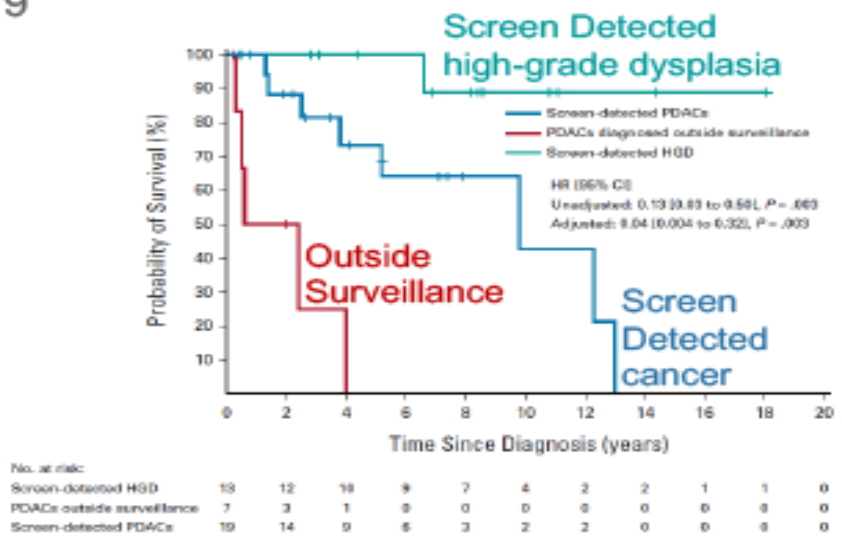
BRCA2, ATM, BRCA1, PALB2, or Lynch syndrome–associated genes with family history of PDAC
FAMMM *(CDKN2A)*
Peutz-Jeghers *(STK11)*

Family history of at least one first-degree and one second-degree relative with PDAC

Meeting age criteria for surveillance

N = 1731 in screening





N = 26 PDAC
N= 13 HGD

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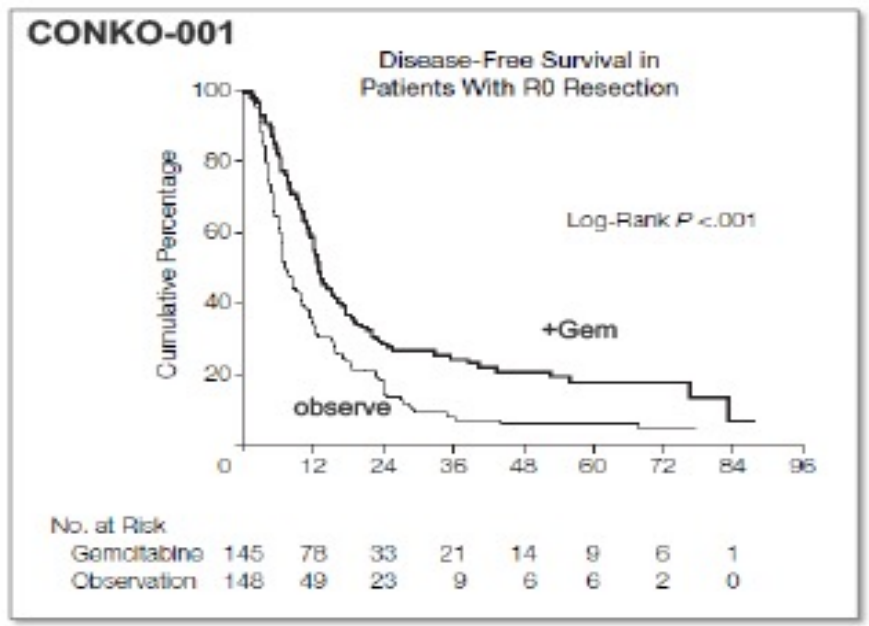
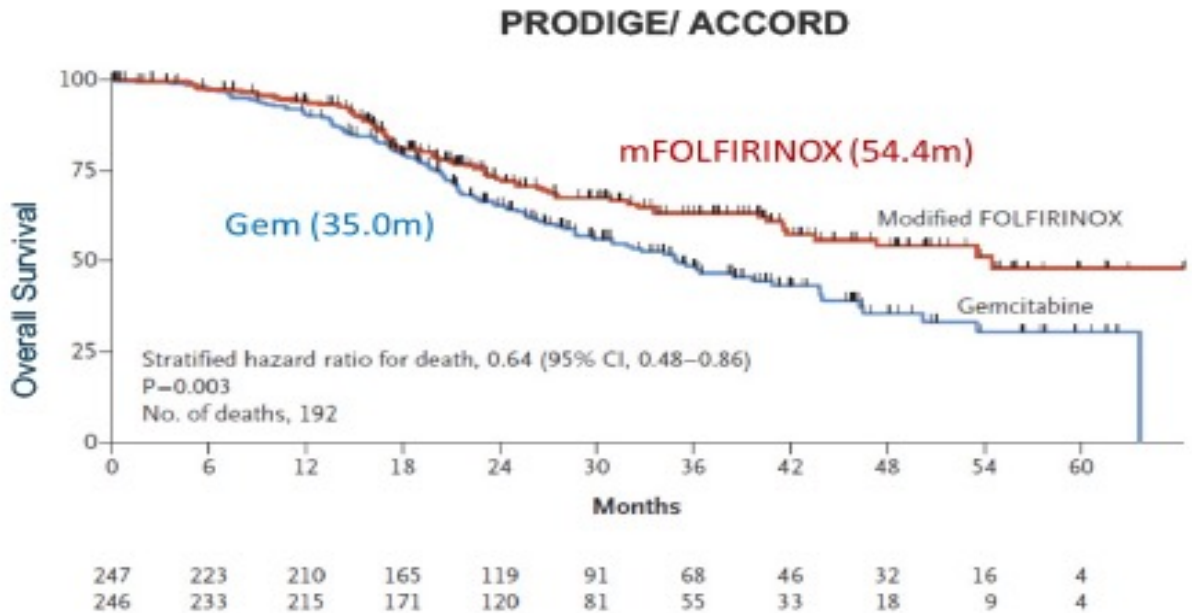
Dbouk et al, *Clin. Canc. Res.*, 2022

Surgery plus chemotherapy

Early Stage Disease: Surgery + Chemotherapy



Oettle et al, *JAMA*, 2007



Conroy et al, *NEJM*, 2018

Neoadjuvant chemotherapy (chemo BEFORE surgery) is currently being tested in clinical trial and may provide additional survival advantage

Neoantigen qualities

LETTER

doi:10.1038/nature24462

Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer

Vinod P. Balachandran[1,2,3], Marta Łuksza[4], Julia N. Zhao[1,2,3], Vladimir Makarov[5,6], John Alec Moral[1,2,3], Romain Remark[7], Brian Herbst[2], Gokce Askan[2,8], Umesh Bhanot[8], Yasin Senbabaoglu[9], Daniel K. Wells[10], Charles Ian Ormsby Cary[10], Olivera Grbovic-Huezo[2], Marc Attiyeh[1,2], Benjamin Medina[1], Jennifer Zhang[1], Jennifer Loo[1], Joseph Saglimbeni[1], Mohsen Abu-Akeel[9], Roberta Zappasodi[9], Nadeem Riaz[6,11], Martin Smoragiewicz[12], Z. Larkin Kelley[13,14], Olca Basturk[8], Australian Pancreatic Cancer Genome Initiative*, Mithat Gönen[15], Arnold J. Levine[4], Peter J. Allen[1,2], Douglas T. Fearon[13,14], Miriam Merad[7], Sacha Gnjatic[7], Christine A. Iacobuzio-Donahue[2,5,8], Jedd D. Wolchok[3,9,16,17,18], Ronald P. DeMatteo[1,2], Timothy A. Chan[3,5,6,11], Benjamin D. Greenbaum[19], Taha Merghoub[3,9,18]§ & Steven D. Leach[1,2,5,20]§

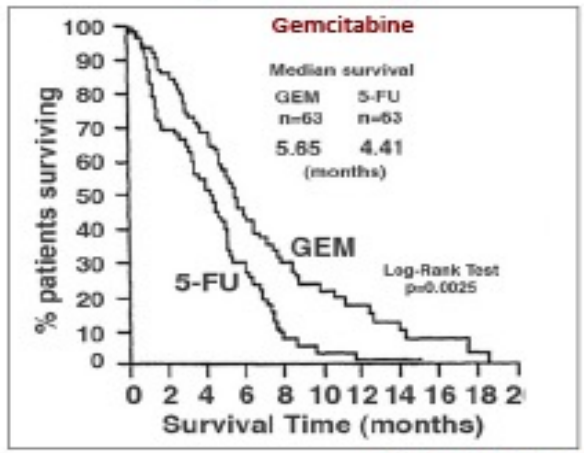
- Abundant CD8⁺ T Cell Infiltrate
- Neoantigen quality promotes T Cell Activity in Long-term survivor

Balachandran et. al., *Nature*, 2017

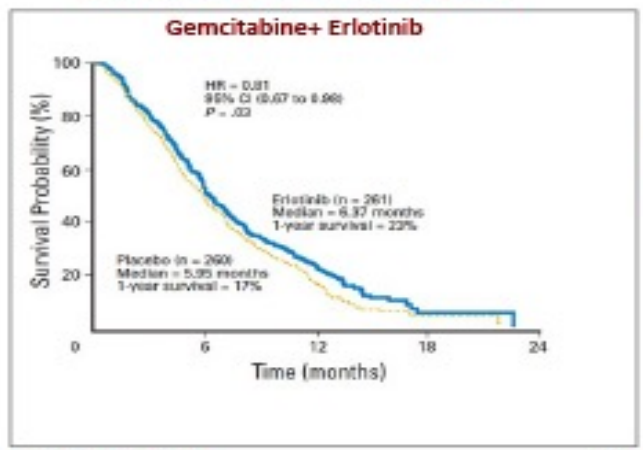
Combination chemo

Treatment for Advanced Pancreatic Cancer is Combination Chemo

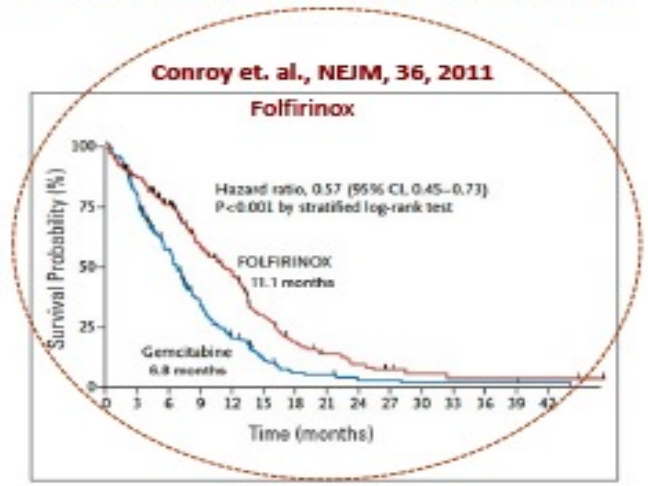
Burris et. al., J. Clin. Oncol., 15, 1997



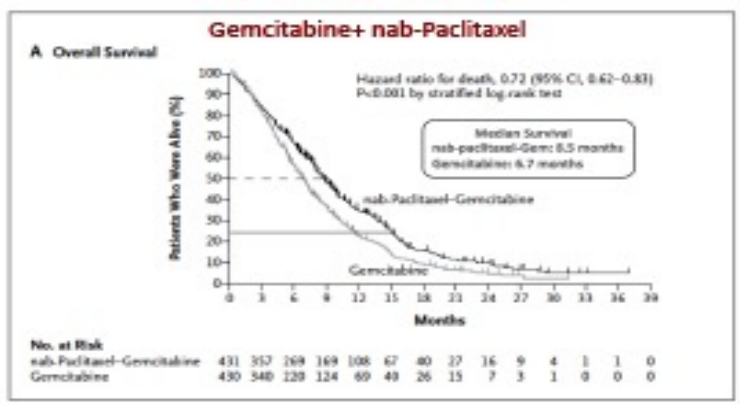
Moore et. al., J. Clin. Oncol. 25, 2007



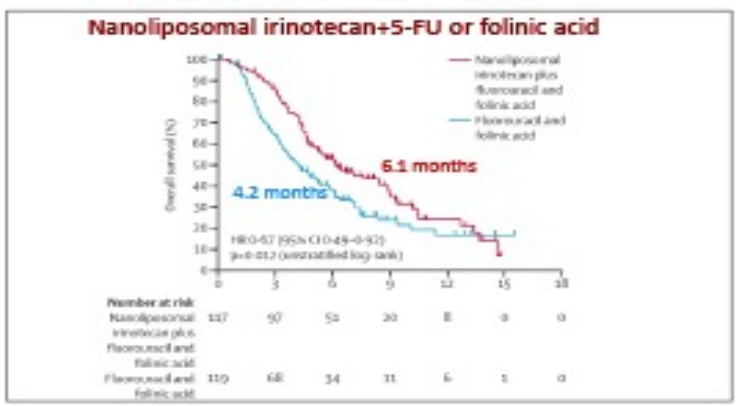
Conroy et. al., NEJM, 36, 2011



Von Hoff, D.D. et. al, NEJM, 369, 2013

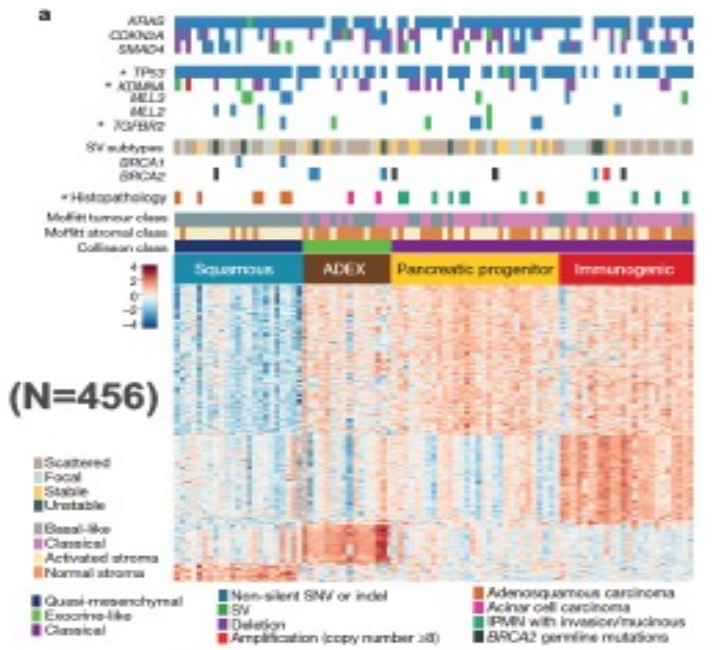


Wang-Gillam A., et. al., Lancet, 2015

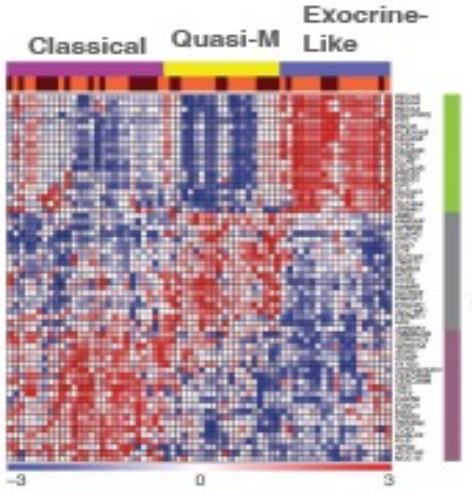


Pancreatic subtypes

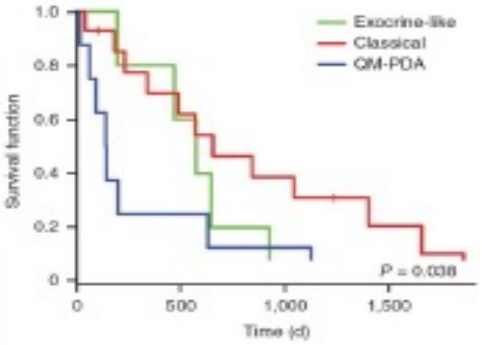
Transcriptomic profiling of PDAC has identified "subtypes"

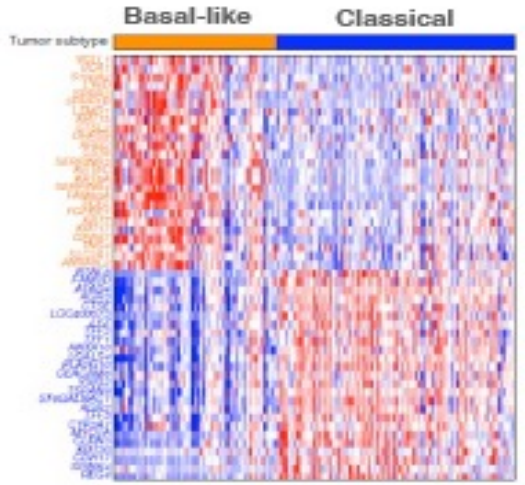


Bailey et. al., *Nature*, 2016

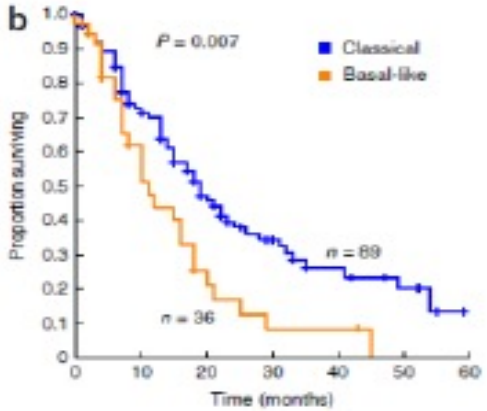


Collisson et. al., *Nat. Med.*, 2011



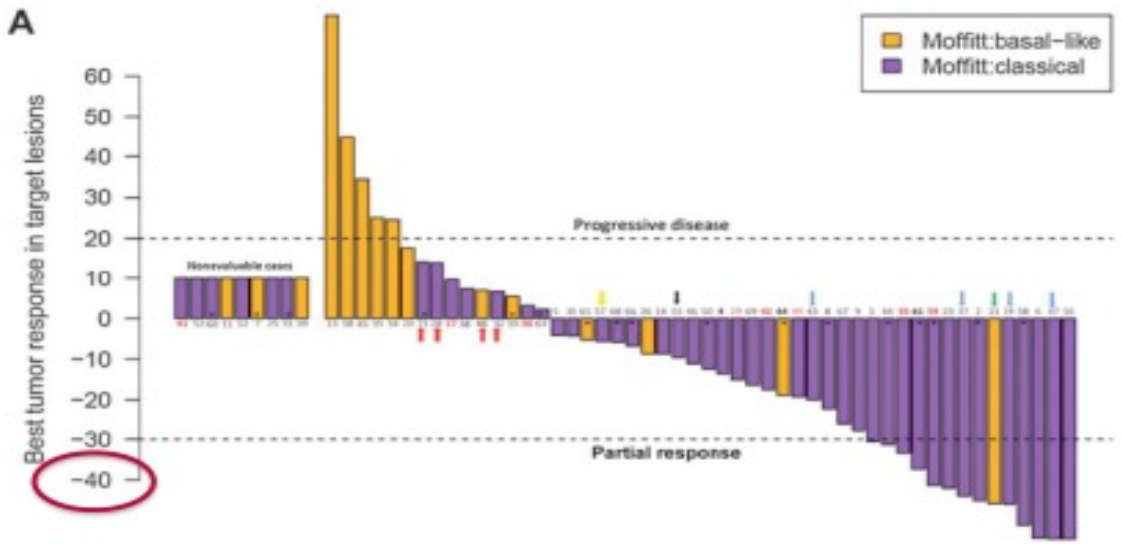


Moffit et. al., *Nat. Gen.*, 2015



Classical subtype

Classical subtype responds better to chemotherapy

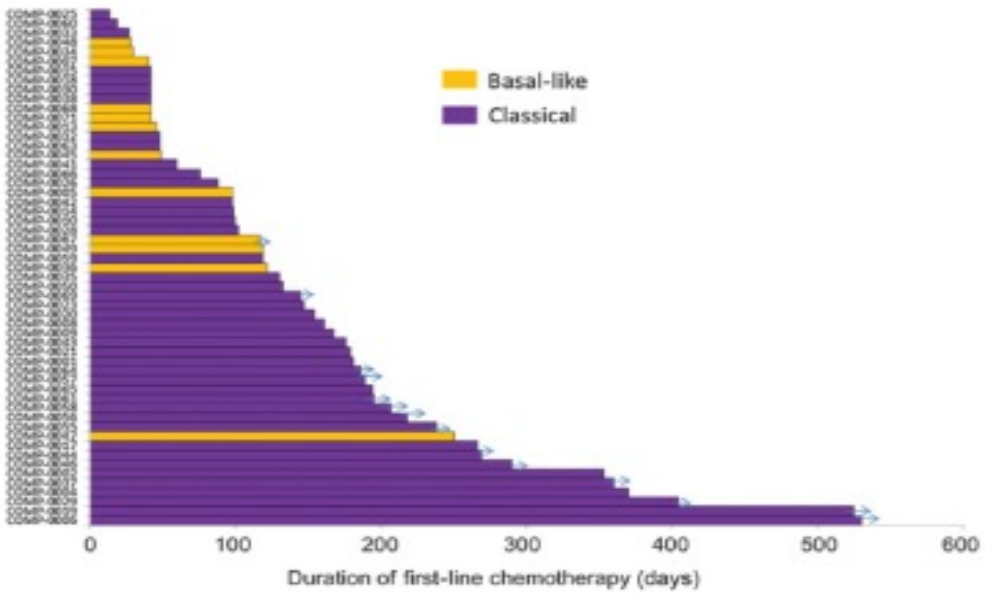


Waterfall plot: how deep is the response?

"Deep" = the tx shrinks the tumor a lot

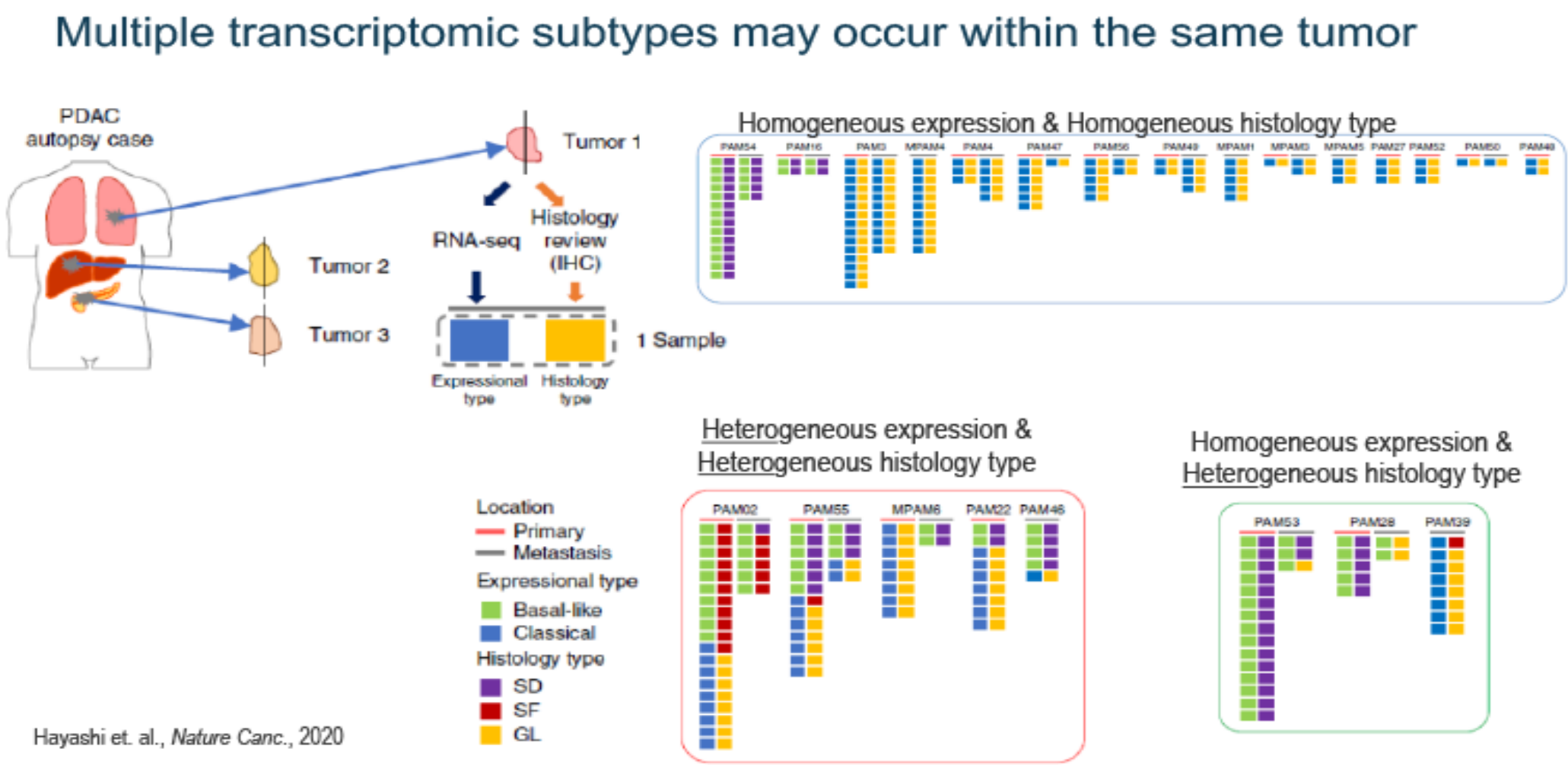
Swimmer plot: how durable?

"durable" = the tx works a long time



Aung et. al., *Clin. Canc. Res.*, 2019

Multiple subtypes

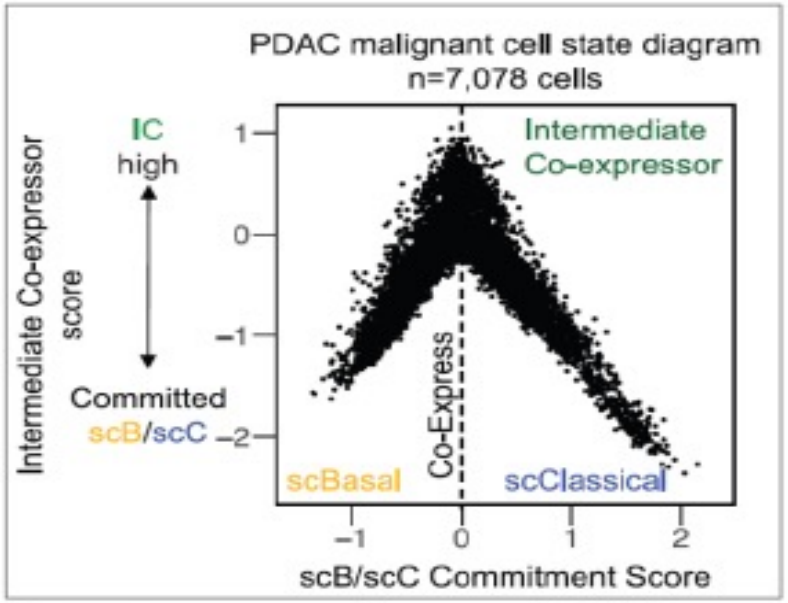


Hayashi et. al., *Nature Canc.*, 2020

Environmental subtype regulation

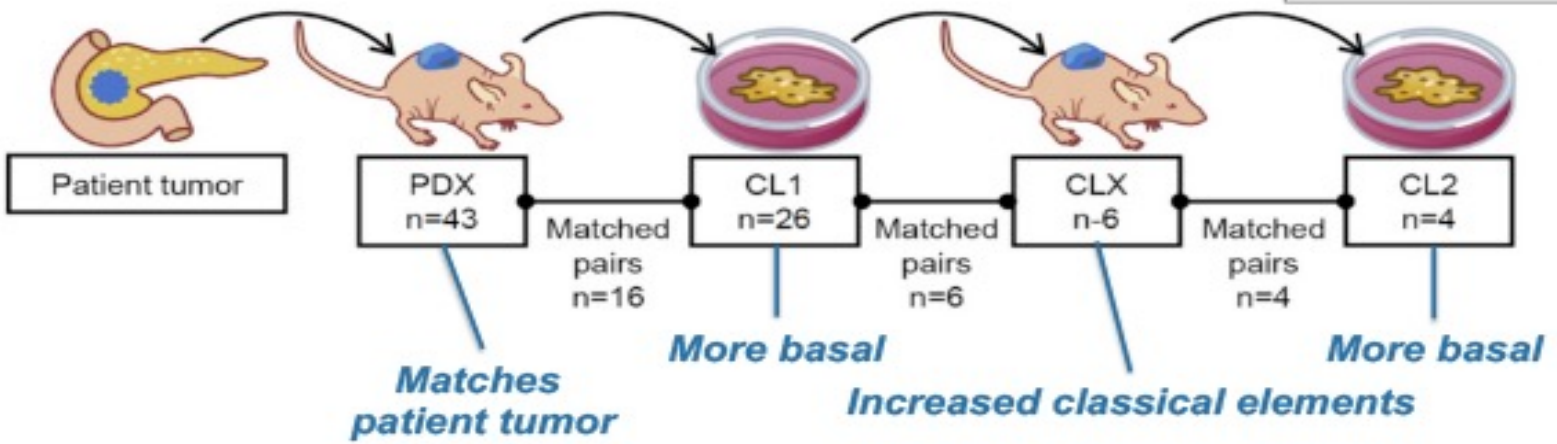
Transcriptomic subtypes are plastic and regulated environmentally

- An intermediate subtype exists
- Environmental cues influence subtype



Rhagavan et. al., *Cell*, 2021

- Our models change subtype:



Baba et. al., *Gastroenterology.*, 2022

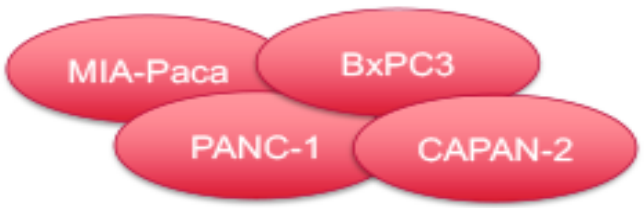
Gene alterations

Cowley et al, *J. Hepatobiliary Panc. Sci*, 2013

Preclinical models

Preclinical models of PDAC

1) Standard cell lines

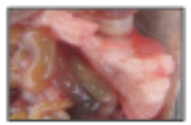


Implant subq into mice

- Highly cellular tumors don't resemble human disease
- Models fail to predict response to therapy

2) KPC spontaneous autochthonous model

KC model
- PanINs
- AdCa in old age



KPC mice
- Most mice have AdCa by 4 mo
- Dense stroma
- Gem resistant

3) Patient-derived xenograft (PDX)

- Predictive of patient response to treatment
- NSG mice required

4) Organoids

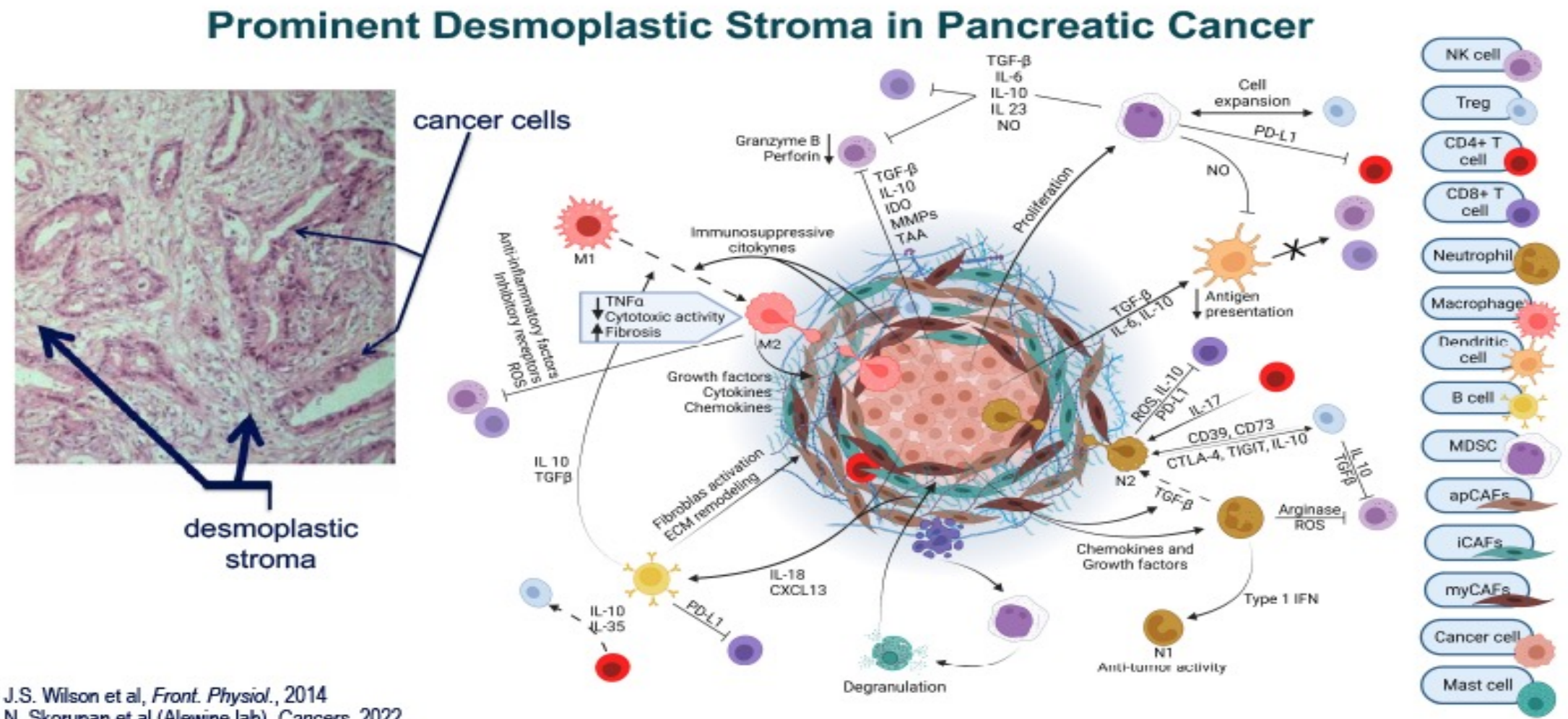
- Predictive of patient response to treatment
- Cannot be used to evaluate immuno-oncology drugs or stromal modulators

5) Tissue slice culture

- Transient, non-renewable
- Intact immune/ stromal TME

S Hingorani et al, *Cancer Cell*, 2005
Tiriac et al, *Cancer Disc.*, 2018

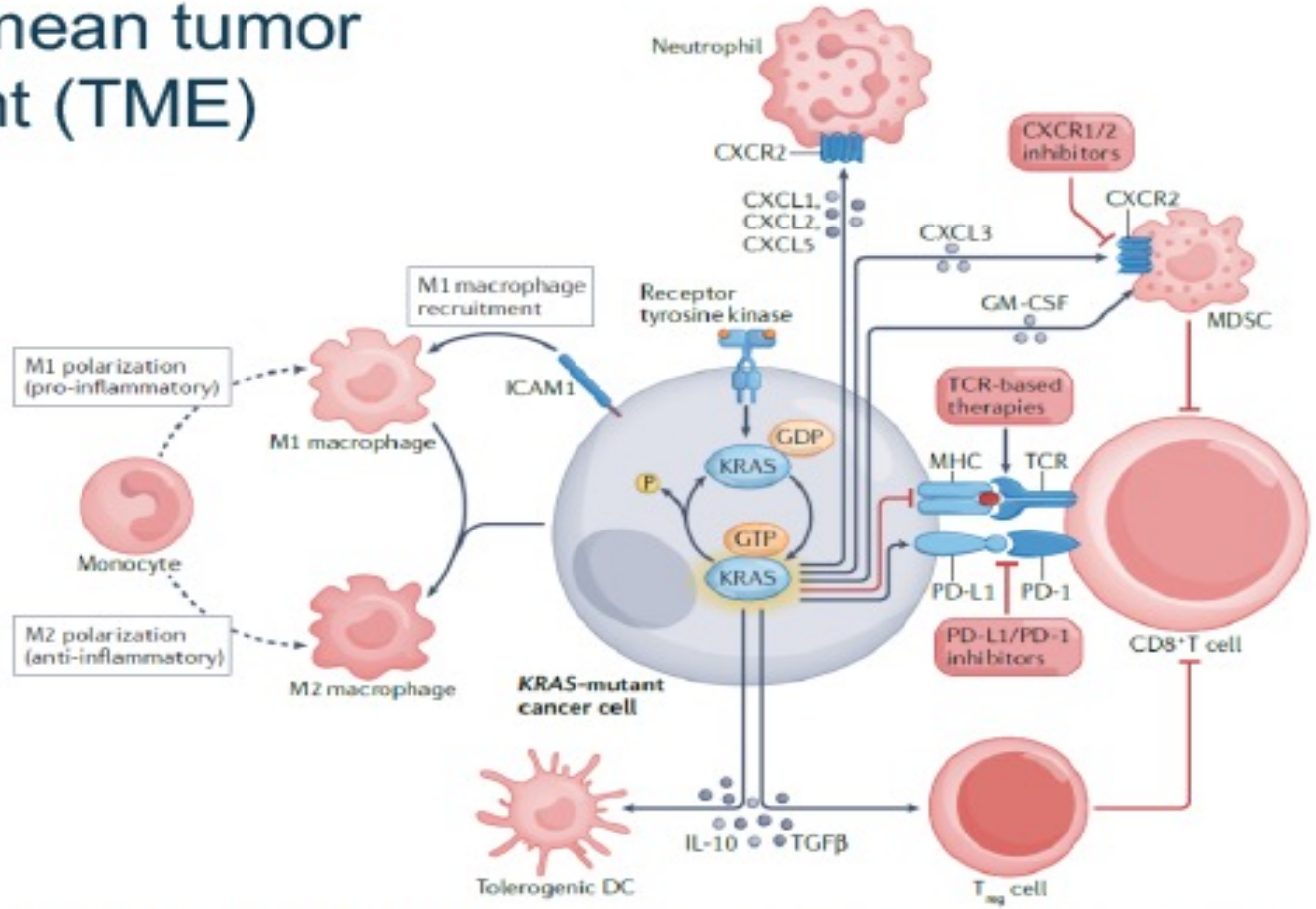
Stroma



J.S. Wilson et al, *Front. Physiol.*, 2014
N. Skorupan et al (Alewine lab), *Cancers*, 2022

KRAS

KRAS makes a mean tumor microenvironment (TME)



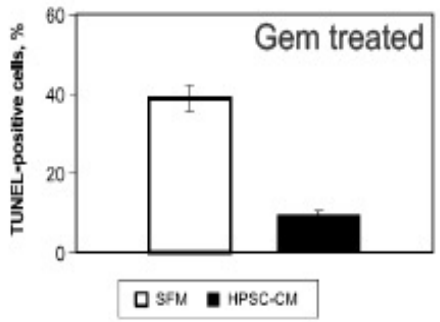
Punekar et al, *Nat. Rev. Clin. Onc.*, 2022

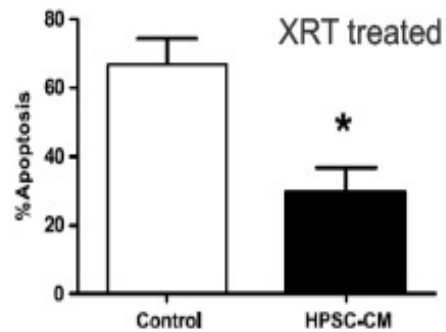
Fig. 3 | **The influence of mutant KRAS on the tumour immune microenvironment.** Activating *KRAS* mutations have

Resistance

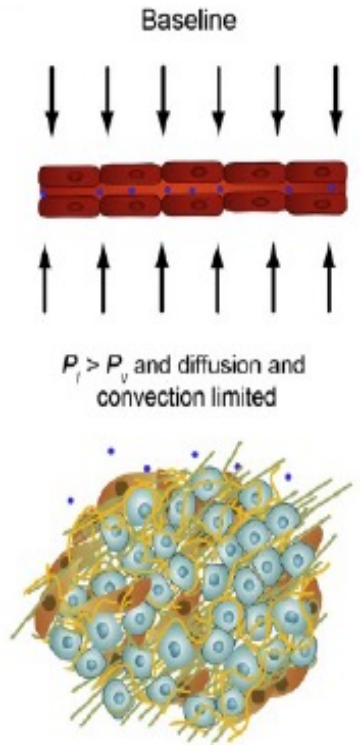
Stroma makes PDAC resistant to treatment

- Factors secreted by CAFs help cancer cells survive
- ECM collapses blood vessels limiting drug delivery to tumors



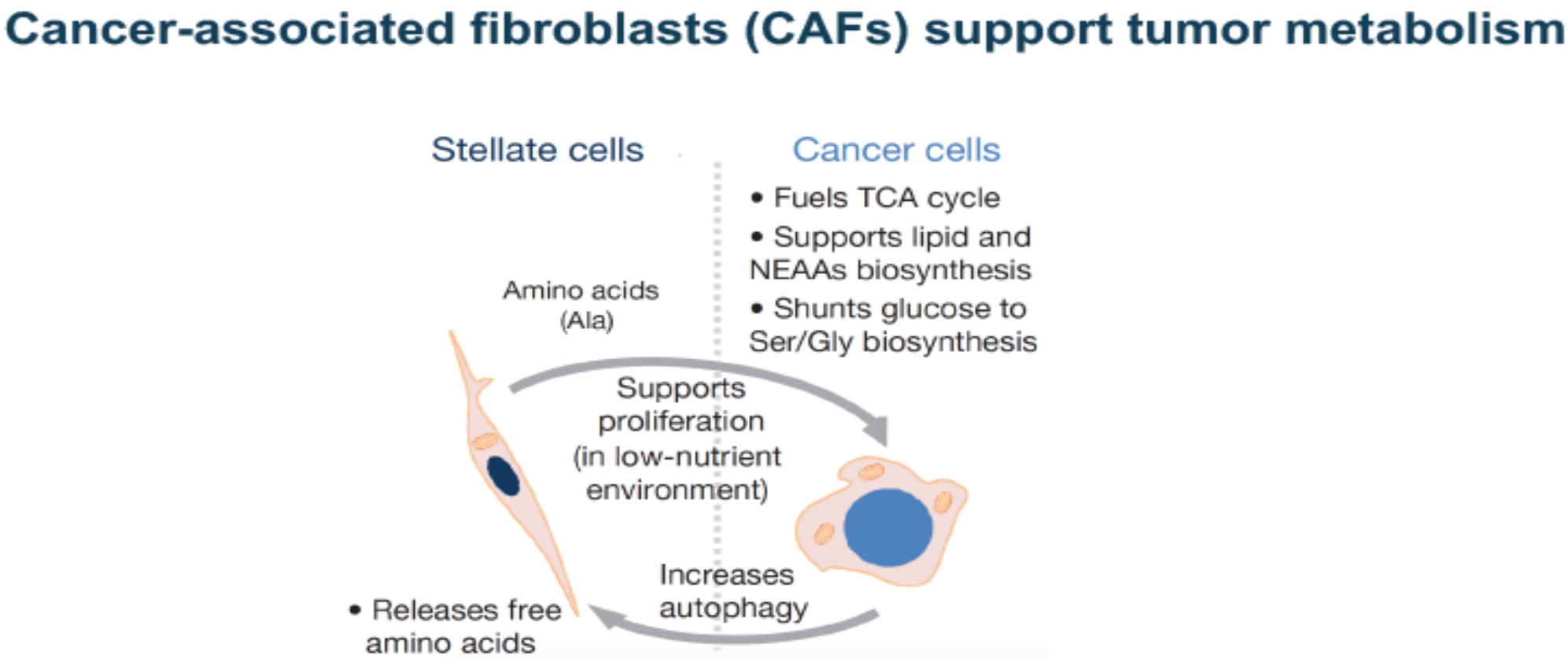


Hwang et. al., *Cancer Res.*, 2008



Provenzano et. al., *Cancer Cell*, 2012

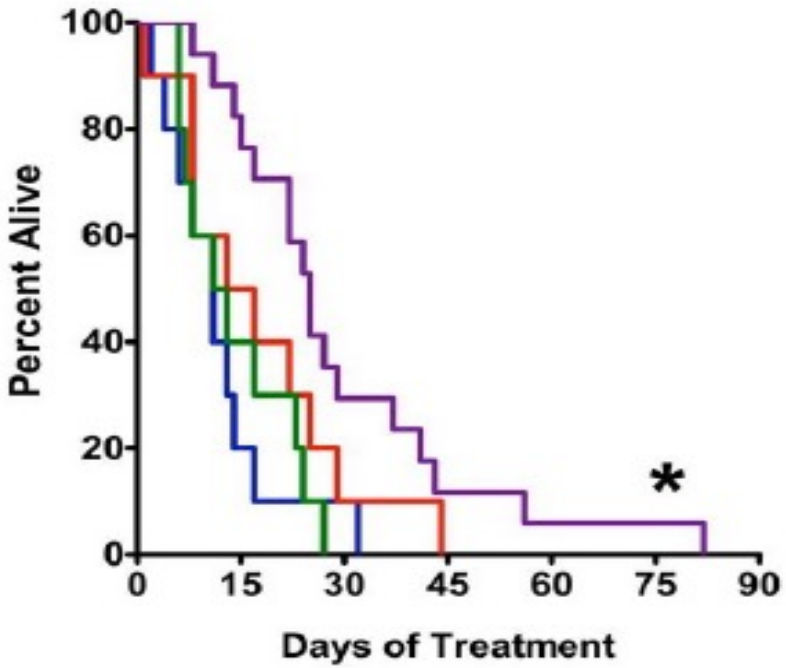
Cancer associated fibroblasts

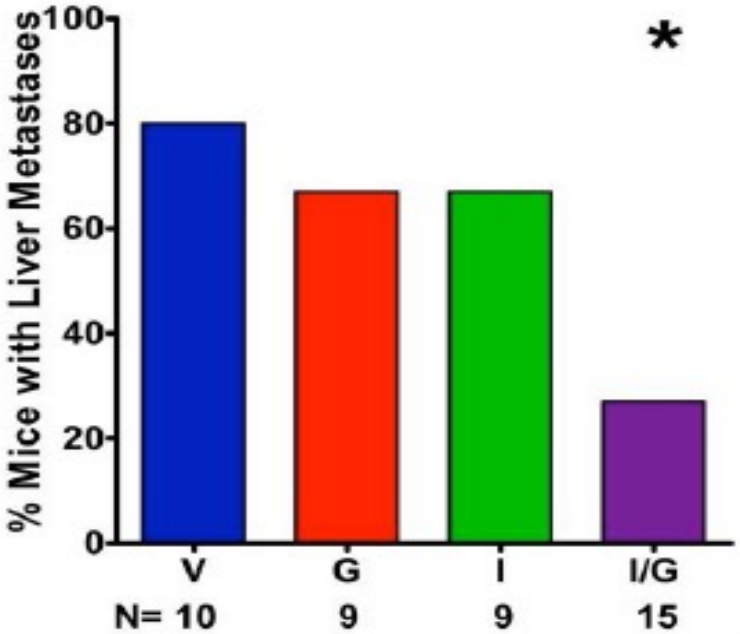


Sousa, et. al., *Nature*, 2016

Hedgehog signaling

Inhibition of Hedgehog Signaling Depleted Stroma, Enhanced Drug Delivery and Improved Survival in Mice



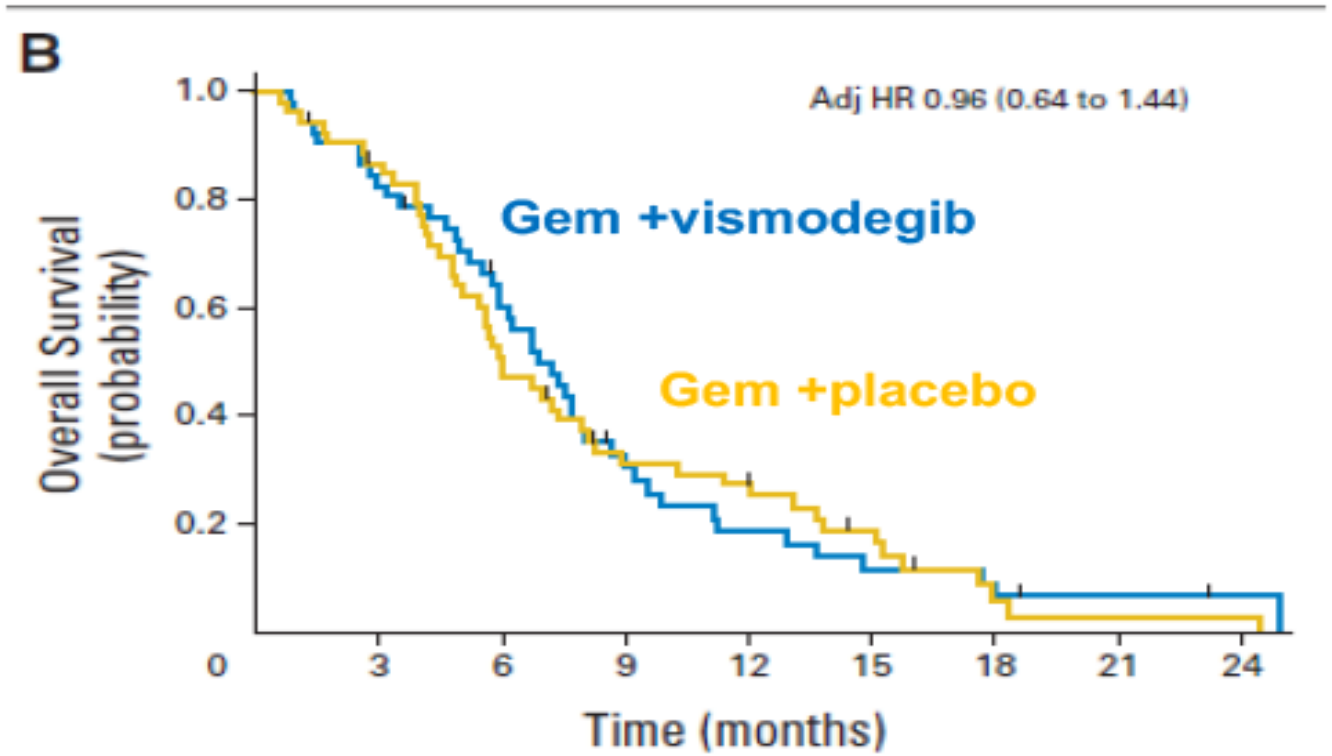


V=Vehicle
G=Gemcitabine
I= IPI-926 (Hedgehog Inhibitor)
I/G= IPI-926/Gem

Olive KP et. al., *Science*, 2009

SHH inhibitor

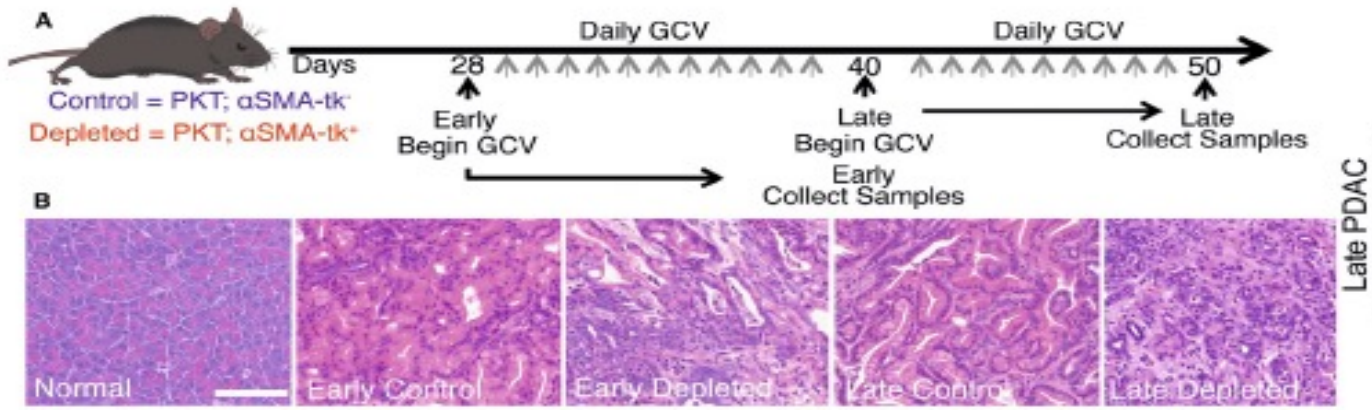
SHH inhibitor ineffective in clinic



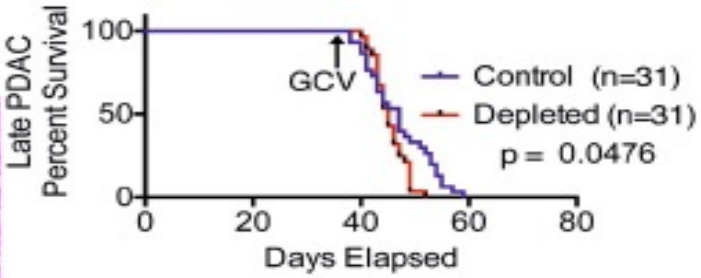
Catenacci et. al., *J. Clin. Onc.*, 2015

CAF destruction

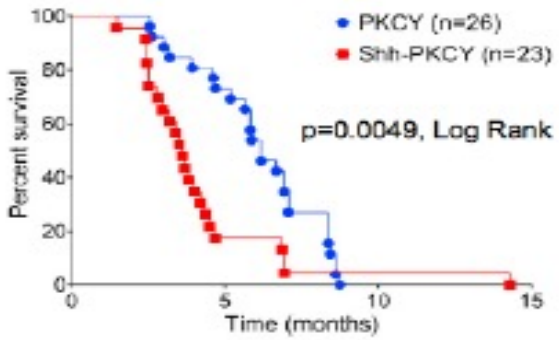
Destruction of CAFs => more metastatic, poorly diffentiated tumors

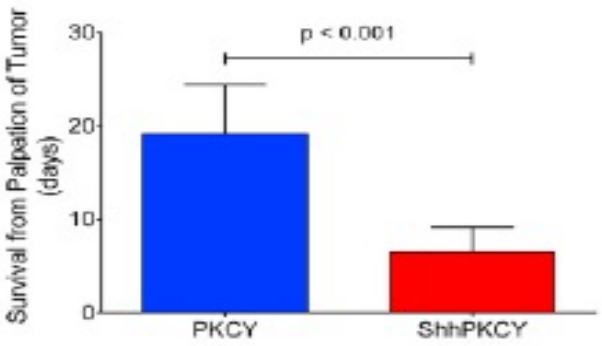


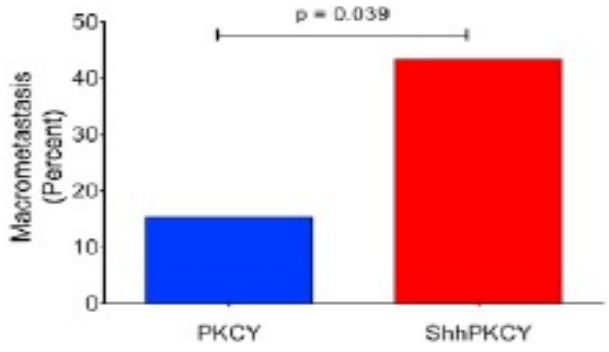
Ozdemir, BC et. al., *Cancer Cell*, 2014



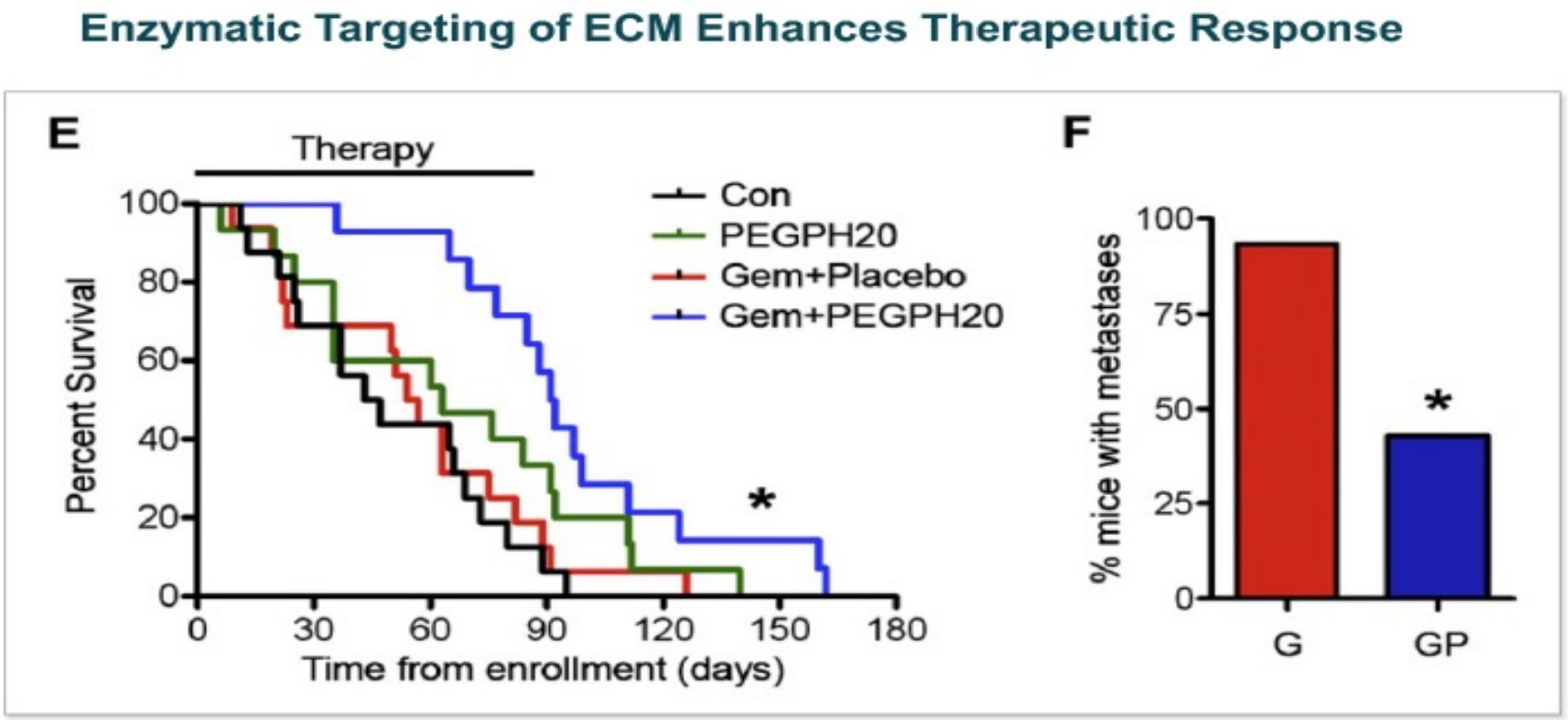
Rhim et. al., *Cancer Cell*, 2014







Extracellular matrix



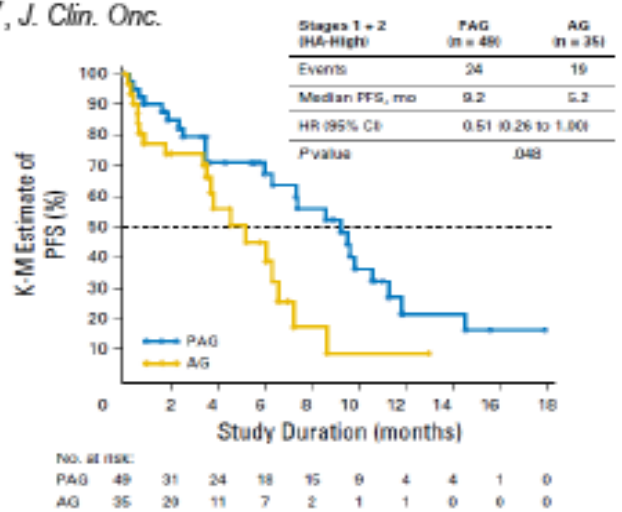
Provenzano et. al., *Cancer Cell*, 2012

PEGPH20

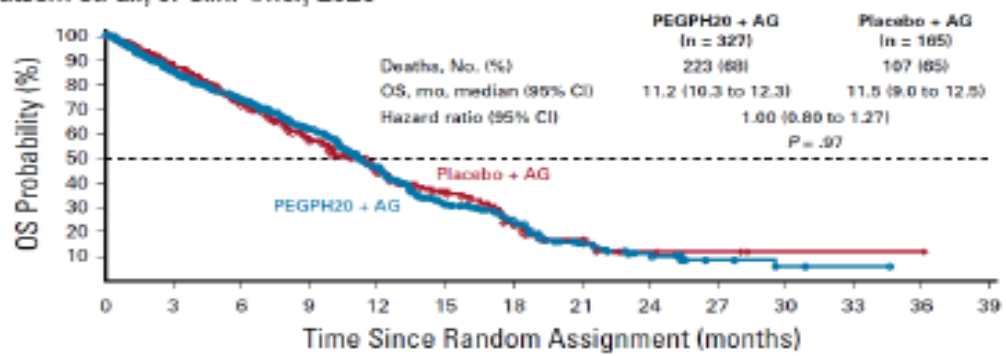
PEGPH20 in Clinic

- Phase 1
  - PEGPH20 caused blood clots
  - Must give with blood thinner
- Arms:
  - Gem + nab-p
  - Gem + nab-p + PEGPH20
- Phase 2
  - Patients with advanced PDAC
  - No benefit in the whole study population (negative study)
  - Hyaluronin(HA) high patients had better outcome
- Phase 3
  - Patients with HA high metastatic PDAC
  - No survival benefit

Hingorani et al 2017, *J. Clin. Onc.*



Van Cutsem et. al., *J. Clin. Onc.*, 2020



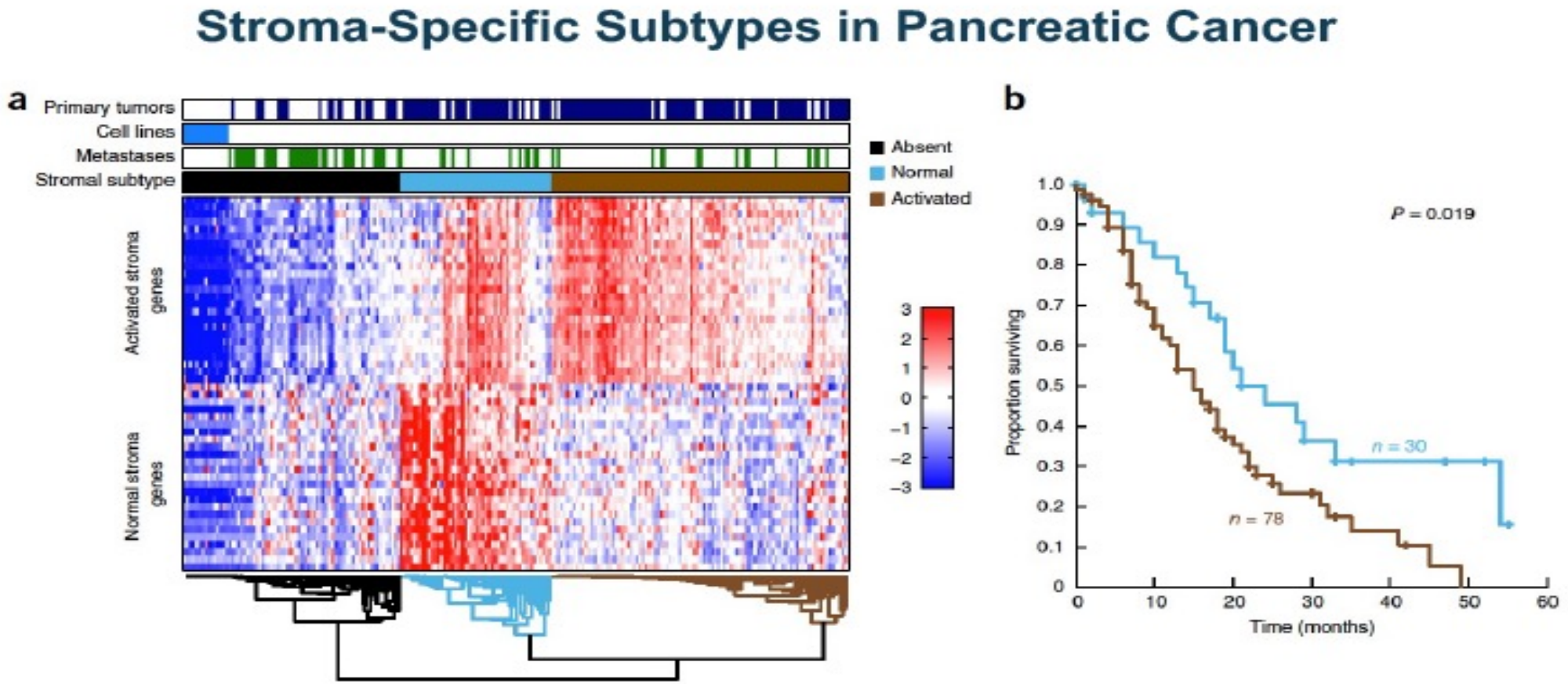
Stromal target

Carefully choose your stromal target!

**Stromal-targeting may not (always)
have beneficial therapeutic response**

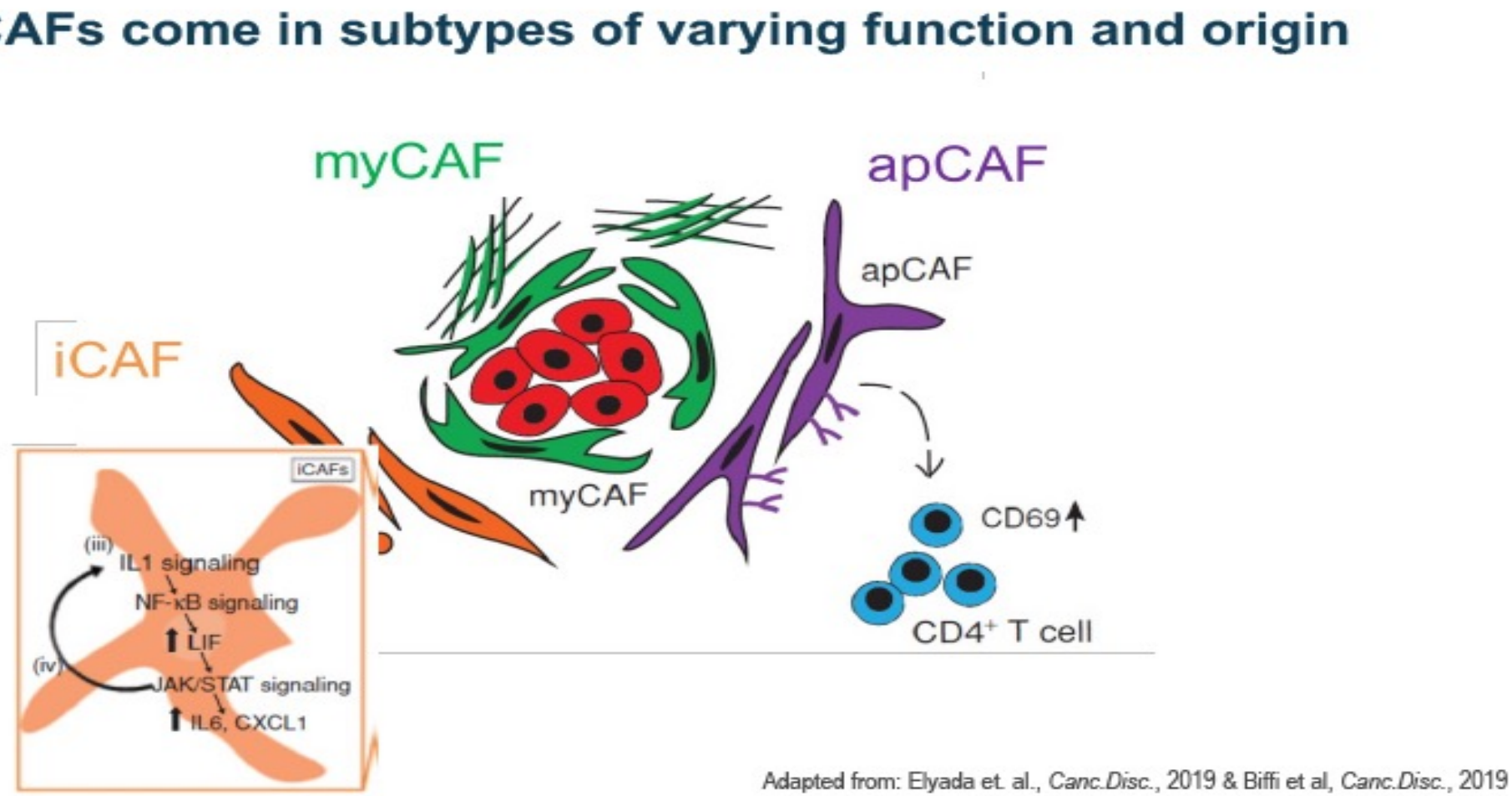
Tumor-Stromal interaction is complex
and caution is required for therapeutic approaches
targeting stroma

Stromal subtypes



Moffitt et. al., *Nat. Genetics*, 2015

CAF subtypes



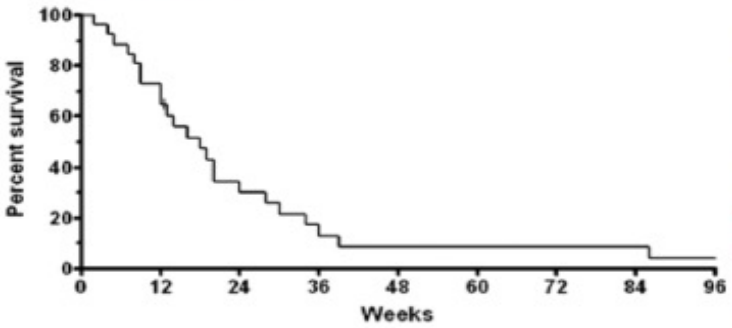
Adapted from: Elyada et. al., *Canc.Disc.*, 2019 & Biffi et al, *Canc.Disc.*, 2019

Immunotherapy

PDAC and immunotherapy

PDAC does not respond to single agent immunotherapy agents

Anti-CTLA4



Royal et al 2010, *J. Immunother.*

Anti-PD1 Cohort-Tumor Type	N*	ORR %	mPFS (mo)	mOS (mo)
Overall	471	14	2.2	11.3
Mesothelioma (MPM)	25	20	5.5	18.7
Nasopharyngeal Carcinoma	27	26	6.5	16.5
Neuroendocrine Carcinomas	16	6	4.5	21
Ovarian Epithelial FTC/PPC	26	12	1.9	13.8
Pancreatic ACA	24	0	1.7	3.9
Prostate ACA	23	17	3.5	7.9
Salivary Gland Carcinoma	26	12	3.8	13.2
SCLC	24	33	1.9	9.7

Ott et al 2019, *J. Clin. Onc.*

Immunotherapy combinations

Table 1. Selected completed clinical trials of immunotherapy in patients with pancreatic cancer[a].

…or to combinations (so far)

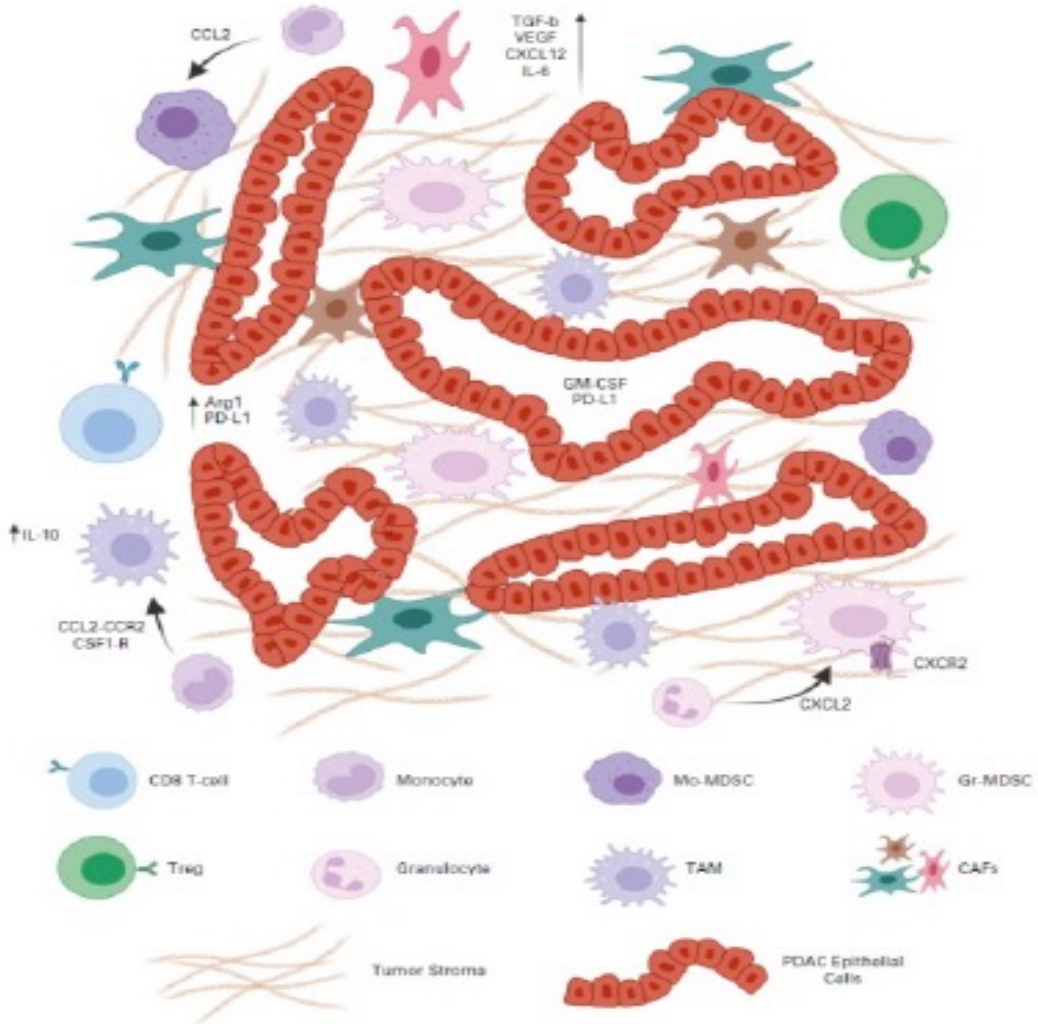
Trial identifier number and study name	Phase	Population	N	Investigational treatment	Comparator treatment	Results	Reference
NCT02734160	1	mPDAC, ≤2 lines	32	Galunisertib (TGFβi) + Durvalumab	–	DCR 25%; mOS 5.72 months (95% CI, 4.0–8.4)	*26*
NCT00112580	2	LA and mPDAC	27	Ipilimumab	–	ORR 0% per RECIST, 1 delayed PR	*23*
NCT02558894	2	mPDAC, 2nd line	65	Arm A: Durvalumab + Tremelimumab	Arm B: Durvalumab	Arm A: ORR 3.1%; mOS 3.1 months (95% CI, 2.2–6.1) Arm B: ORR 0%; mOS 3.6 months (95% CI, 2.7–6.1)	*25*
NCT02879318 Canadian CTG PA.7 trial	2	mPDAC, 1st line	180	Arm A: Gem/NP + Durvalumab + Tremelimumab	Arm B: Gem/NP	Arm A: mOS 9.8 months Arm B: mOS 8.8 months HR = 0.94 (90% CI, 0.71–1.25; $P = 0.72$)	*ClinicalTrials.gov*[a]
NCT02077881	2	mPDAC, 1st line	135	Indoximod (IDO i) + Gem/NP	–	ORR 46.2%; mOS mOS 10.9 months	*27*
NCT03250273	2	mPDAC, ≥2nd line	30	Entinostat (HDACi) + Nivolumab	–	ORR 16.7%; mOS 3.9 months (95% CI, 1.9–9.4)	*ClinicalTrials.gov*[a]
NCT01417000	2	mPDAC, ≥1st line	90	Arm A: Cy/GVAX + CRS-207	Arm B: Cy/GVAX	Arm A: mOS 6.1 months Arm B: 3.9 months HR = 0.59 (95%CI, 0.36–0.97; $P = 0.02$)	*28*
NCT02826486 COMBAT trial	2	mPDAC, 2nd line	43	Motixafortide (CXCR4 i) + Pembrolizumab + NAPOLI-1 chemo	–	ORR 21.1%; DCR 63.2%; mOS 6.6 months (95% CI, 4.5–8.7 months)	*33*
NCT03214250 PRINCE	2	mPDAC, 1st line	93	Arm A: Gem/NP + Nivolumab Arm B: Gem/NP + Sotigalimab (aCD40 agonist) Arm C: Gem/NP + Sotigalimab + Nivo	Historical 1-y OS of 35% for Gem/NP	Arm A: 1-y OS 57%, $P = 0.007$ Arm B: 1-y OS 51%, $P = 0.029$ Arm C: 1-y OS 41%, $P = 0.236$	*29*
NCT01836432 PILLAR trial	3	BR or LA PDAC, neoadjuvant	303	Arm A: Algenpantucel-L + SOC chemo + RT	Arm B: SOC chemo + RT	Arm A: mPFS 14.3 months Arm B: mPFS 14.9 months HR = 1.02 (95% CI, 0.66–1.58; $P = 0.98$)	*30*
NCT02923921 SEQUOIA trial	3	mPDAC, 2nd line	567	Arm A: FOLFOX + Pegilodecakin (peg-rIL10)	Arm B: FOLFOX	Arm A: mOS 5.8 months Arm B: mOS 6.3 months HR = 1.05 (95% CI, 0.86–1.27)	*31*
NCT02436668 RESOLVE trial	3	mPDAC, 1st line	424	Arm A: Gem/NP + Ibrutinib (BTK i)	Arm B: Gem/NP	Arm A: mOS 9.7 months Arm B: mOS 10.8 months HR = 1.1 (95% CI, 0.9–1.3)	*32*

Bockorny et al., *Clin. Canc. Res.*, 2022

Cold tumor

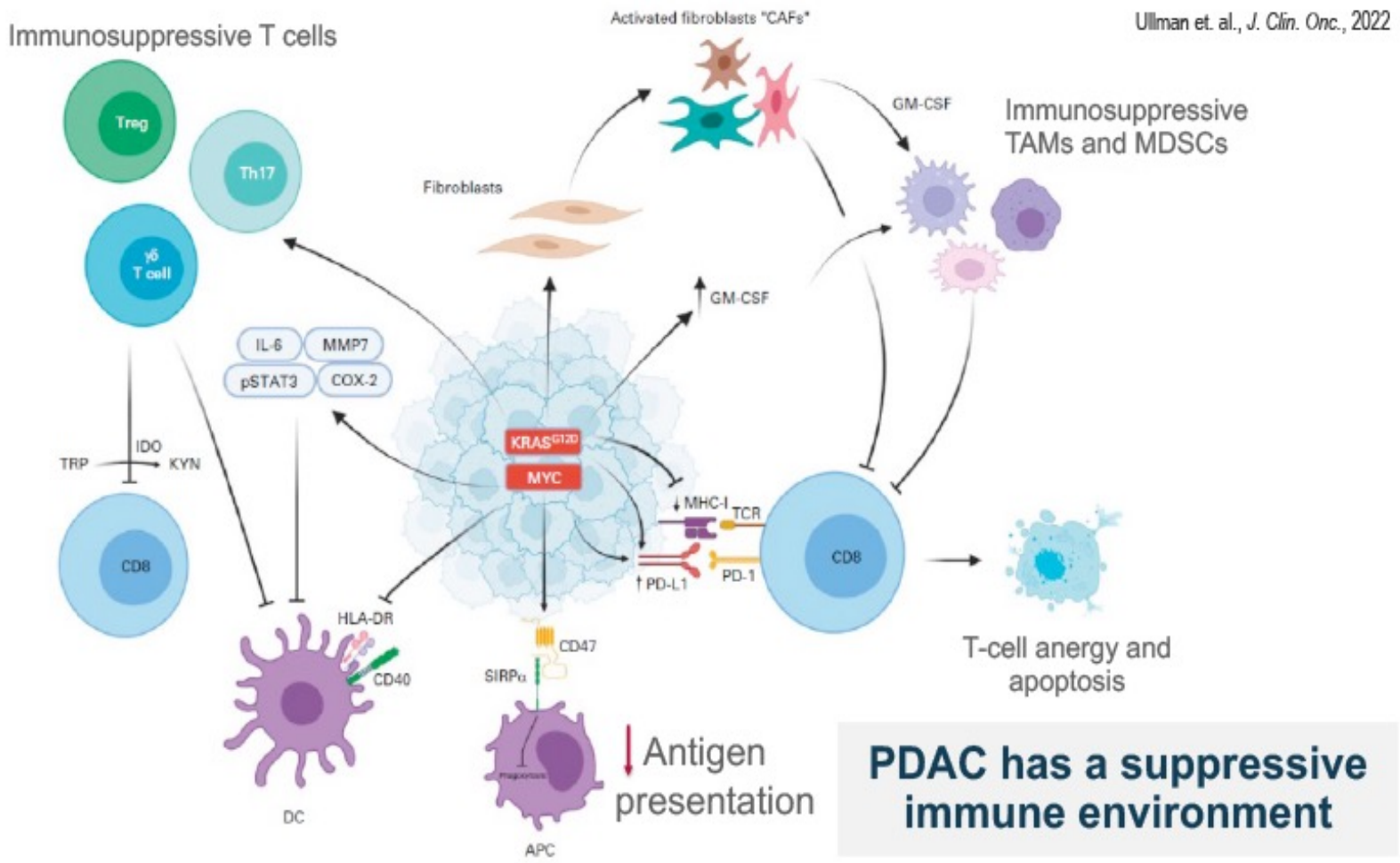
Why is PDAC a “cold” tumor?

- Low tumor mutational burden (TMB)
- Effector T cell are rare within stroma close to cancer cells (few TIL)
- Nutrient poor, hypoxic and acidic TME hinders proliferation and function of TIL
- Decreased number and function of dendritic cells (DCs)
- Heavy infiltration of immune-suppressing myeloid cells



Ullman et. al., *J. Clin. Onc.*, 2022

Immune suppression



Ullman et. al., *J. Clin. Onc.*, 2022

Novel immunotherapies

Novel immunotherapies- an active area of investigation

- Make “cold” tumor hot by combining with agents that stimulate immune response
  - Radio frequency ablation
  - Tumor vaccine
  - Oncolytic virus
- Block the macrophage “don’t eat me” signal
- Novel engineered cell therapies
  - Including NK cells
- Combine with anti-cytokines and/or stromal modulating agents

Precision medicine

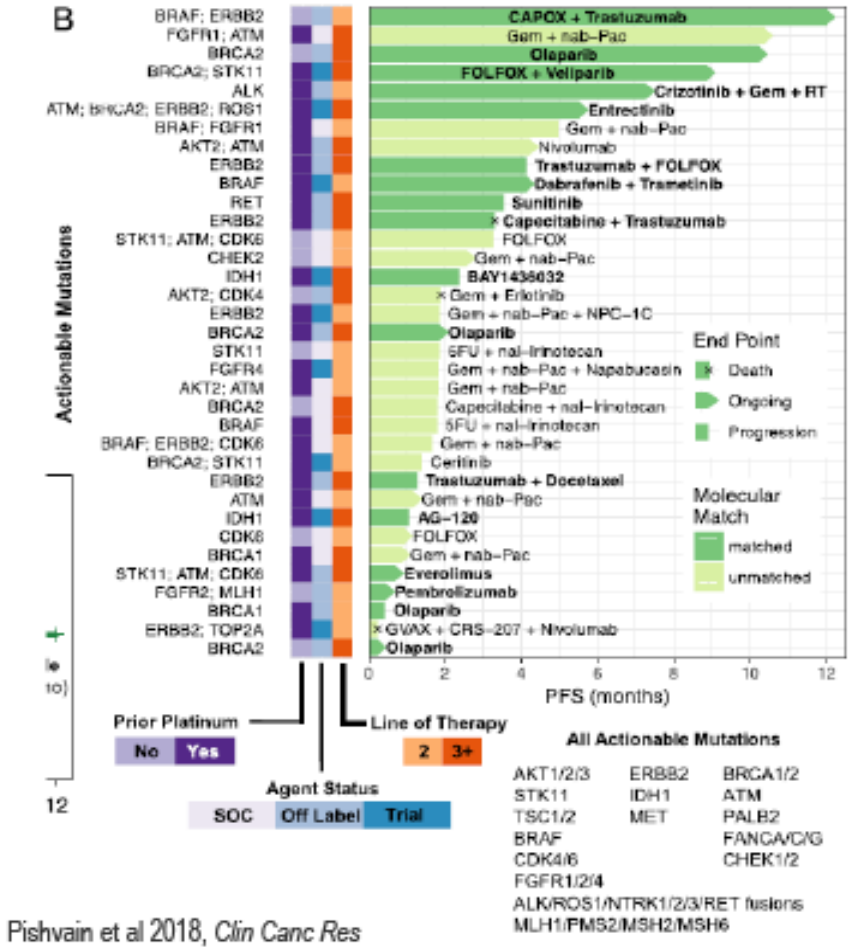
NIH NATIONAL CANCER INSTITUTE

Cowley et al, *J. Hepatobiliary Panc. Sci*, 2013

PDAC

Know Your Tumor: Precision Medicine for PDAC

- N = 640 patients accrued
- Adequate samples for sequencing in >90%
- "50% with actionable mutations (27% highly actionable)"
  - DNA repair genes (BRCA, ~8%)
  - Cell cycle genes (CCND1/2/3, CDK4/6, ~8%)
- Effect of matched therapy
  - N = 18
  - PFS 4.1 vs. 1.9 m (HR 0.47, p = 0.03)

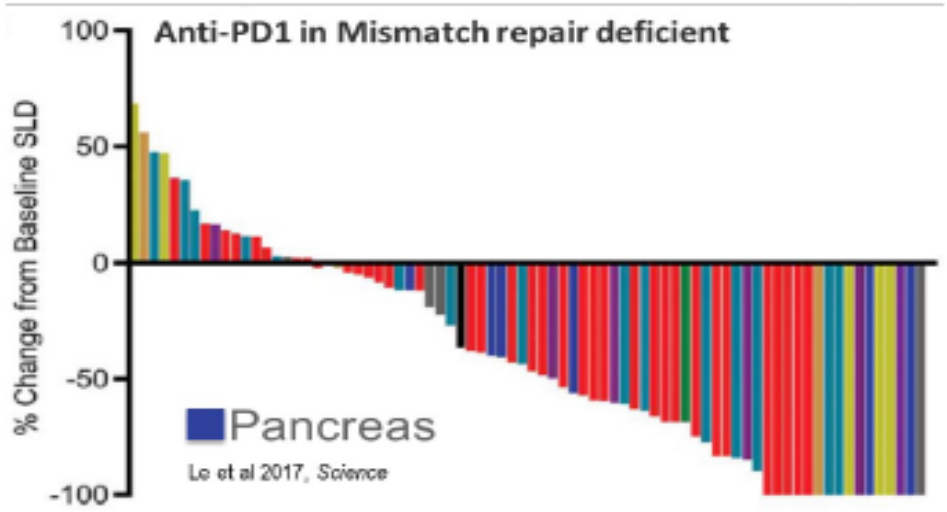


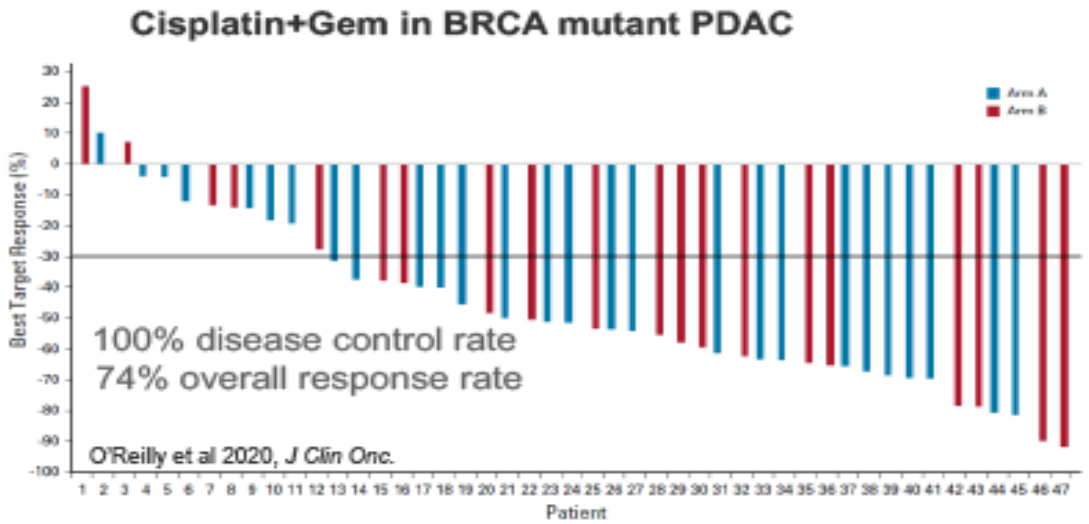
Pishvain et al 2018, *Clin Canc Res*

Waterfall plot

Precision Medicine Targets in PDAC

Profile	Give	Incidence
MSI	immunotherapy	<2%
BRCA mut	platinum chemo, olaparib maintenance	~5-12%
NTRK fusion	larotrectininb	<<1%
KRAS G12C	*sotorasib?*	1%





KRAS

KRAS: the no longer undruggable target

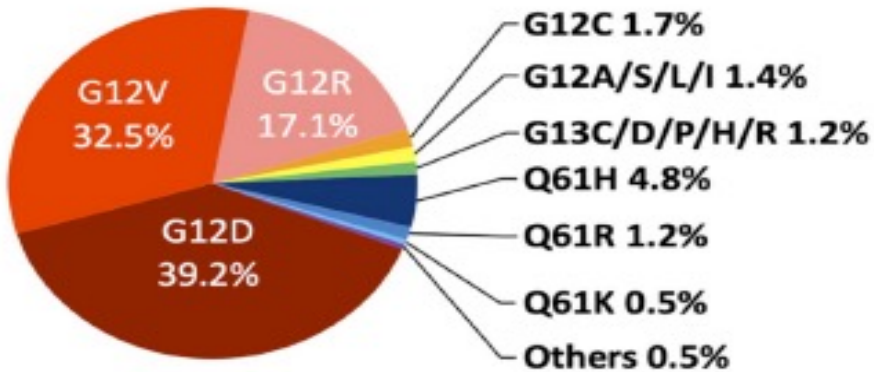
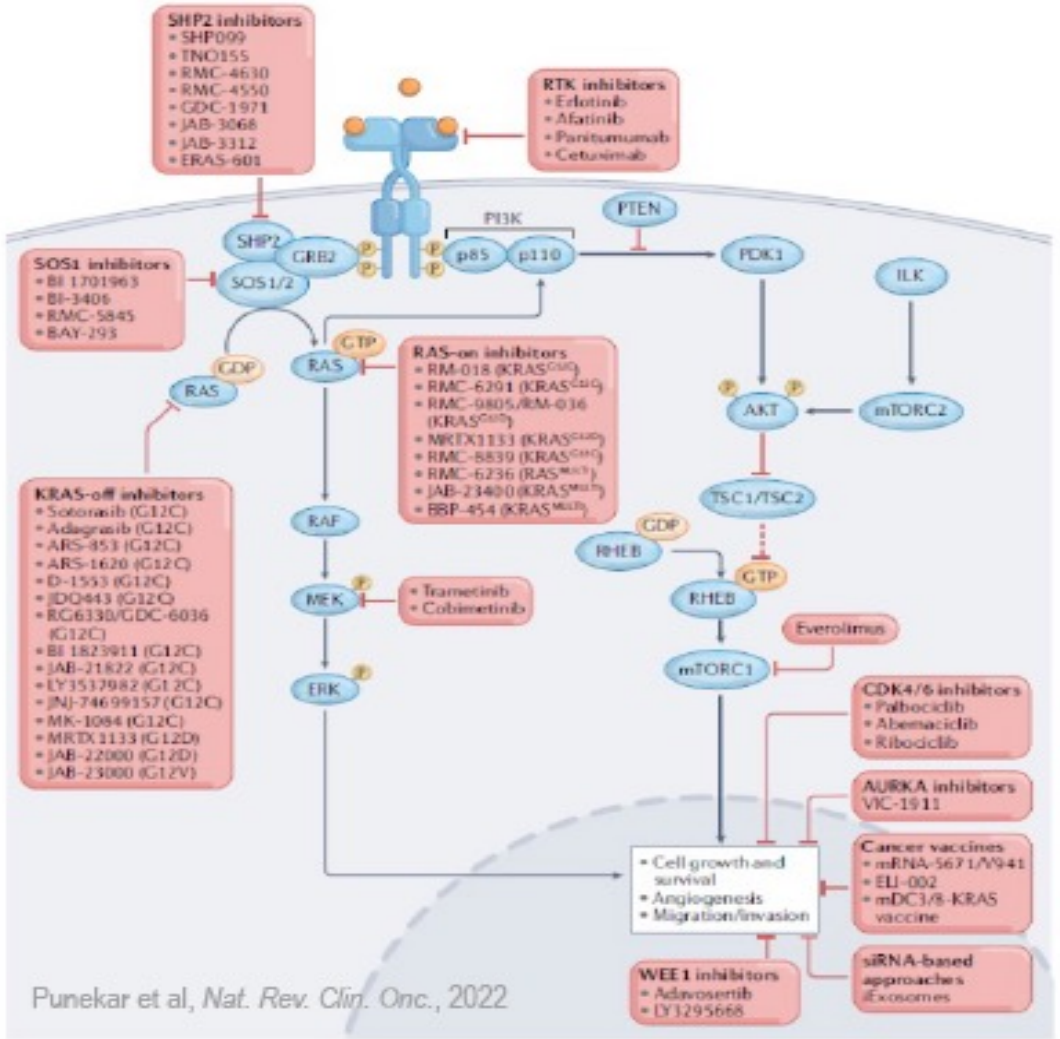


Fig. 3. Distribution of *KRAS* mutations in pancreatic cancer. The analysis was done using publicly available data from the cBioPortal database [48,49] that includes 665 *KRAS* mutant tumor samples from four large scale pancreatic cancer studies [50-53].

Luo et al, *Seminars in Onc*, 2021



Punekar et al, *Nat. Rev. Clin. Onc.*, 2022

KRASc12d inhibitor

The KRAS^{G12D} inhibitor MRTX1133 elucidates KRAS-mediated oncogenesis

Hallin et al 2022, *Nat. Med.*

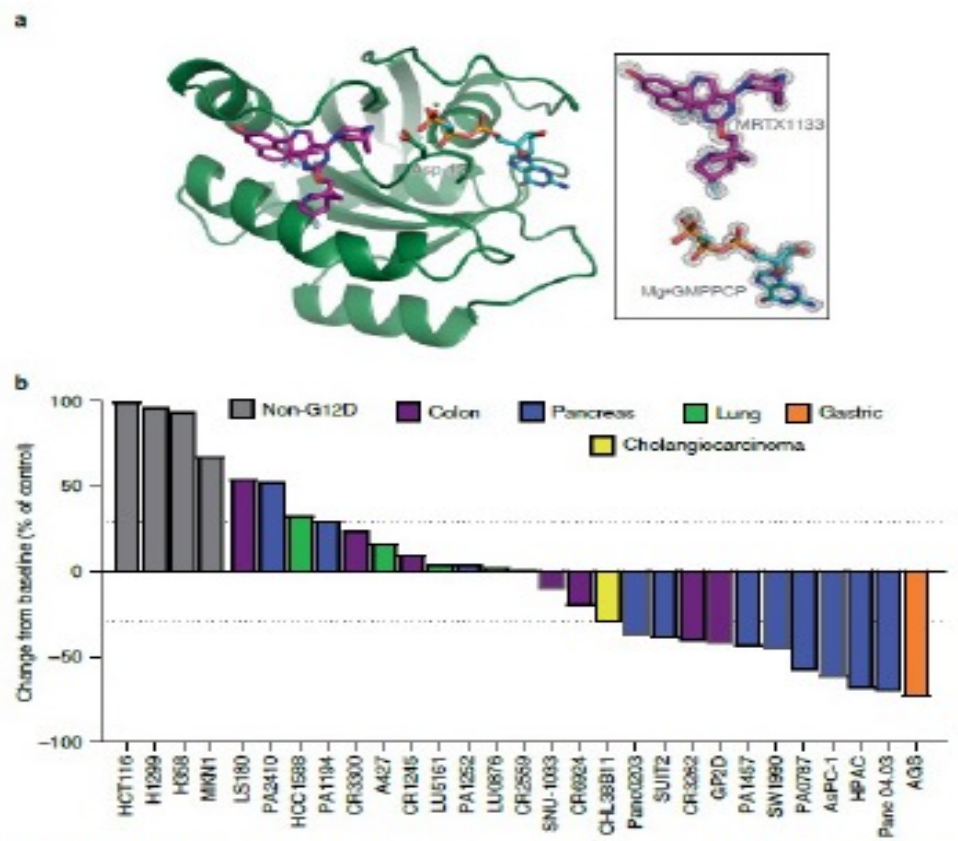


Fig. 1 | MRTX1133 potently inhibits both the active state and the inactive state of KRAS^{G12D} and has anti-cancer activity in KRAS^{G12D}-bearing human tumor xenograft models. a, Crystal structure of KRAS^{G12D} in complex with MRTX1133 and the GTP analog GMPPCP. b, Anti-tumor activity of MRTX1133 in various KRAS^{G12D}-mutant and KRAS non-mutant xenograft models. Intraperitoneal injections of MRTX1133 were administered twice daily at a dose of 30 mg per kg body weight. The percentage change in tumor size from baseline was calculated at about day 14. © 2022, Hallin, J. et al.

SUMMARY

Summary

- Patients with pancreatic cancer have poor outcomes and few therapy choices
- Most pancreatic cancer is driven by mutation of *KRAS* oncogene
- Early detection remains an elusive goal for pancreatic cancer
- Screening programs are effective for those with known genetic risk
- PDAC has a unique TME that is paucicellular, stroma dense, immune-suppressive, poorly vascularized and hypoxic
- CAFs support to tumor cell growth and proliferation but also restrain metastasis
- Vigorous work to identify effective immune therapy for PDAC remains in progress
- New KRAS inhibitors likely to herald a new era in PDAC treatment

Questions?