

Pancreatic cancer

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Improving Treatments for Pancreatic Cancer

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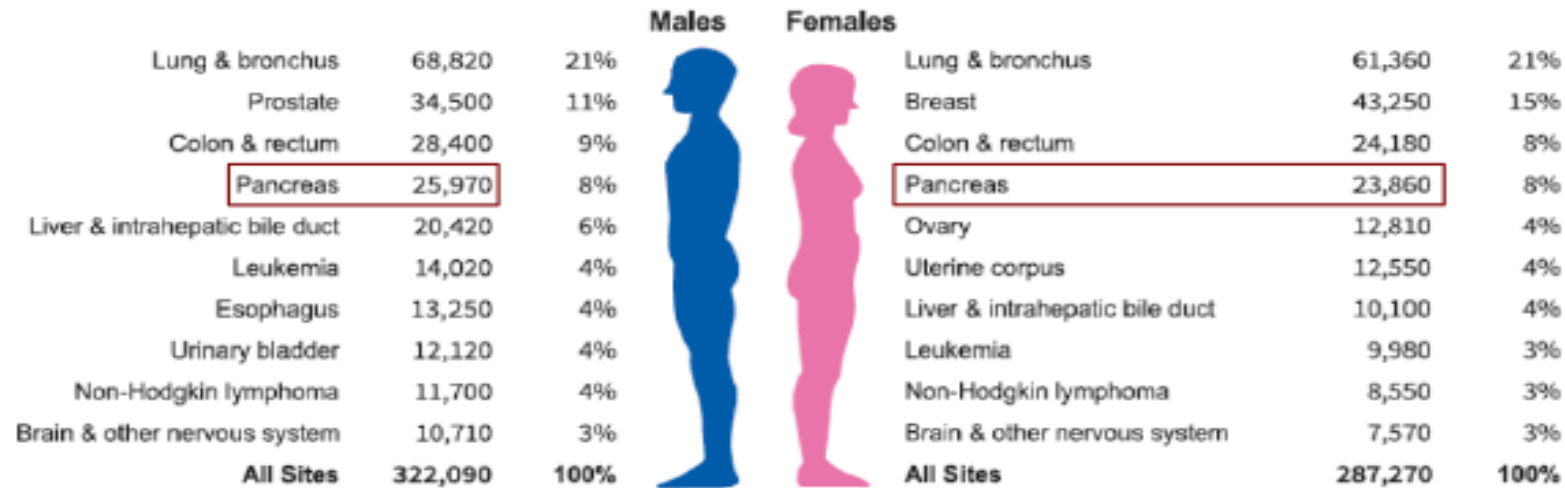
NCI Center for Cancer Research

Cancer incidence and mortality

Pancreatic Cancer Incidence and Mortality

Estimated Deaths

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



- **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

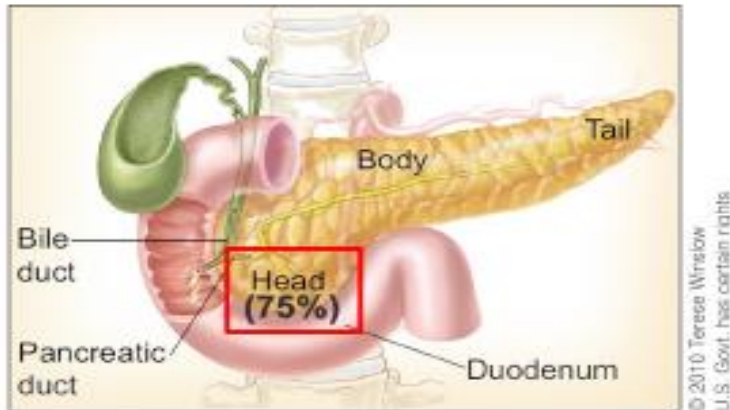
Table 1. Risk Factors and Inherited Syndromes Associated with Pancreatic Cancer.*

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 (<i>PRSS1</i> , <i>SPINK1</i>) ⁸	50
Familial atypical multiple mole and melanoma syndrome (<i>p16</i>) ⁹	10–20
Hereditary breast and ovarian cancer syndromes (<i>BRCA1</i> , <i>BRCA2</i> , <i>PALB2</i>) ^{10,11}	1–2
Peutz-Jeghers syndrome (<i>STK11</i> [<i>LKB1</i>]) ¹²	30–40
Hereditary nonpolyposis colon cancer (Lynch syndrome) (<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i>) ¹³	4
Ataxia-telangiectasia (<i>ATM</i>) ¹⁴	Unknown
Li-Fraumeni syndrome (<i>P53</i>) 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.

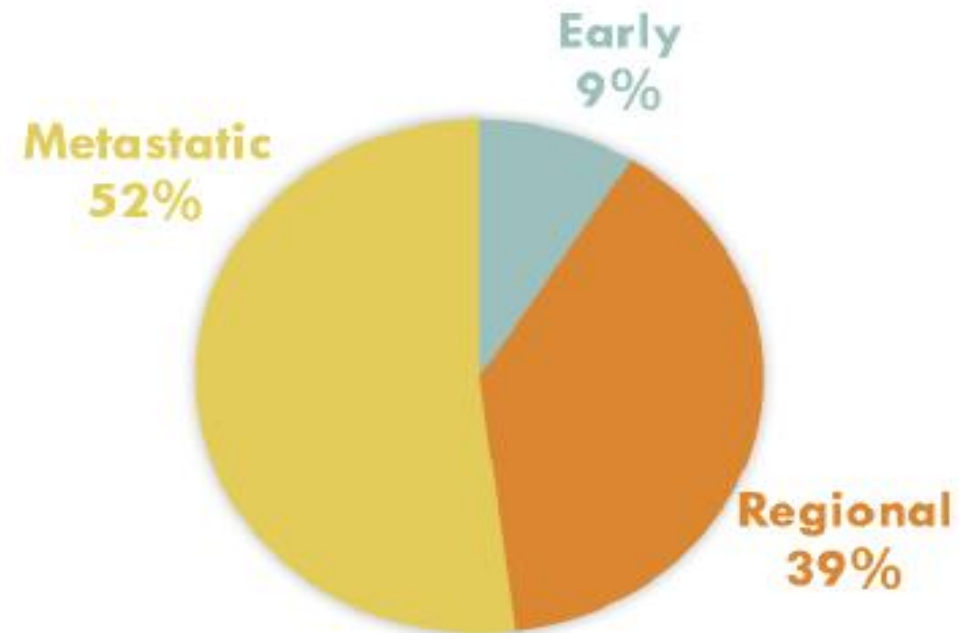
Pancreatic cancer types and stage

Pancreatic Cancer: Types and Stage at Diagnosis



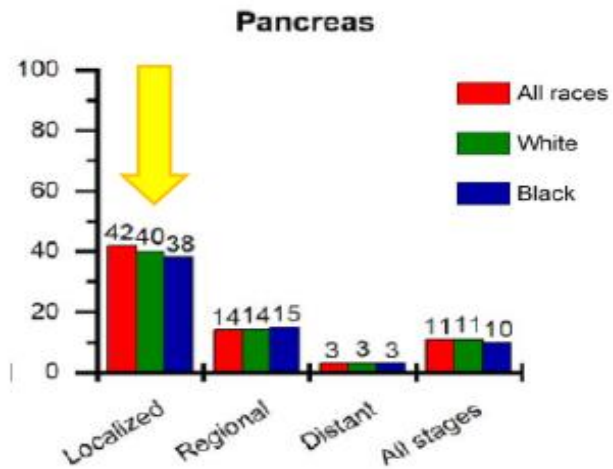
- **Adenocarcinoma (~90%)**
- Neuroendocrine (<5%)
- Rare exocrine tumors

American Cancer Society, *Cancer Facts and Figures 2017*

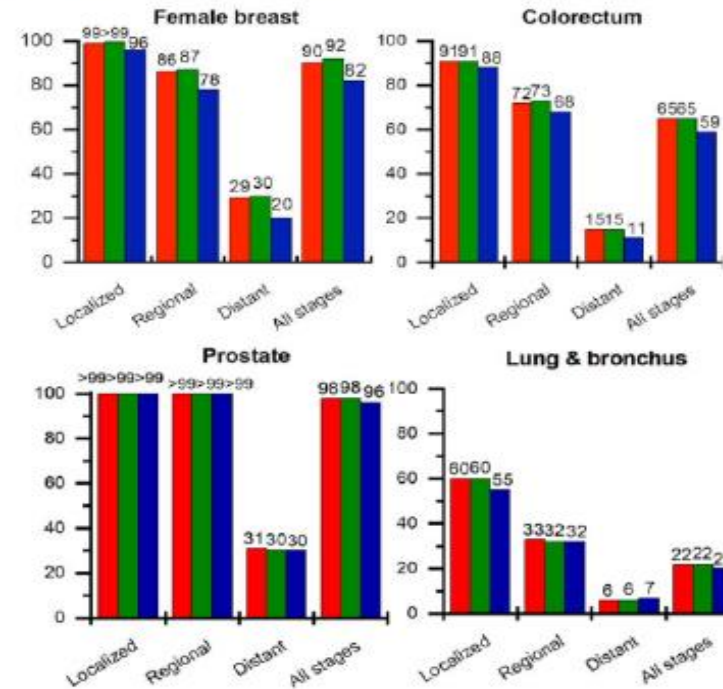


Prognosis and stage

Prognosis is better for patients with early-stage disease



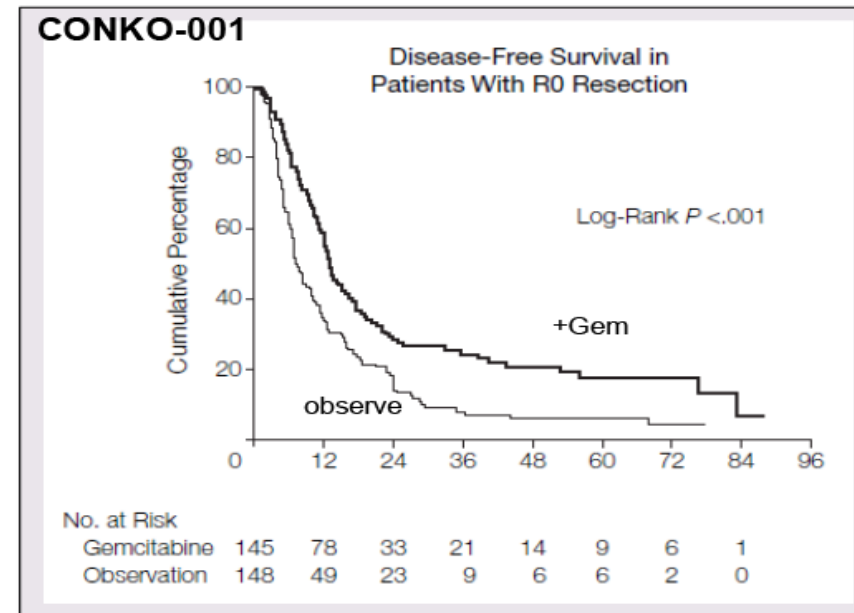
American Cancer Society, Cancer Facts and Figures 2022



Pancreatic cancer treatment

All patients with “early-stage” disease recur even with a “perfect” surgery

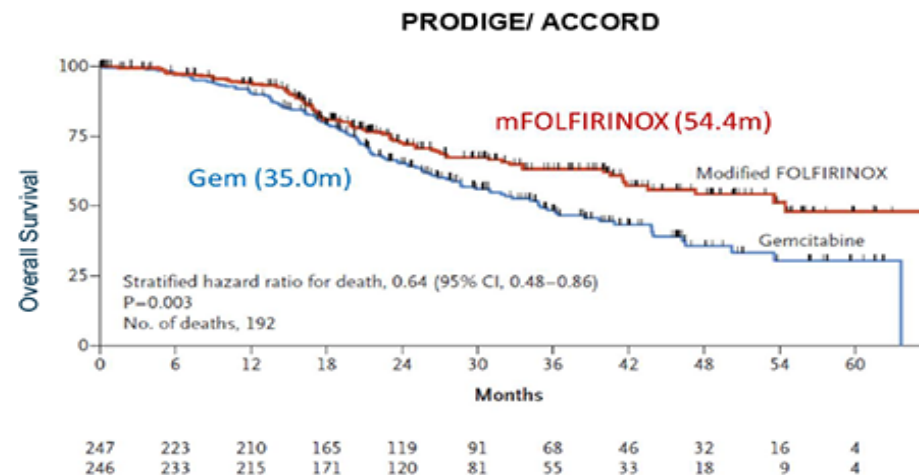
- Perfect surgery alone is ineffective at curing PDAC
- All patients with PDAC have micrometastatic disease
- Must be combined with chemotherapy to kill micrometastatic disease



Oettle et al, *JAMA*, 2007

Chemotherapy regimens

Giving modern combination chemotherapy regimens following surgery increases the cure rate for early-stage PDAC



Conroy et al, *NEJM*, 2018

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

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)

Familial disease

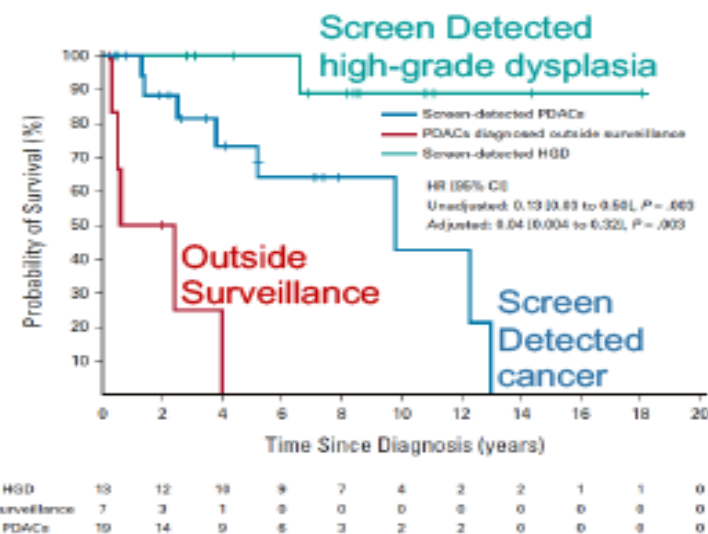
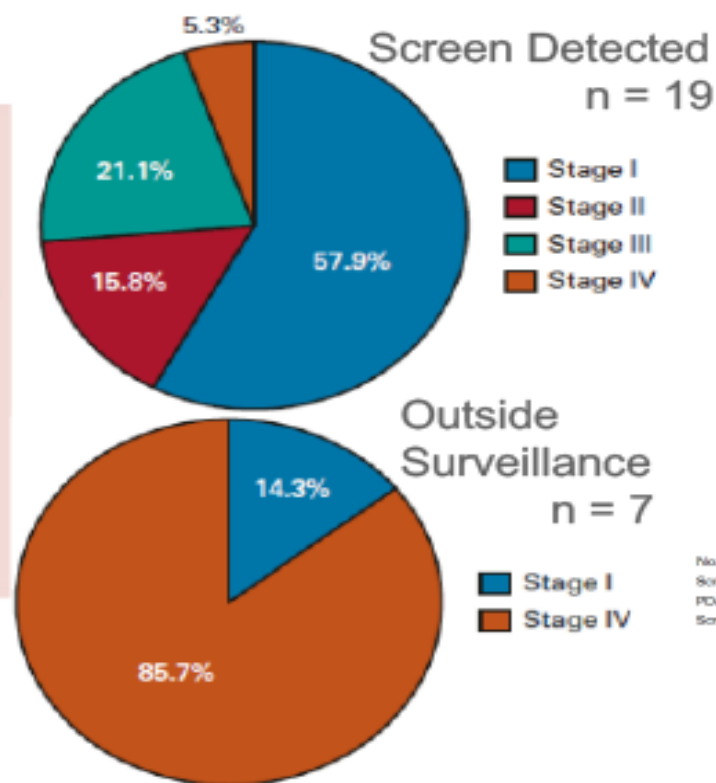
Progress in Screening Patients with Familial Disease- CAPS

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

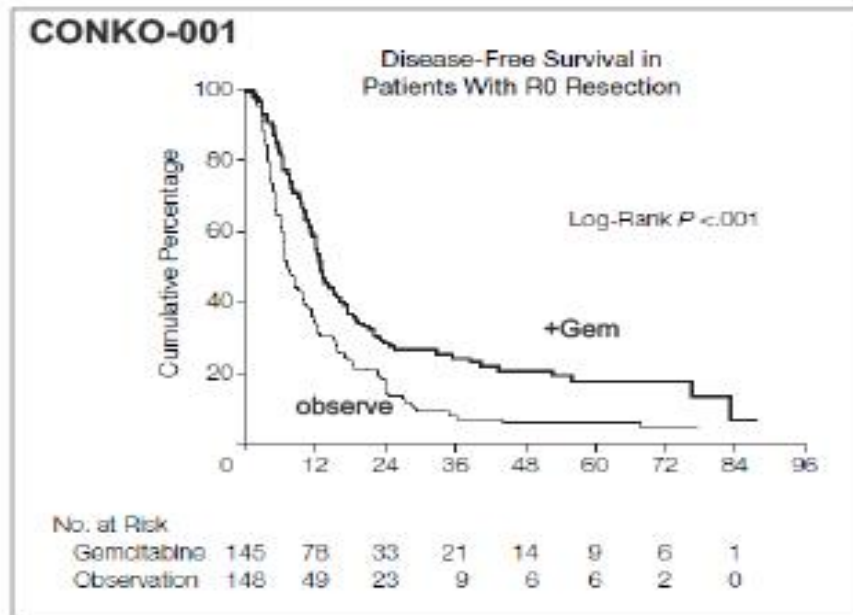
N = 1731 in screening



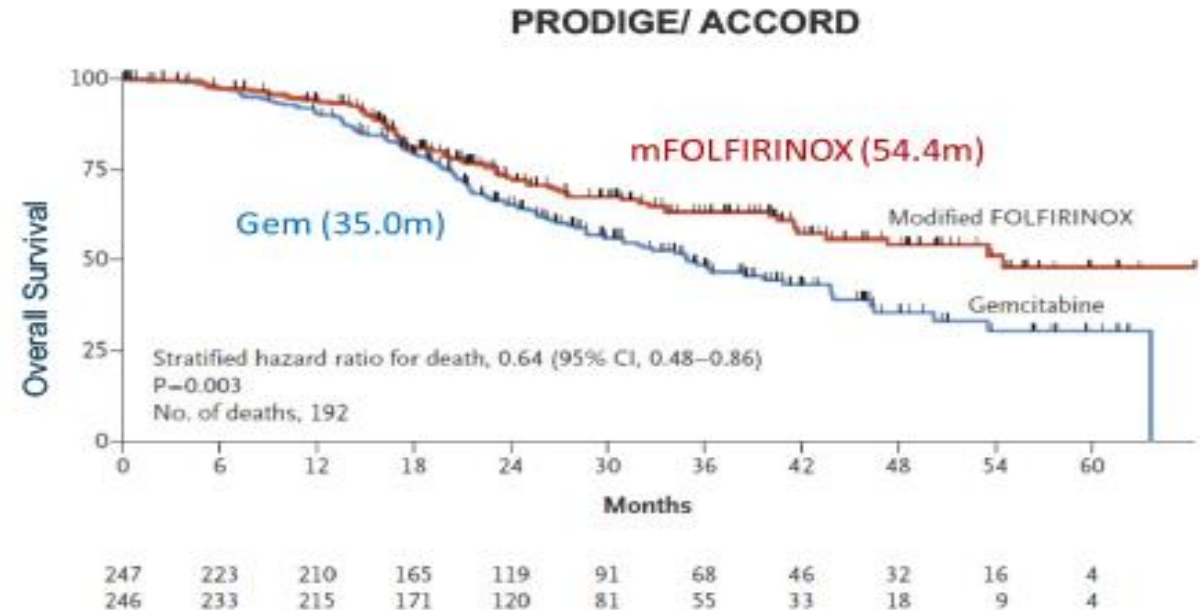
N = 26 PDAC
N = 13 HGD

Surgery plus chemotherapy

Early Stage Disease: Surgery + Chemotherapy



Oettle et al, *JAMA*, 2007



Conroy et al, *NEJM*, 2018

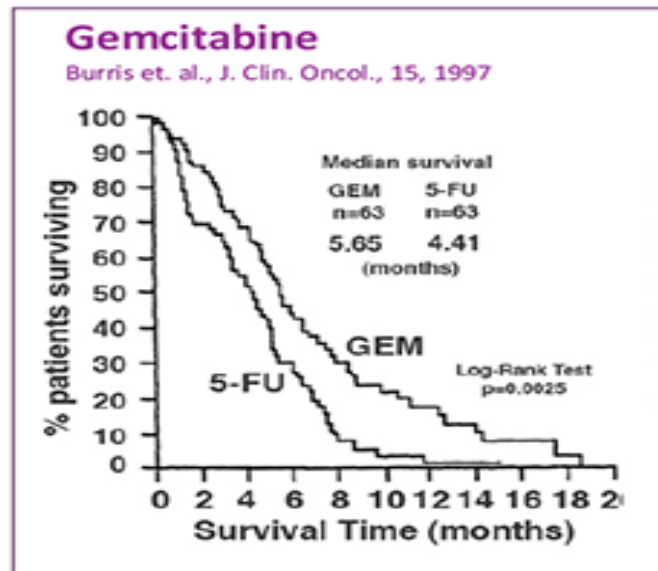
Neoadjuvant chemotherapy (chemo BEFORE surgery) is currently being tested in clinical trial and may provide additional survival advantage

PDAC treatment

How do we treat advanced
PDAC in the clinic?

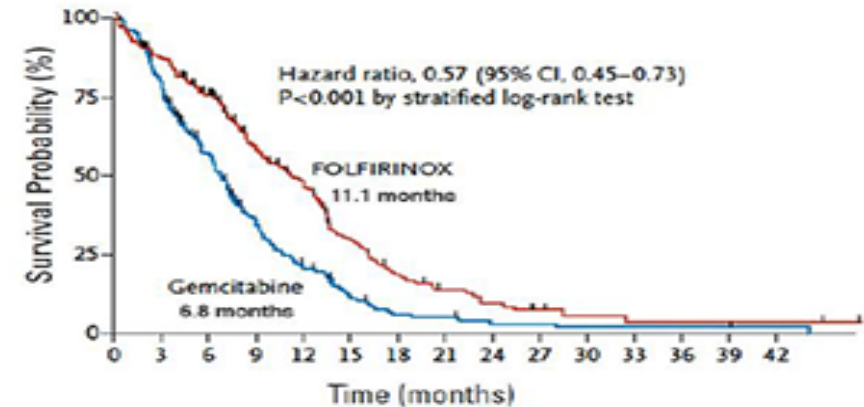
Combination chemotherapy

Combination Chemo is the mainstay of pancreatic cancer treatment



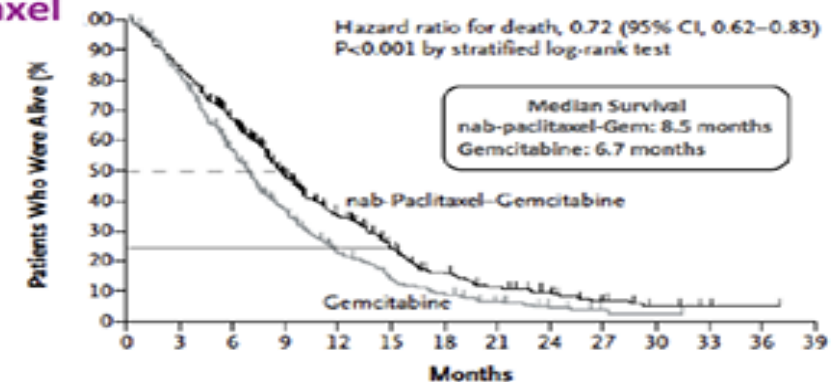
FOLFIRINOX

Conroy et. al., NEJM, 36, 2011



Gemcitabine+ nab-Paclitaxel

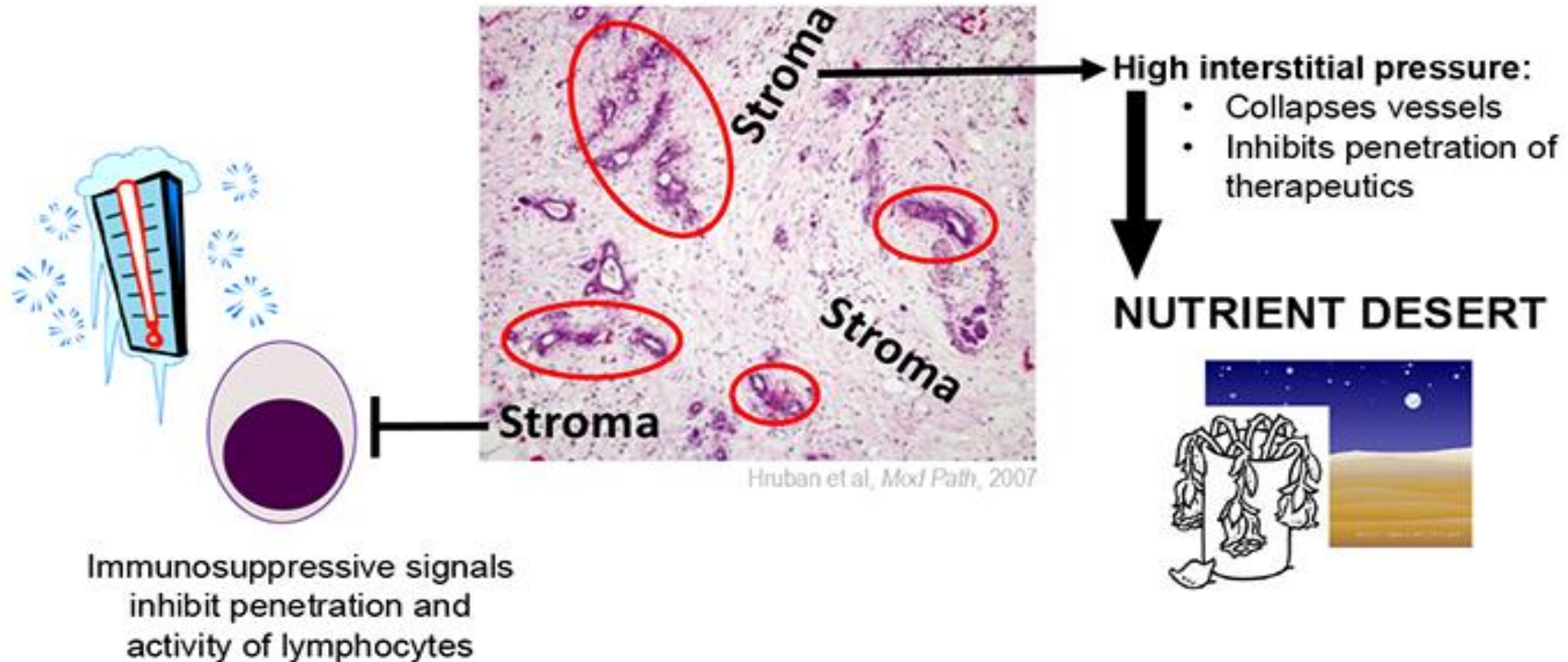
Von Hoff, D.D. et. al, NEJM, 369, 2013



Plenty of room for improvement!

PDAC microenvironment

PDAC Tumor Microenvironment: *"The wound that does not heal"*

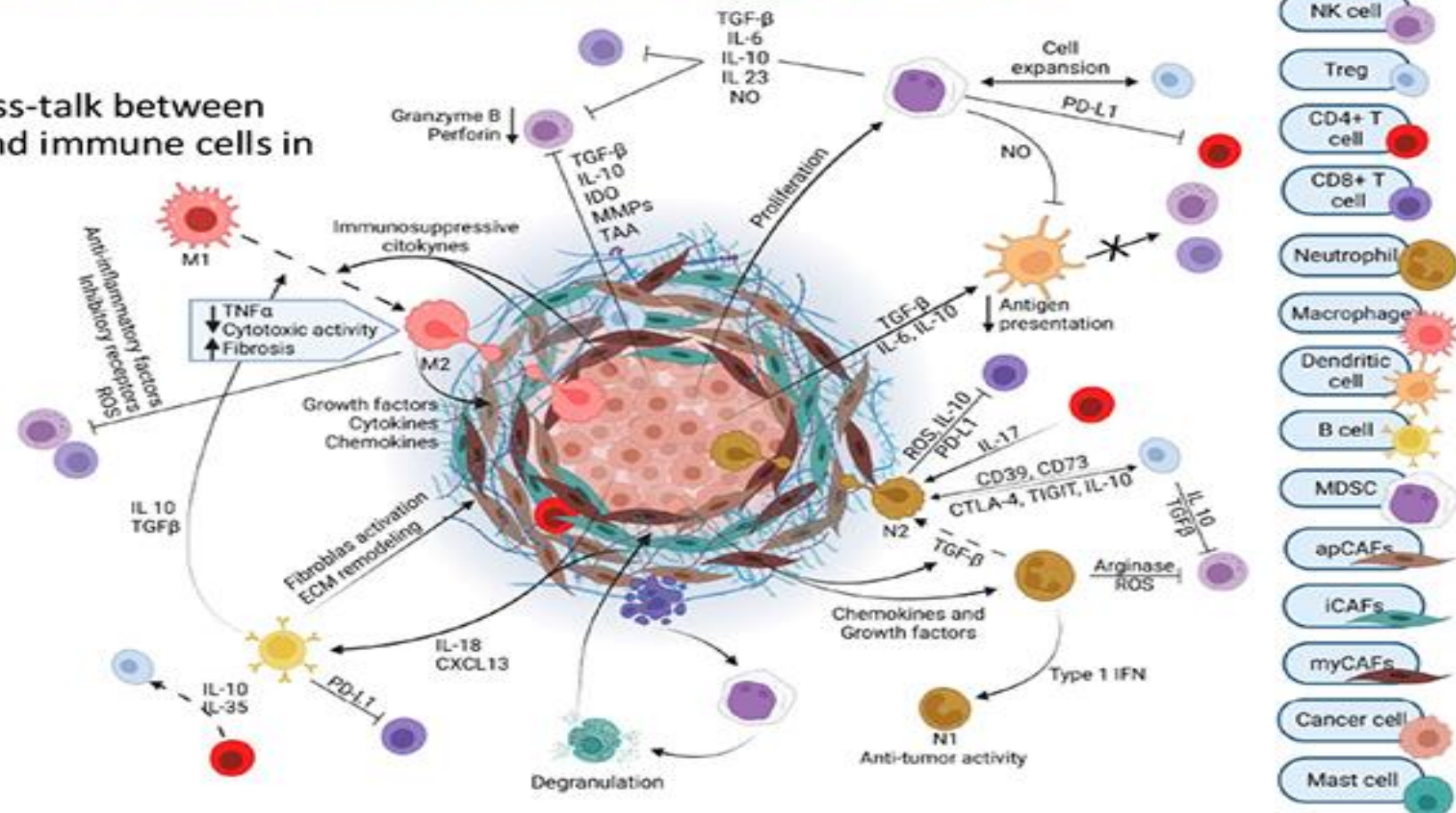


Tumor microenvironment

The complex tumor microenvironment (TME) of PDAC

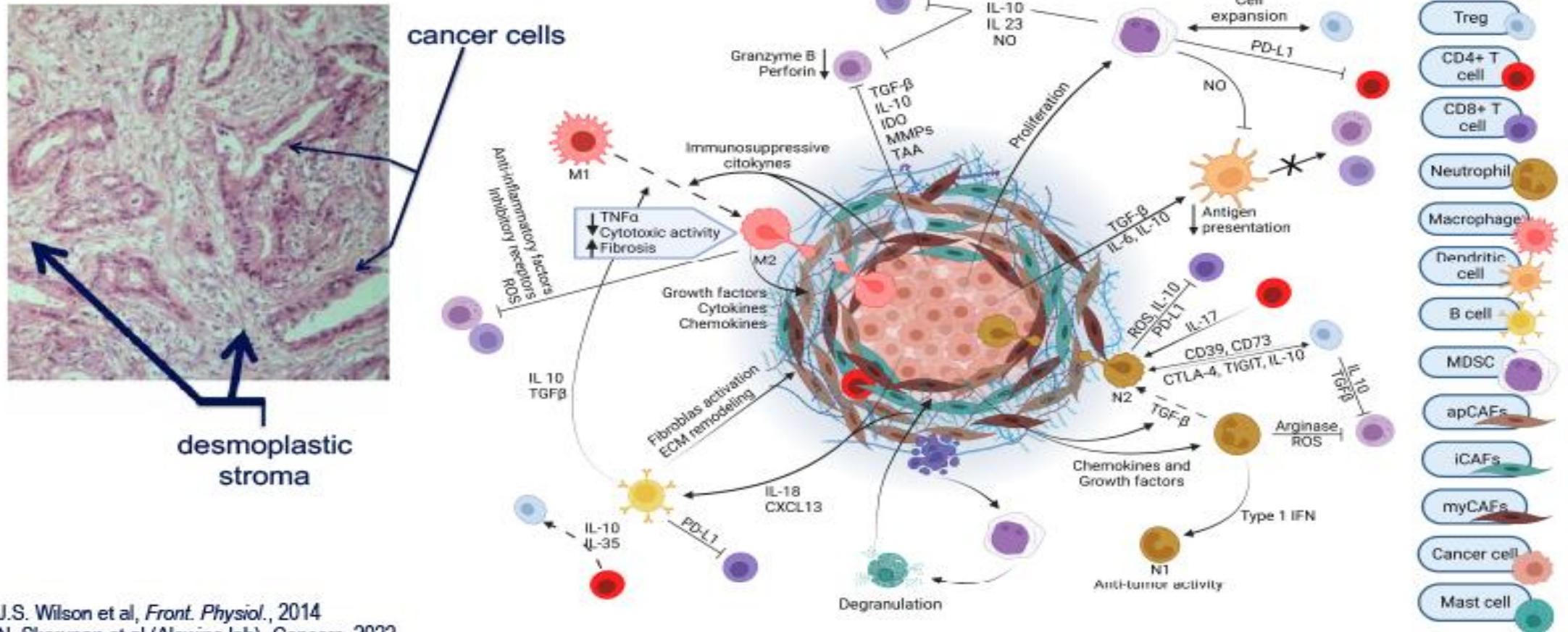
N. Skorupan et al, *Cancers*, 2022

- Extensive signaling cross-talk between cancer cells, stromal and immune cells in the TME



Stroma

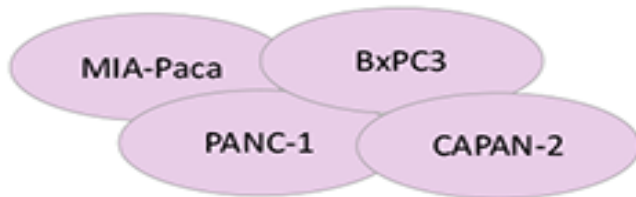
Prominent Desmoplastic Stroma in Pancreatic Cancer



PDAC model

Difficult to model PDAC that resembles the human disease

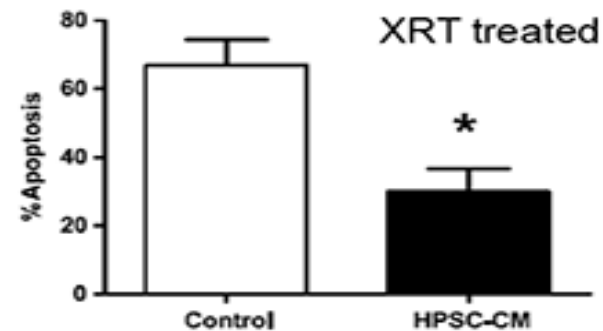
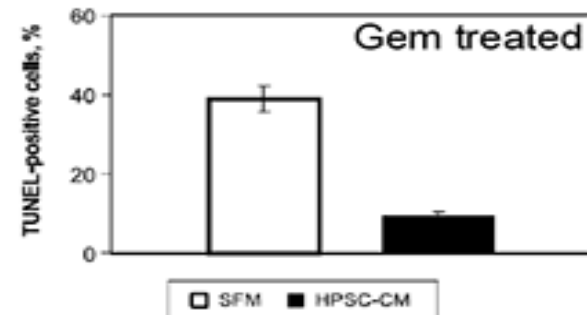
1) Standard cell lines



Implant subq into mice



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



Factors secreted by
Cancer Associated
Fibroblasts (CAFs) help
cancer cells survive
treatment

Human disease models

Models that better resemble the human disease

Cannot evaluate contribution of the immune system

1) Patient-derived xenograft (PDX)

- Predictive of patient response to treatment with cytotoxics and tumor-targeted agents

2) Organoids

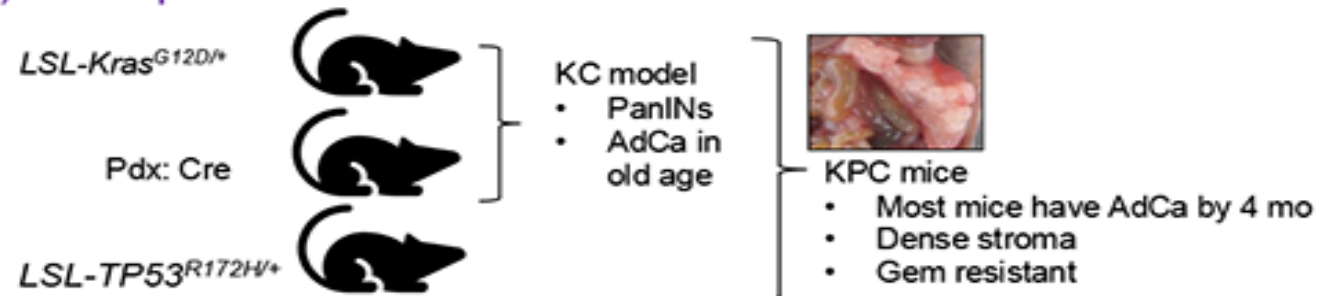
- Predictive of patient response to treatment?
- Cannot be used to evaluate stromal modulators

Immune competent

3) Tissue slice culture

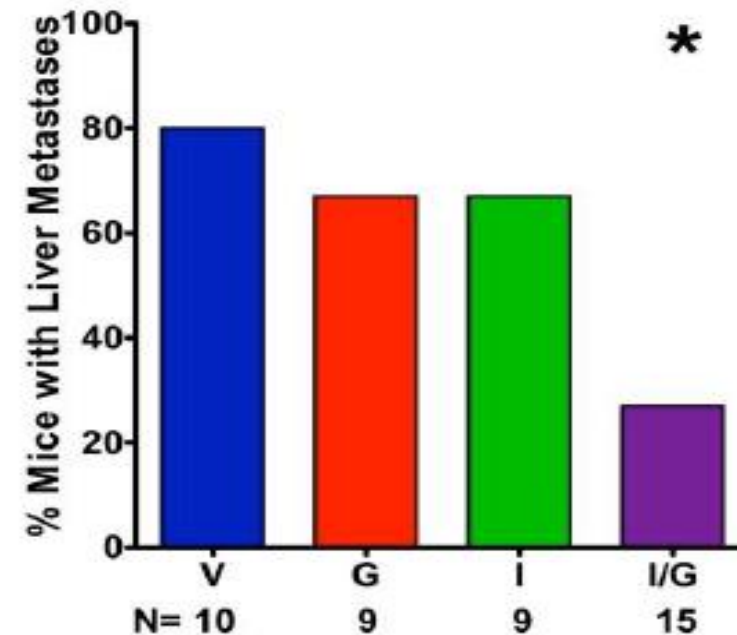
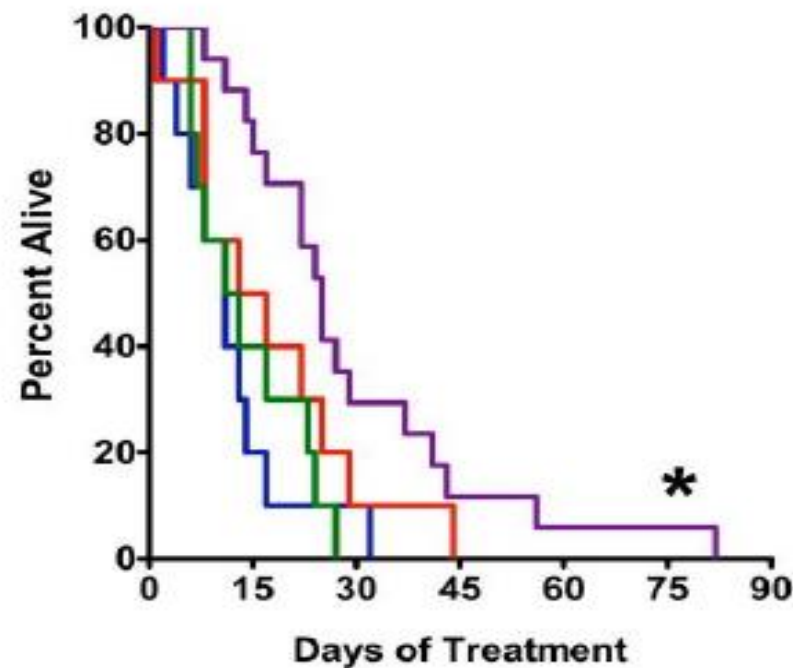
- Human
- Transient, non-renewable
- Intact immune/ stromal TME

4) KPC spontaneous autochthonous model



Hedgehog signaling

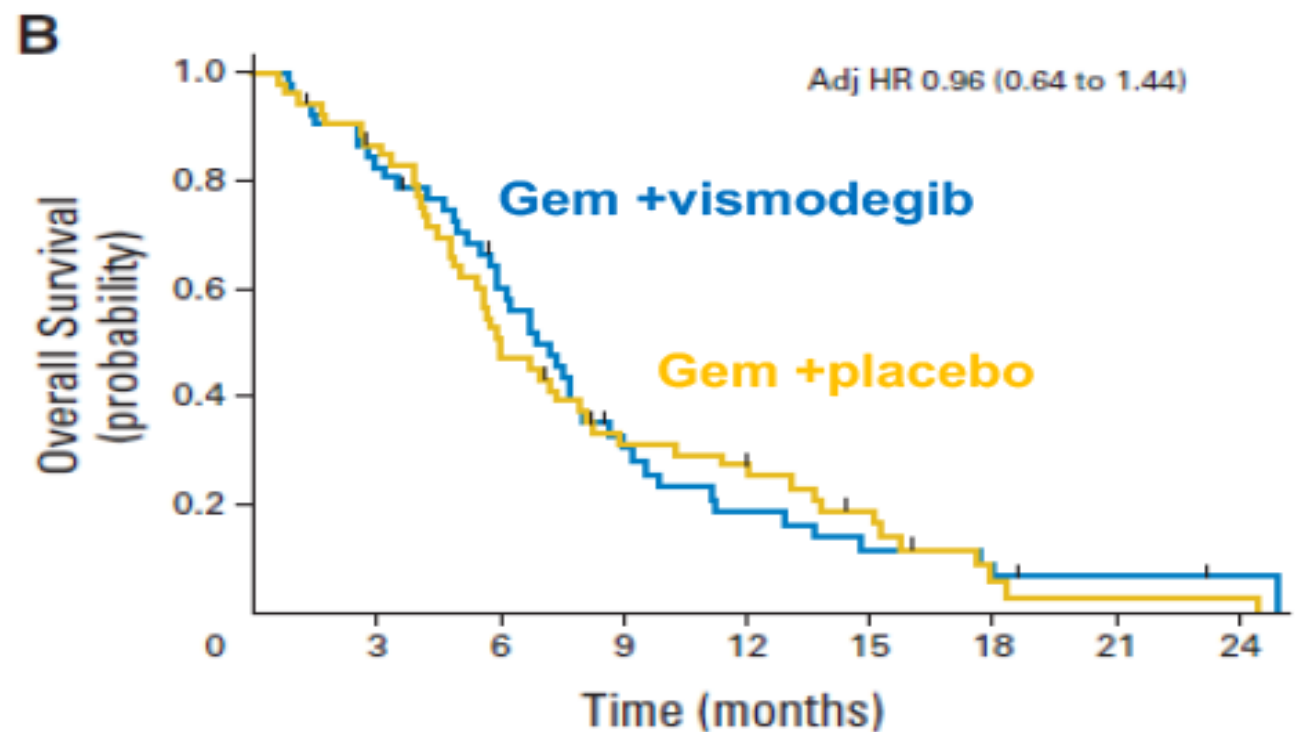
**Inhibition of Hedgehog Signaling Depleted Stroma,
Enhanced Drug Delivery and Improved Survival in Mice**



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

SHH inhibitor

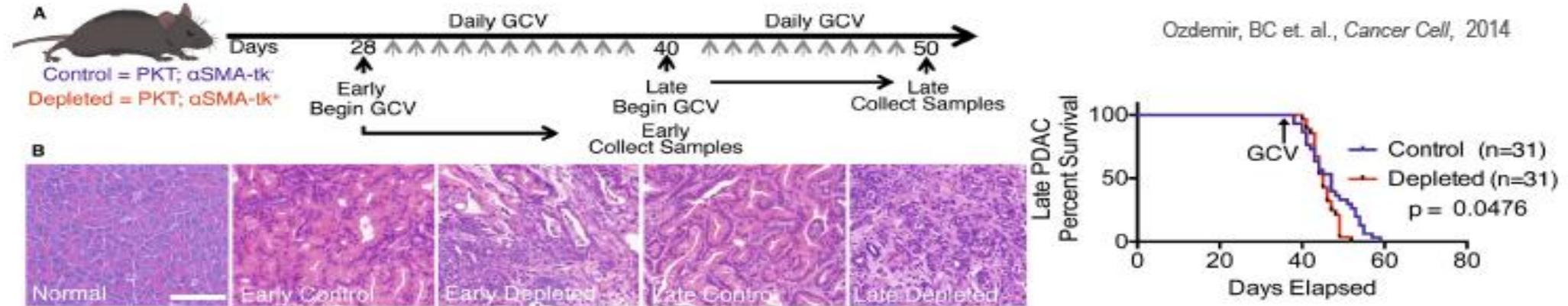
SHH inhibitor ineffective in clinic



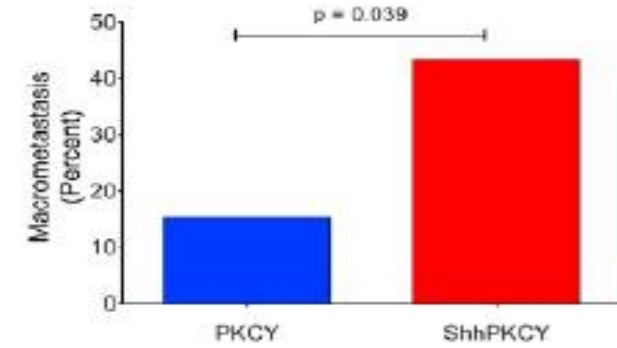
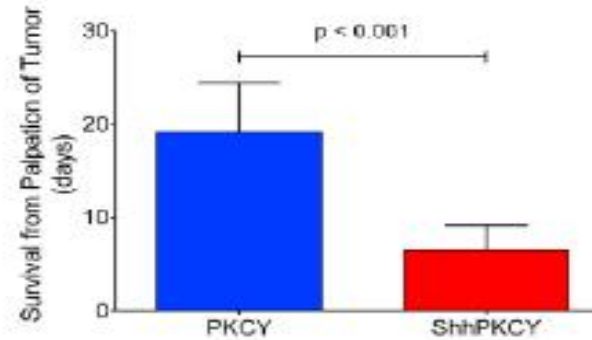
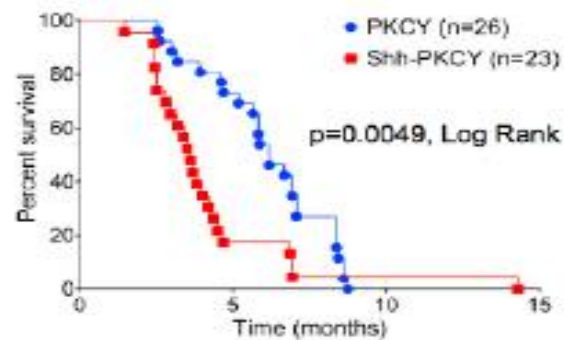
Catenacci et. al., *J. Clin. Onc.*, 2015

CAF destruction

Destruction of CAFs => more metastatic, poorly differentiated tumors

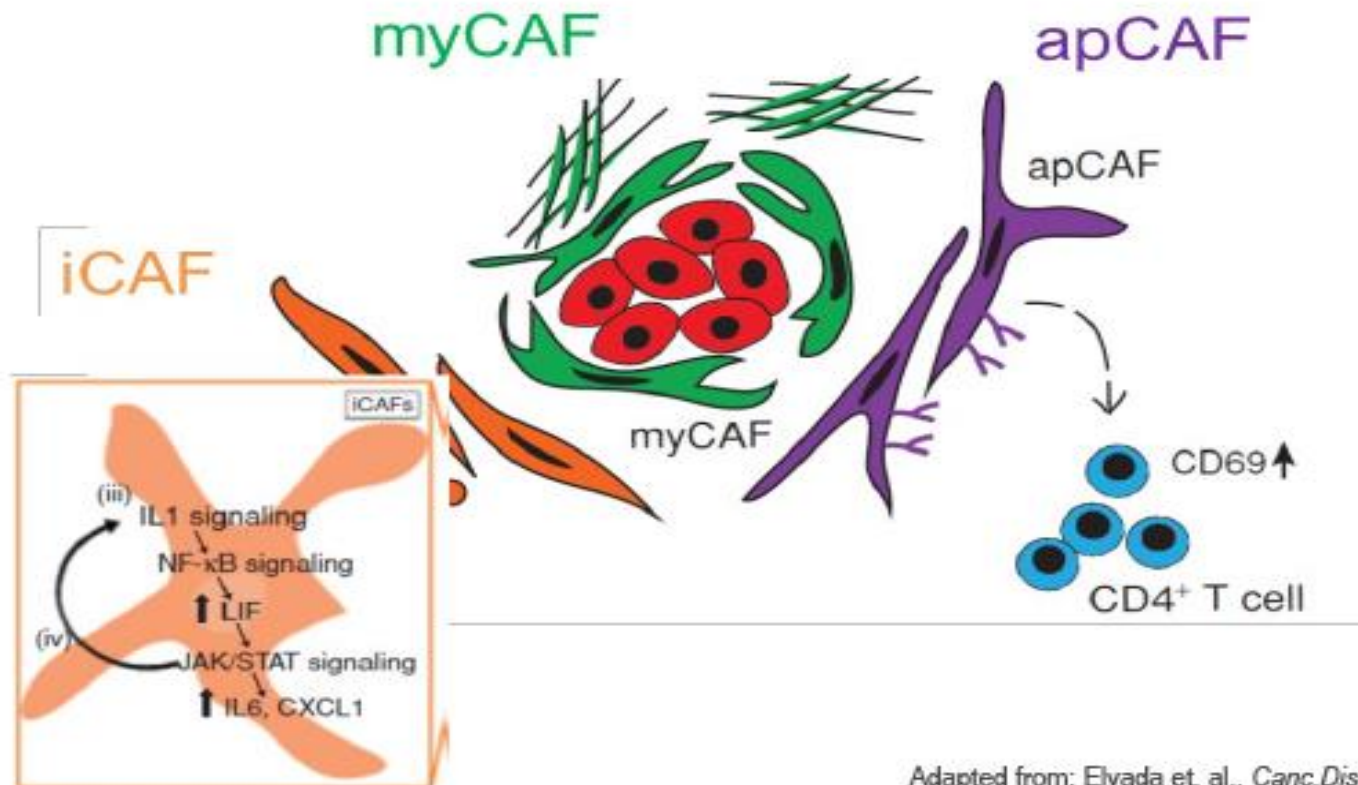


Rhim et. al., *Cancer Cell*, 2014



CAF subtypes

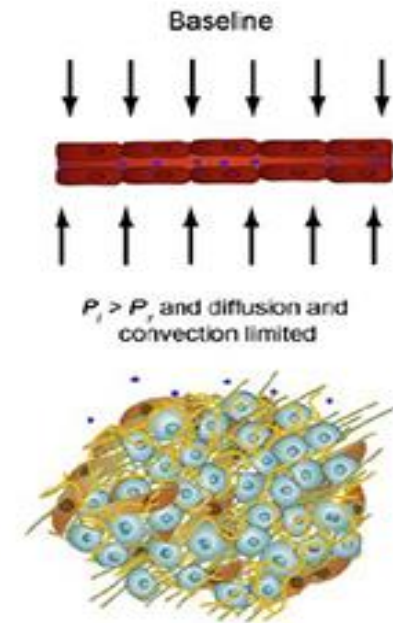
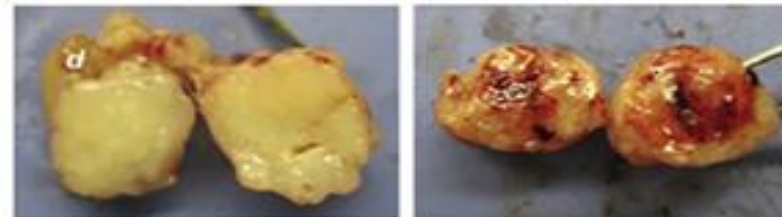
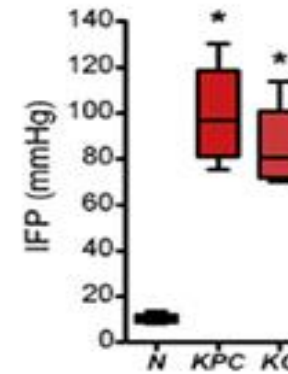
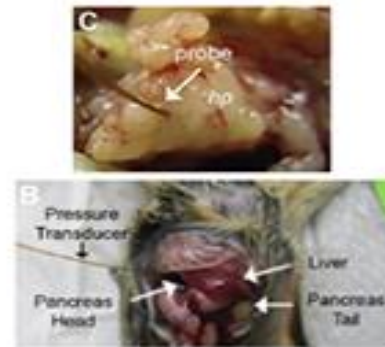
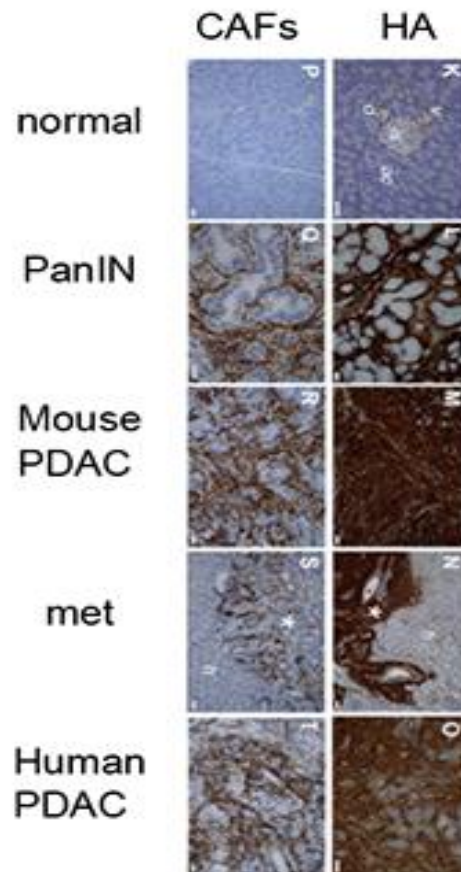
CAFs come in subtypes of varying function and origin



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

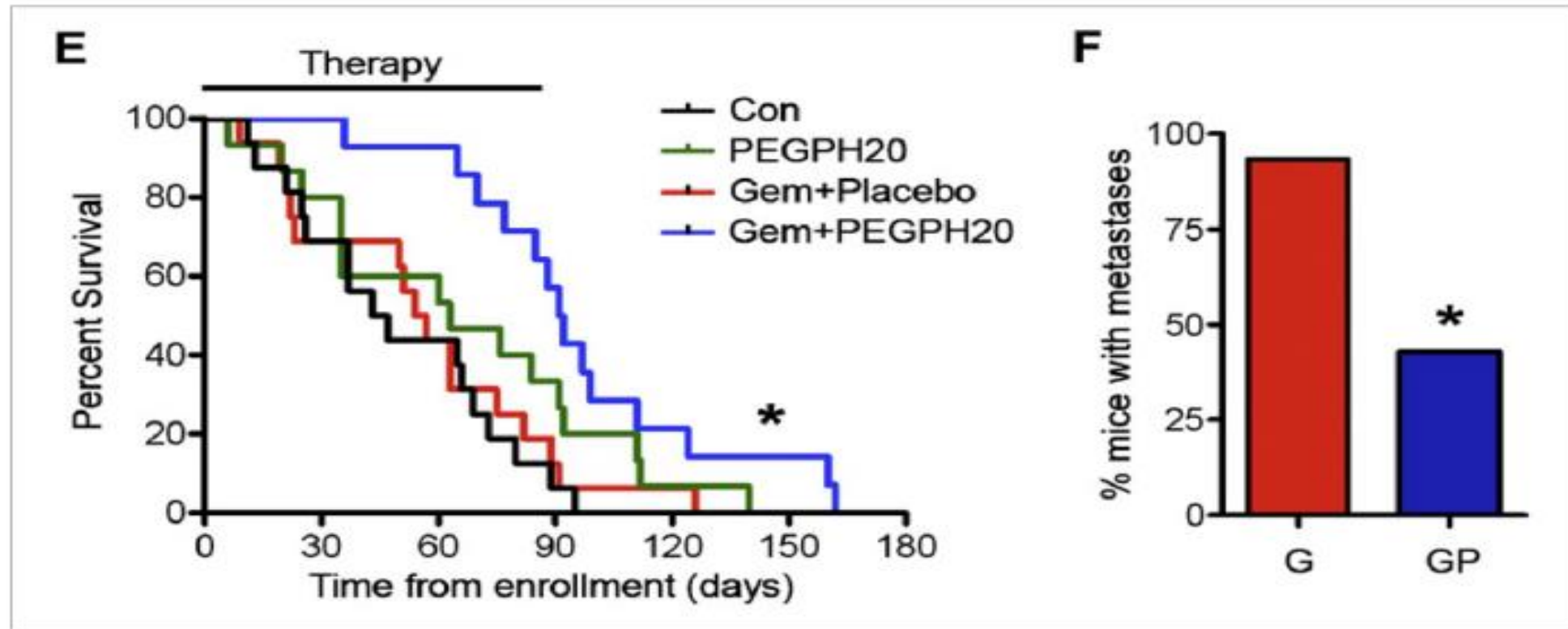
ECM ablation

Ablating ECM HA opens vessels in the tumor



Extracellular matrix

Enzymatic Targeting of ECM Enhances Therapeutic Response



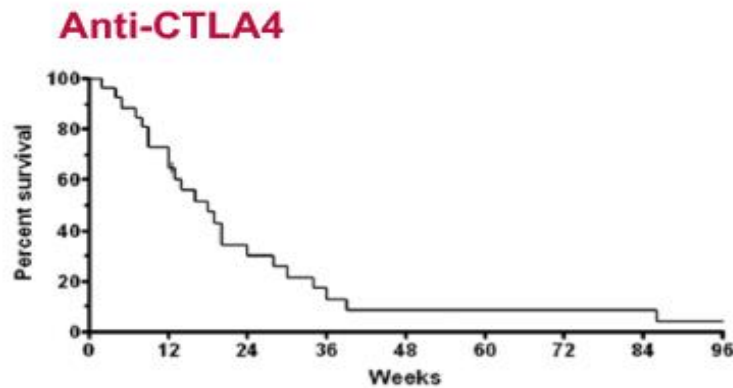
Immunotherapy

Advent of immunotherapy in PDAC



PDAC and immunotherapy

PDAC does not respond to single agent immunotherapy agents



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.

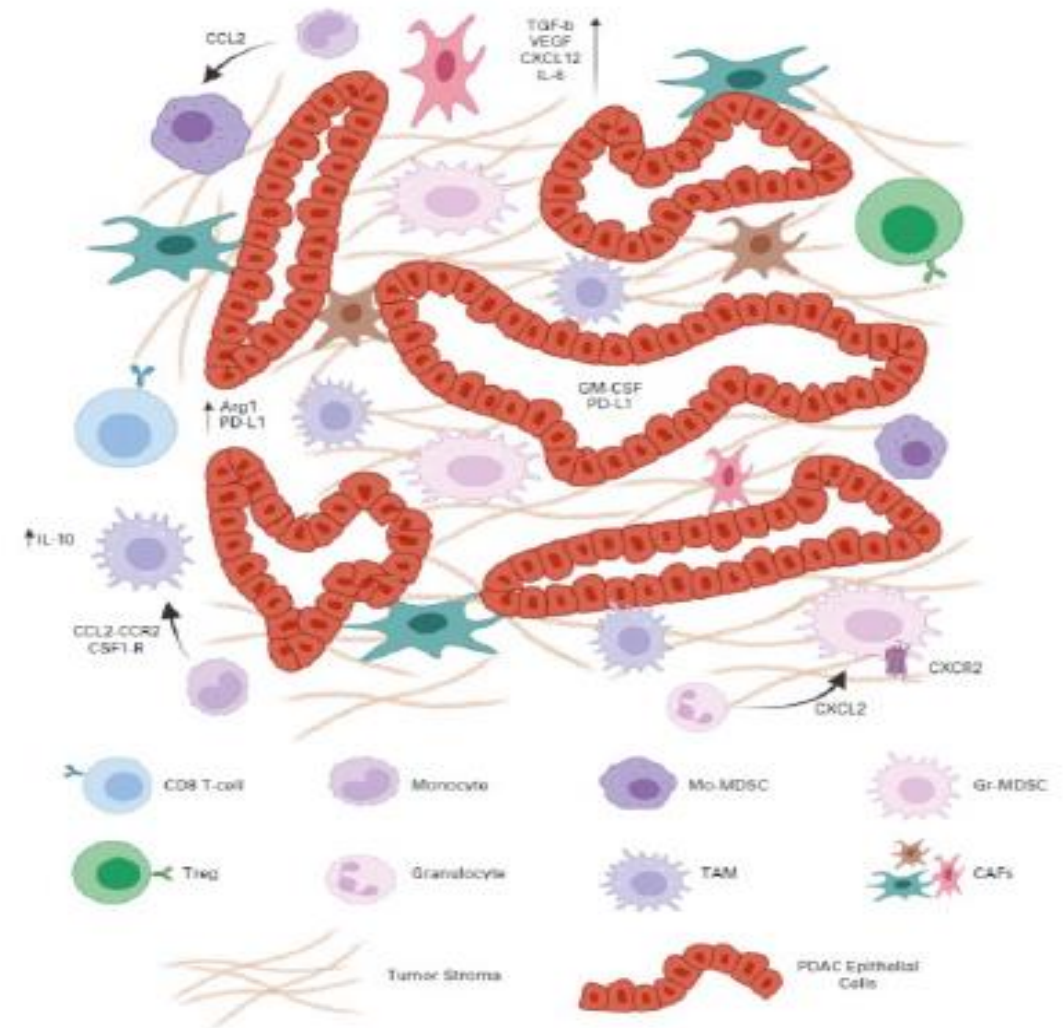
...or to combinations (so far)

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 10.9 months	27
NCT03250275	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 21.7%; 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 (αCD40 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 + Pegilodecafin (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

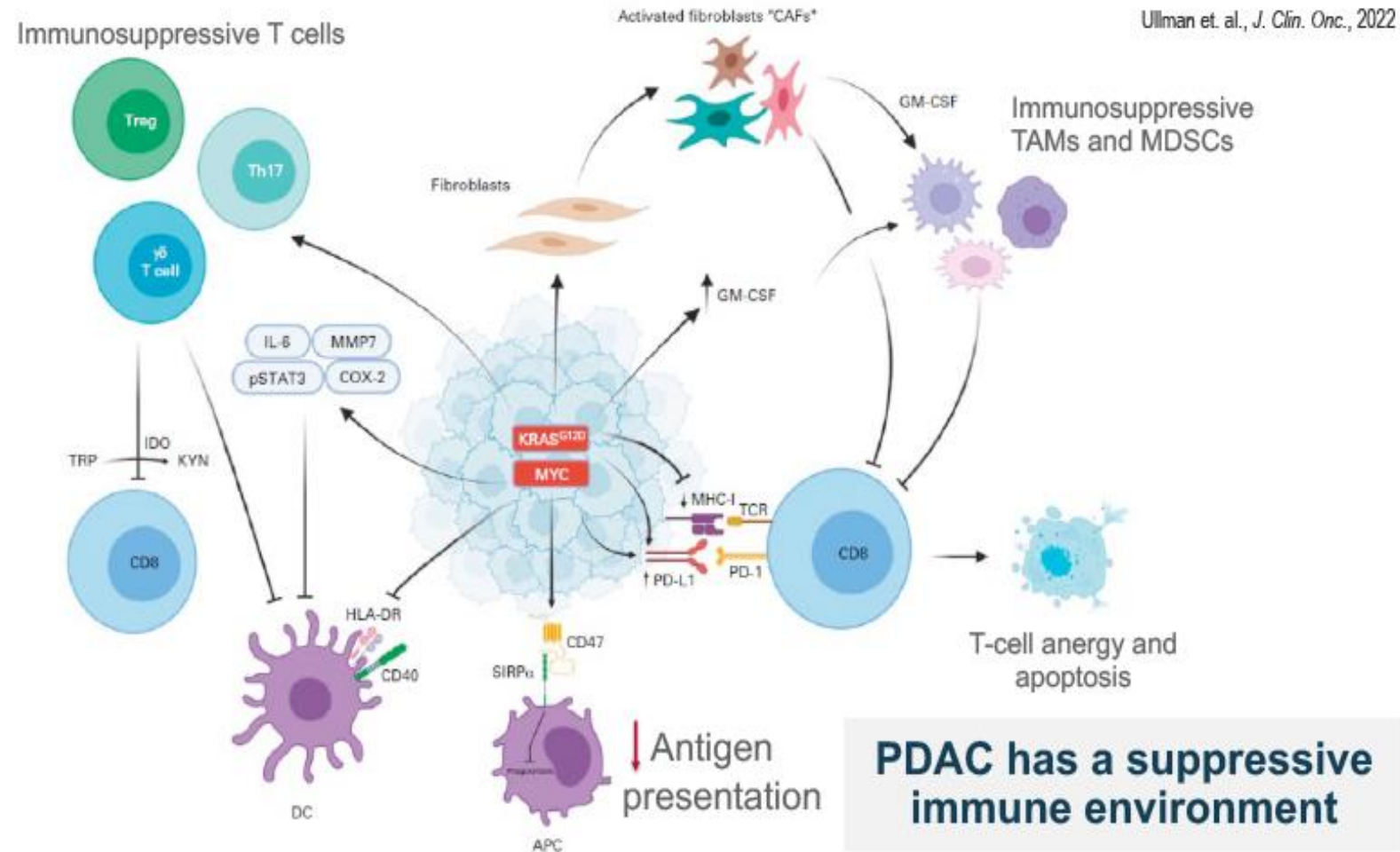
Cold tumor

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



Immune suppression



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

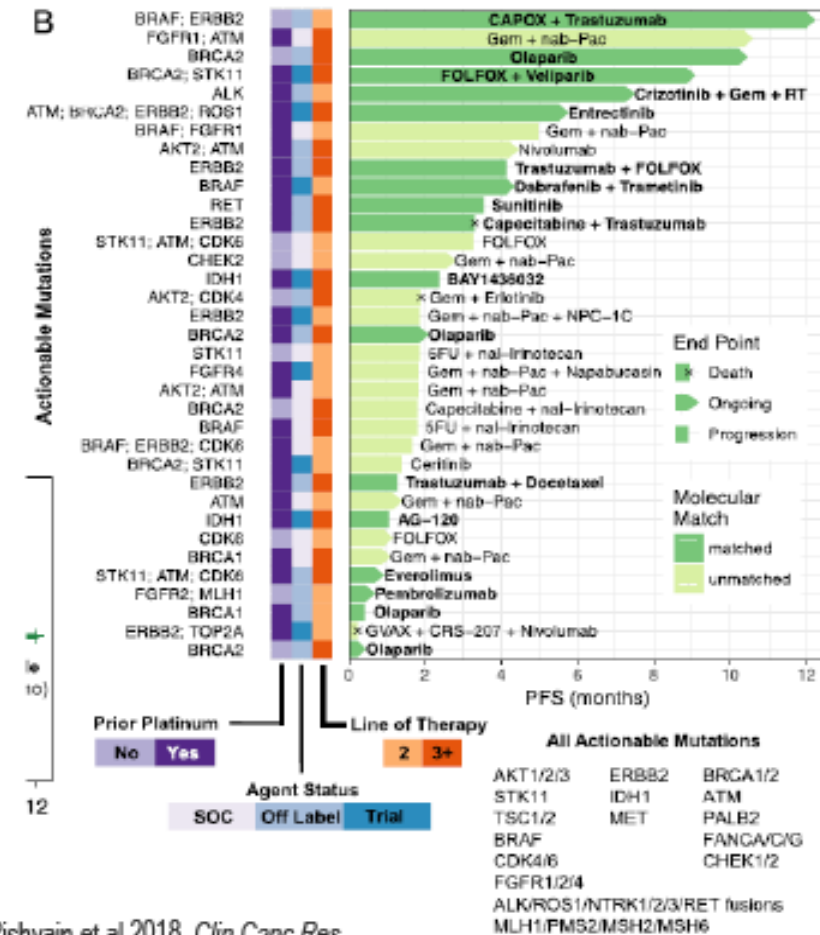
Precision medicine for Pancreatic Cancer



PDAC

Know Your Tumor: Precision Medicine for PDAC

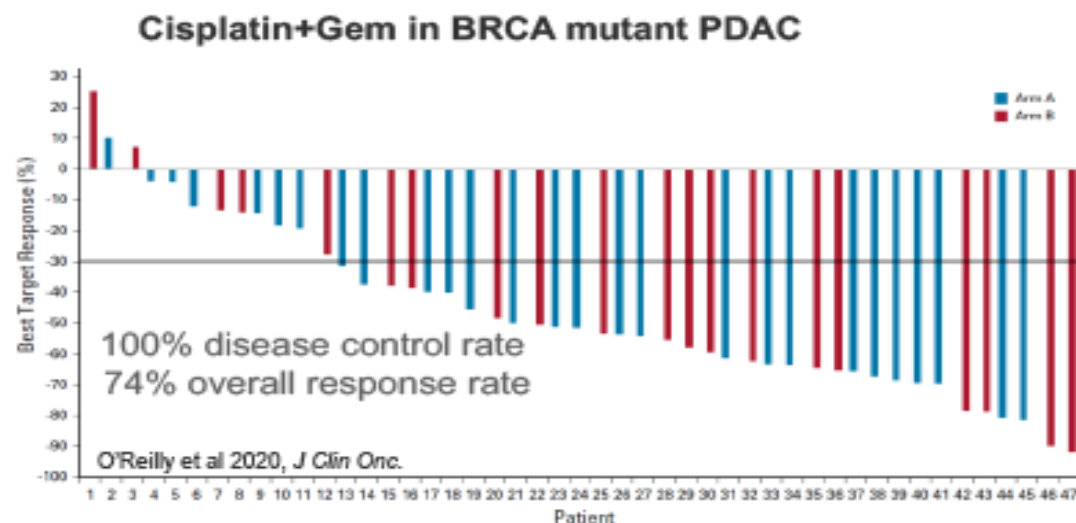
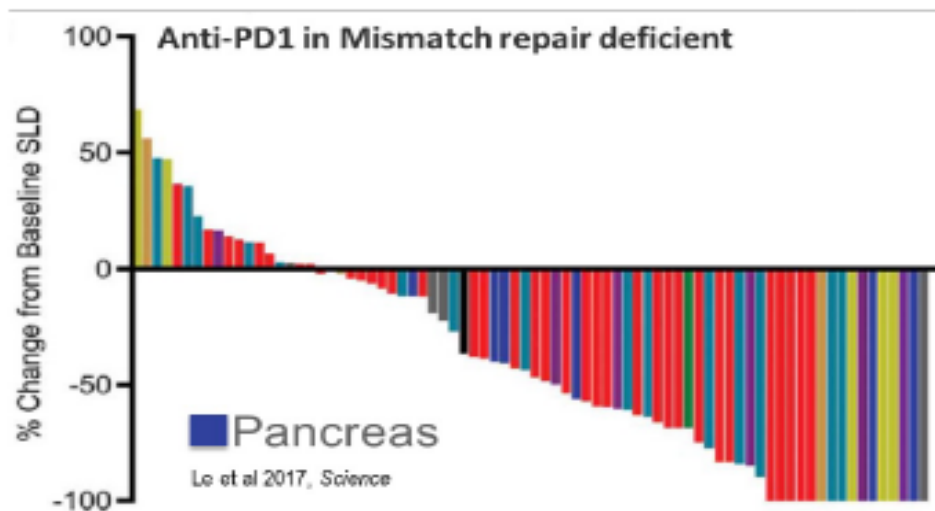
- N = 640 patients accrued
- Adequate samples for sequencing in >90%
- “50% with actionable mutations (27% highly actionable)”
 - DNA repair genes (BRCA, ~8%)
 - Cell cycle genes (CCND1/2/3, CDK4/6, ~8%)
- Effect of matched therapy
 - N = 18
 - PFS 4.1 vs. 1.9 m (HR 0.47, p = 0.03)



Waterfall plot

Precision Medicine Targets in PDAC

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



KRAS

KRAS: the no longer undruggable target

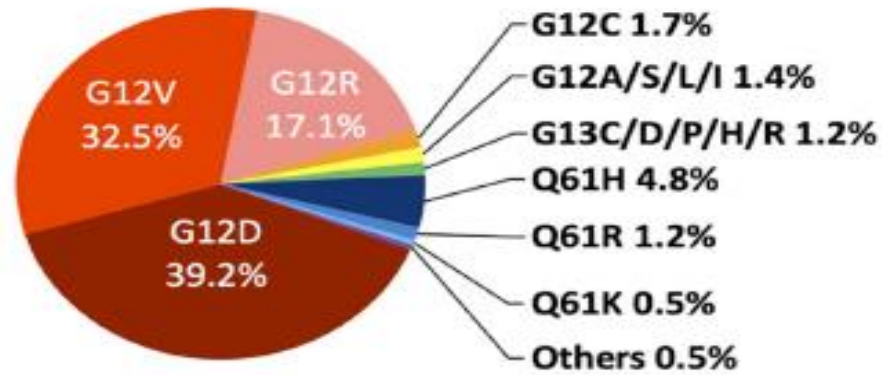
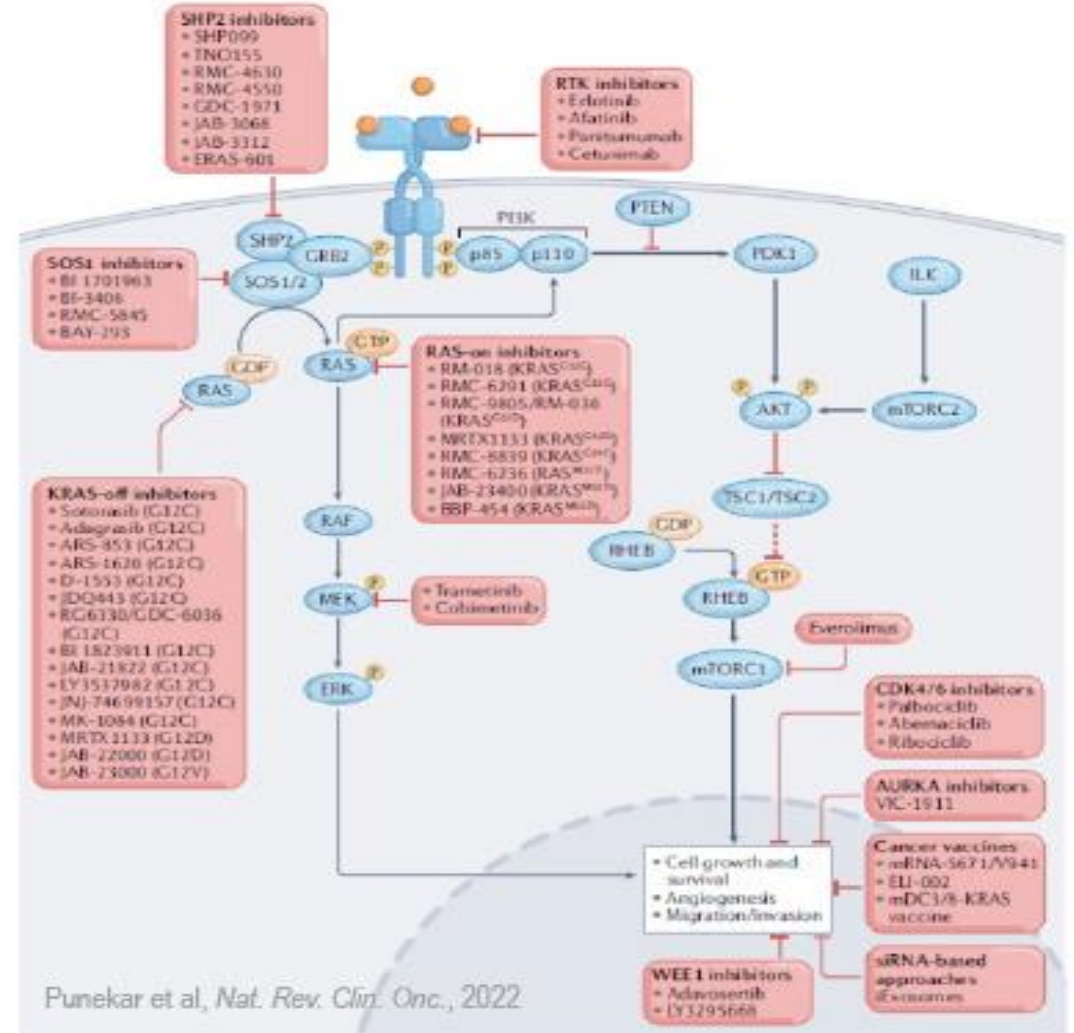


Fig. 3. Distribution of KRAS mutations in pancreatic cancer. The analysis was done using publicly available data from the cBioPortal database [48,49] that includes 665 KRAS mutant tumor samples from four large scale pancreatic cancer studies [50-53].

Luo et al, *Seminars in Onc*, 2021



KRAS^{G12D} inhibitor

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

Hallin et al 2022, *Nat. Med.*

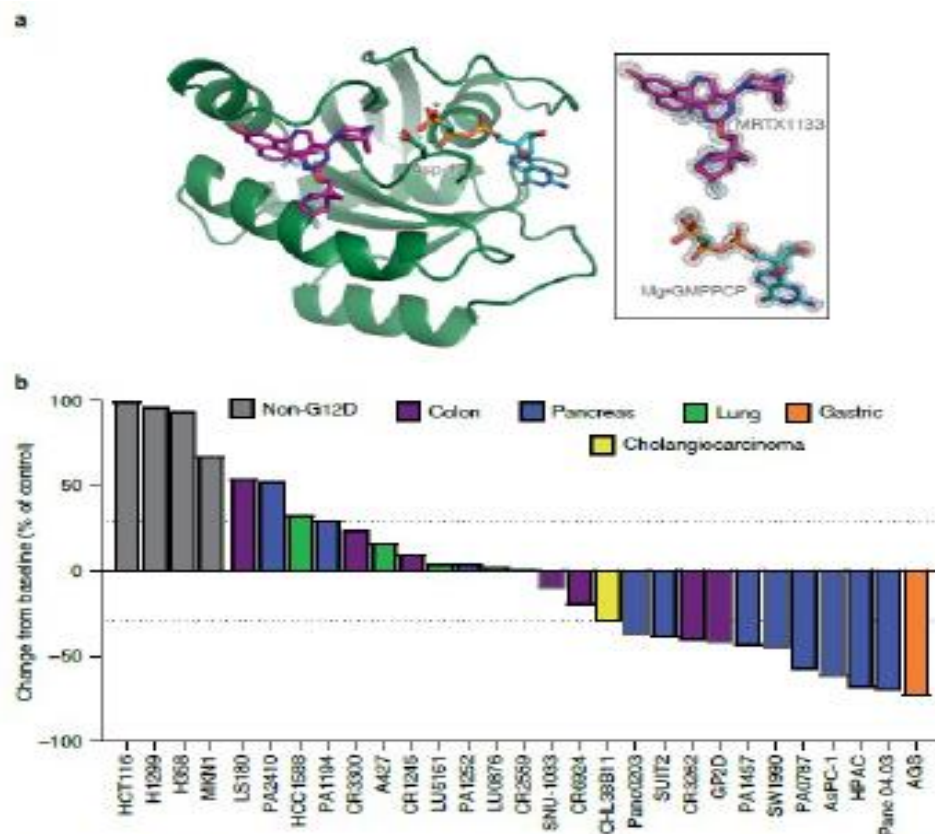


Fig. 1 | MRTX1133 potently inhibits both the active state and the inactive state of KRAS^{G12D} and has anti-cancer activity in KRAS^{G12D}-bearing human tumor xenograft models. a, Crystal structure of KRAS^{G12D} in complex with MRTX1133 and the GTP analog GMPPCP. b, Anti-tumor activity of MRTX1133 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?



Questions?