

Clinical Care of Patients with Pancreatic Cancer

Christine Alewine, M.D., Ph.D.
Clinical Translation Unit
Laboratory of Molecular Biology
Center for Cancer Research
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Pancreatic Cancer Incidence and Mortality

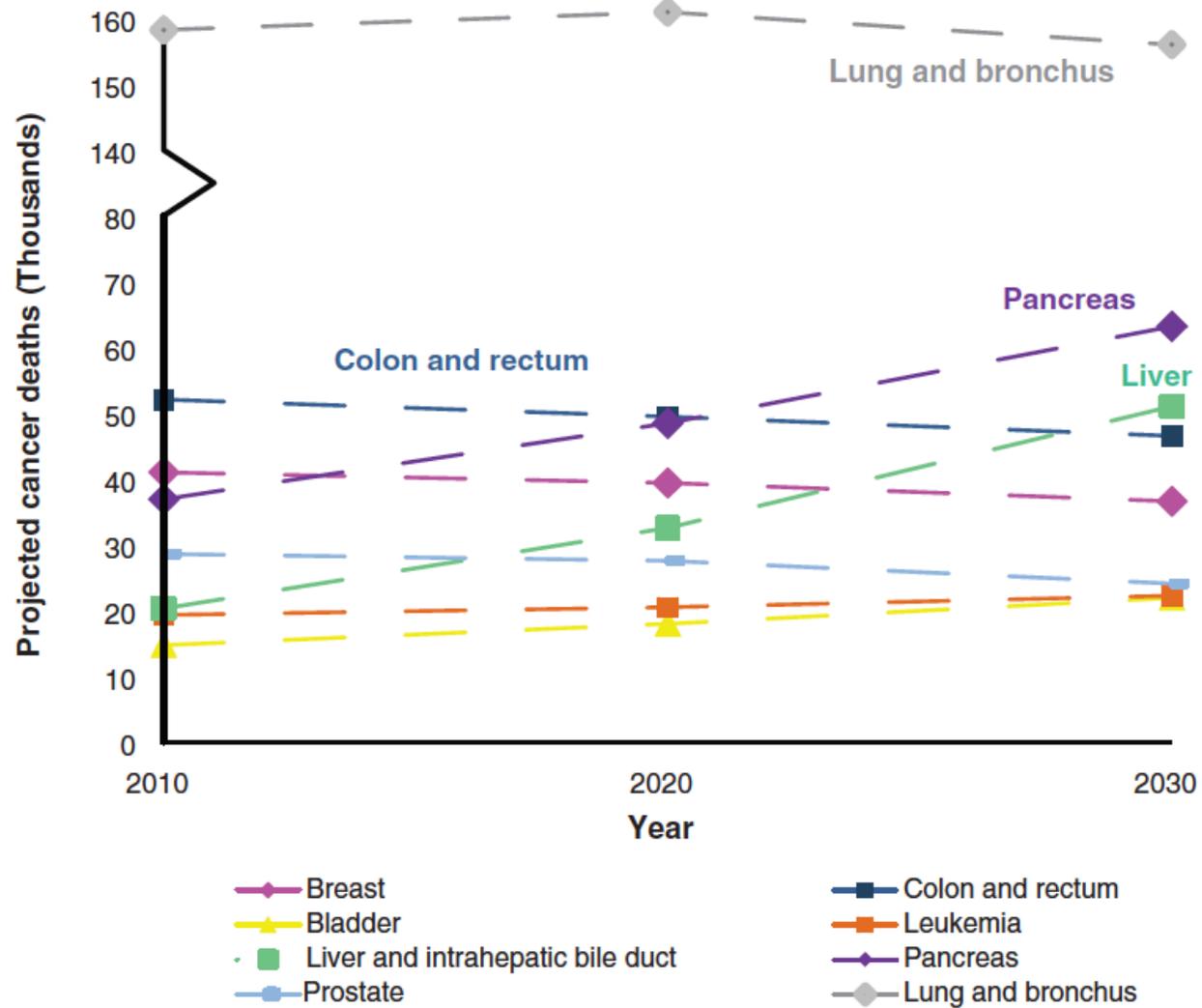
Estimated Deaths

Siegel R et. al., CA Cancer J Clin, 2018

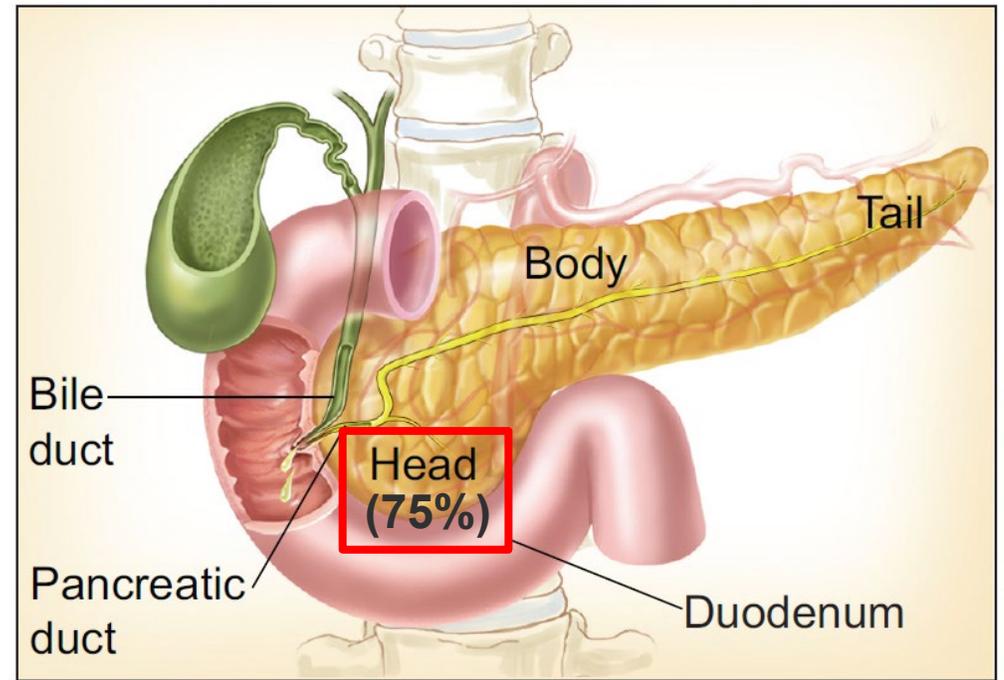
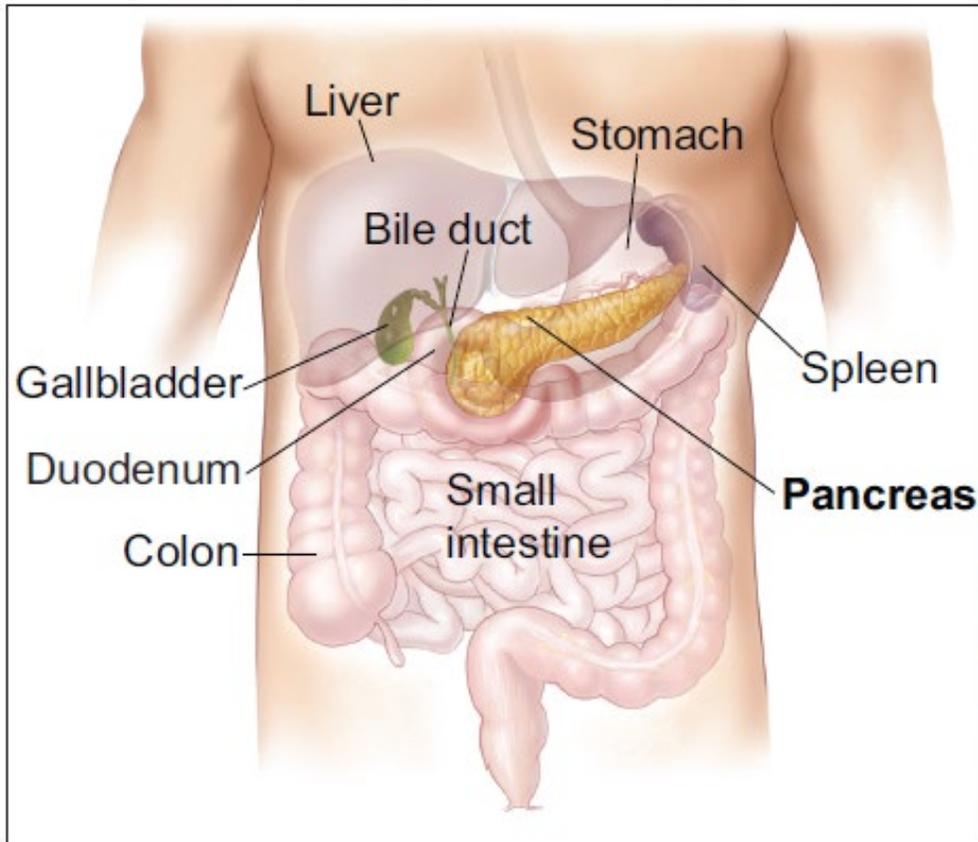
			Males	Females			
Lung & bronchus	83,550	26%			Lung & bronchus	70,500	25%
Prostate	29,430	9%			Breast	40,920	14%
Colon & rectum	27,390	8%			Colon & rectum	23,240	8%
Pancreas	23,020	7%			Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%			Ovary	14,070	5%
Leukemia	14,270	4%			Uterine corpus	11,350	4%
Esophagus	12,850	4%			Leukemia	10,100	4%
Urinary bladder	12,520	4%			Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%			Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%			Brain & other nervous system	7,340	3%
All Sites	323,630	100%			All Sites	286,010	100%

- 3rd leading cause of cancer death in the United States
- Median 5 year survival just reached 10%
- Median overall survival is < 6 months
- Estimated 55,440 new diagnoses and 44,330 deaths in 2018

Pancreatic Cancer: Second Leading Cause of Cancer-related Deaths by 2030



Pancreas Cancer



Subtypes

- Adenocarcinoma (~90%)
- Neuroendocrine (<5%)
- Adenosquamous
- Acinar Cell Carcinoma
- Mucinous cystadenocarcinoma

What you need to Know About Cancer of the Pancreas,
NIH Publication No. 10-1560, 2010

Risk Factors

Ryan, Hong and Bardeesy, NEJM, 371, 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.

New recommendation:

All PDAC patients should have germline testing for inherited mutations

ASCO Guidelines per Expert Consensus Panel (published Jan 2019 in *JCO*):

- 4-20% prevalence
- 40 papers relevant to the topic were analyzed: *“The papers informed the panel members but, ultimately, did not establish a strong evidence base to craft the recommendations... All patients diagnosed with PDAC should undergo assessment of risk for hereditary syndromes known to be associated with an increased risk for pancreatic adenocarcinoma”*

- What unaffected persons are at greater risk for pancreatic cancer?
 - Persons with 2 first-degree relatives with PDAC
 - Persons with 3 relatives on the same side of the family with PDAC
 - Individuals who meet criteria for inherited syndromes associated with PDAC

90% will test negative for inherited mutation

Symptoms of Pancreatic Cancer

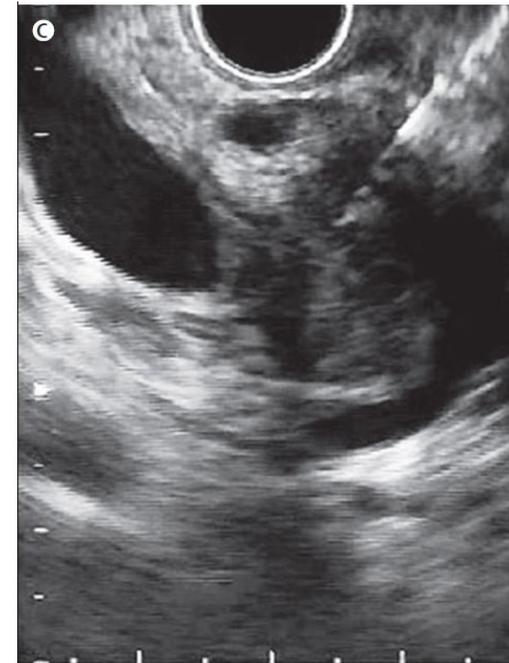
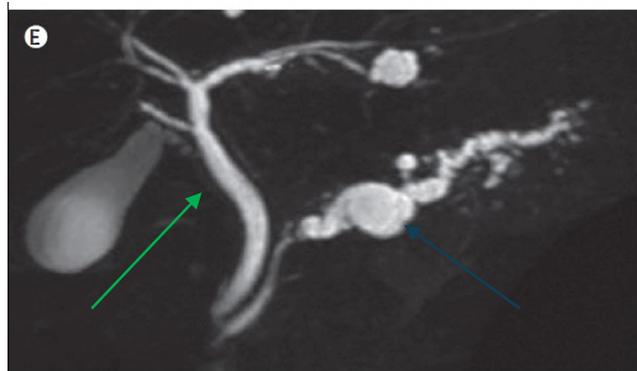
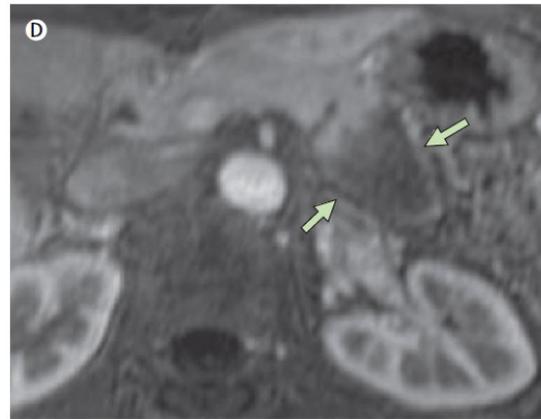
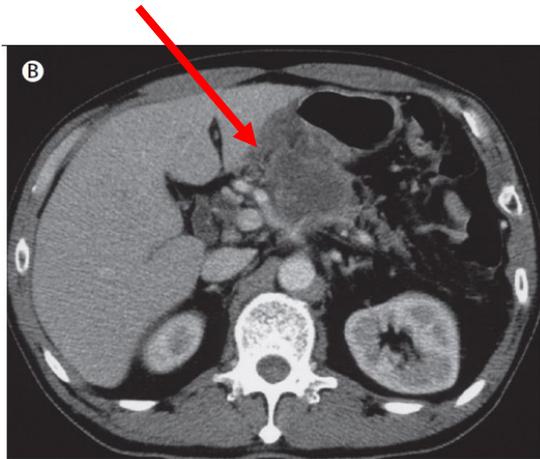


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- ❖ Jaundice (yellow skin and eyes, dark urine)
- ❖ Upper abdominal pain
- ❖ Mid back pain
- ❖ Nausea and vomiting
- ❖ Weight loss
- ❖ Anorexia (loss of appetite)
- ❖ Early satiety (feeling full quickly)
- ❖ Lethargy

Diagnosing Pancreas Cancer

- 1. CT, MRI imaging, or endoscopic ultrasound (EUS)



- 2. Biopsy:
 - Endoscopic
 - Percutaneous liver biopsy
 - Surgical

STAGE AT DIAGNOSIS

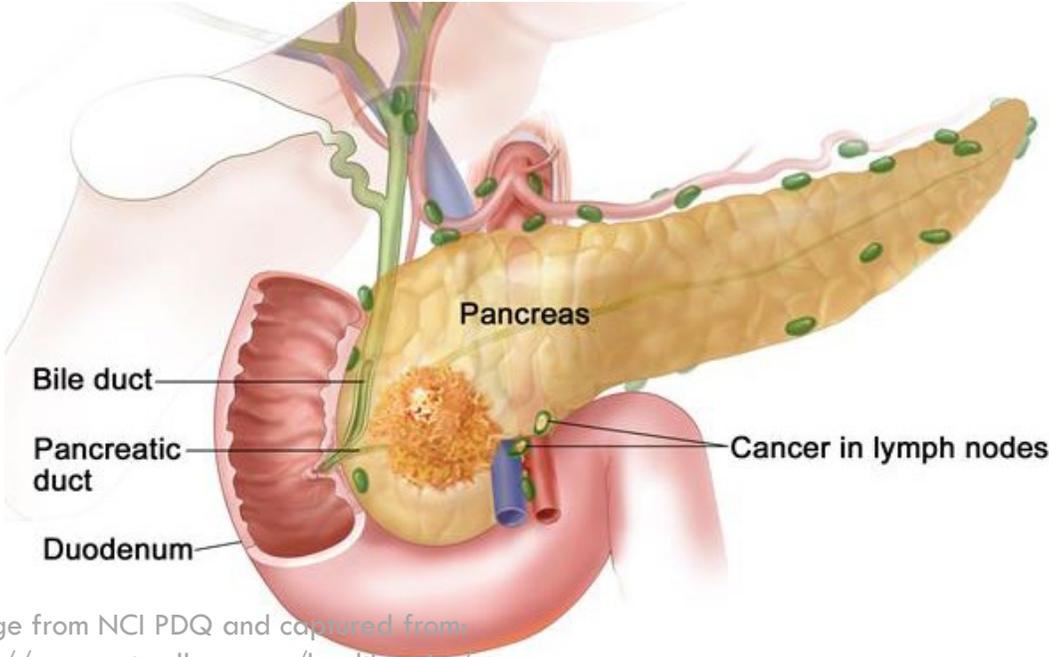
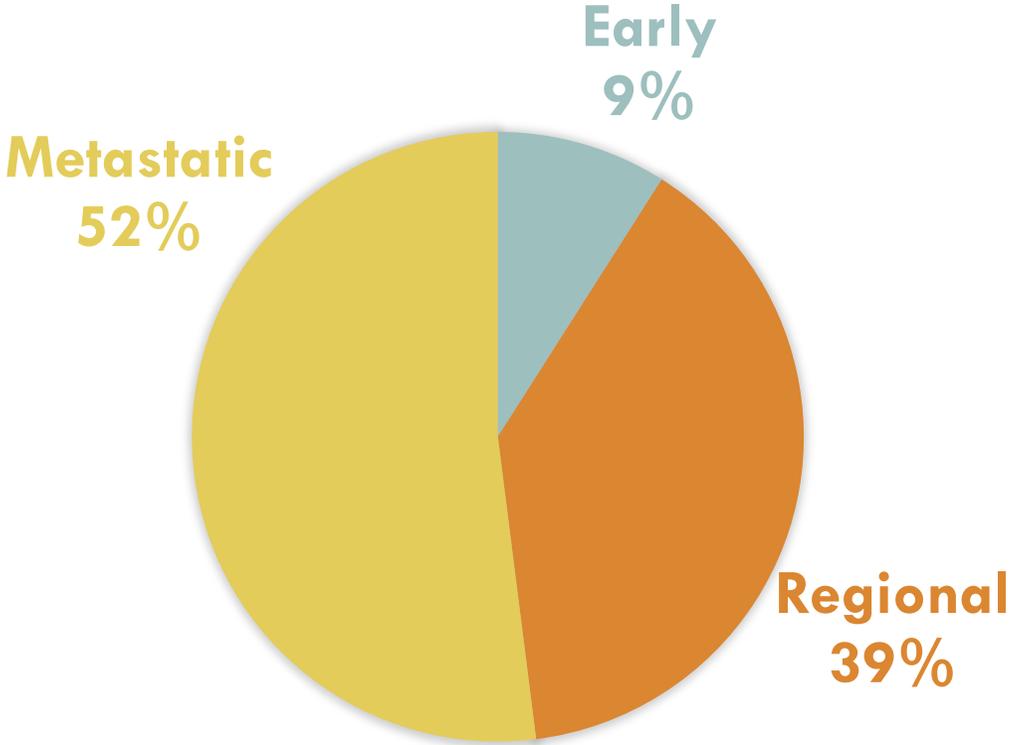


Image from NCI PDQ and captured from: <http://www.netwellness.org/healthtopics/pancreatic/pancreaticcancerstagesimages.cfm>

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U.S. Govt. has certain rigt



Most patients have metastatic disease at diagnosis:

1. Liver
2. Peritoneum
3. Lung

Pancreatic Cancer

Surgery



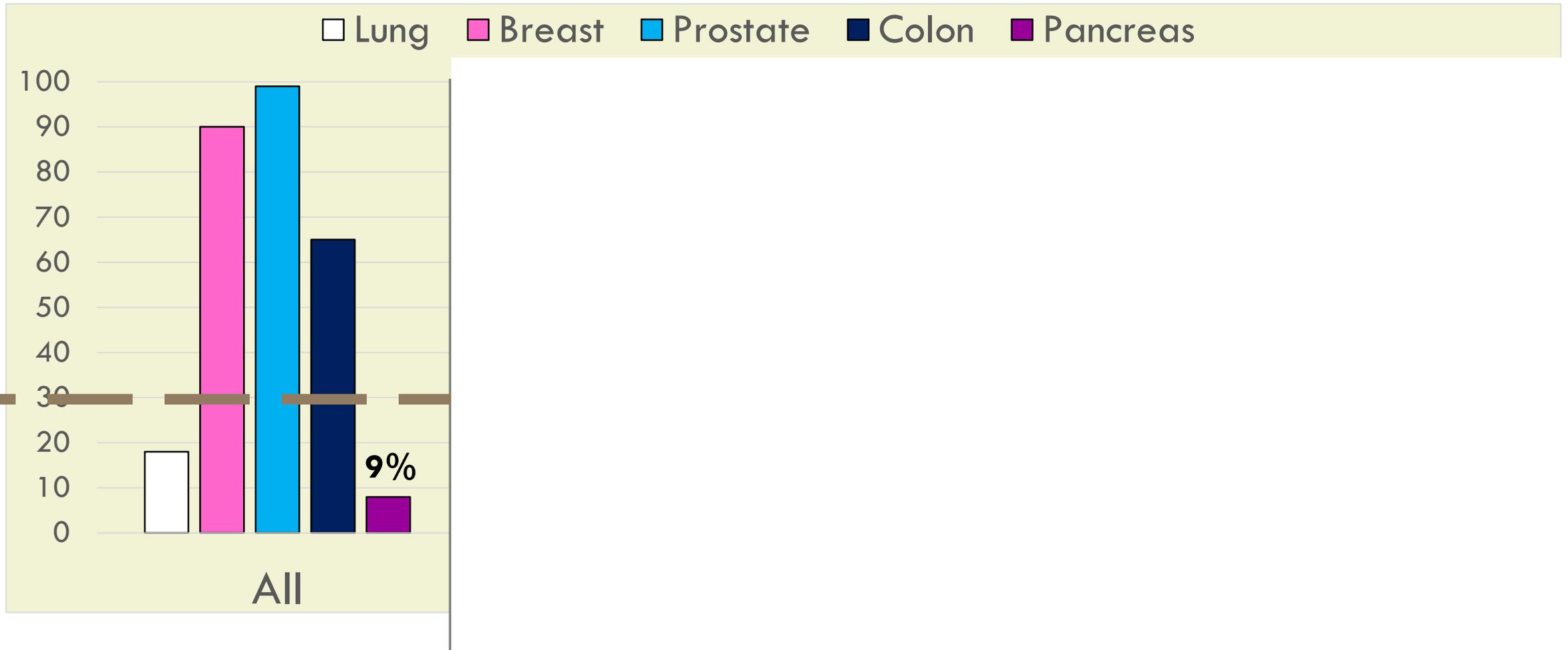
No

Surgery

	Stage	Description
Early Stage (10%)	Stage IA	$\leq 2\text{cm}$
	Stage IB	$> 2\text{cm} \leq 4\text{cm}$
	Stage IIA	$> 4\text{cm}$
Regional (29%)	Stage IIB	+1-3 lymph nodes
	Stage III	≥ 4 lymph nodes or invading unresectable vessels
Distant (53%)	Stage IV	Distant metastasis

NCCN summary of 8th ed. Staging, †NCI SEER & *Roessel et al, *JAMA Surg*, 2018

5-YEAR SURVIVAL % BY STAGE



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

Carbohydrate Antigen 19-9 (CA19-9)

Serum CA19-9 >37 U/ml

Pancreatic Cancer vs Healthy Individual

Sensitivity: 80.3% (95% CI 77.2-82.6)

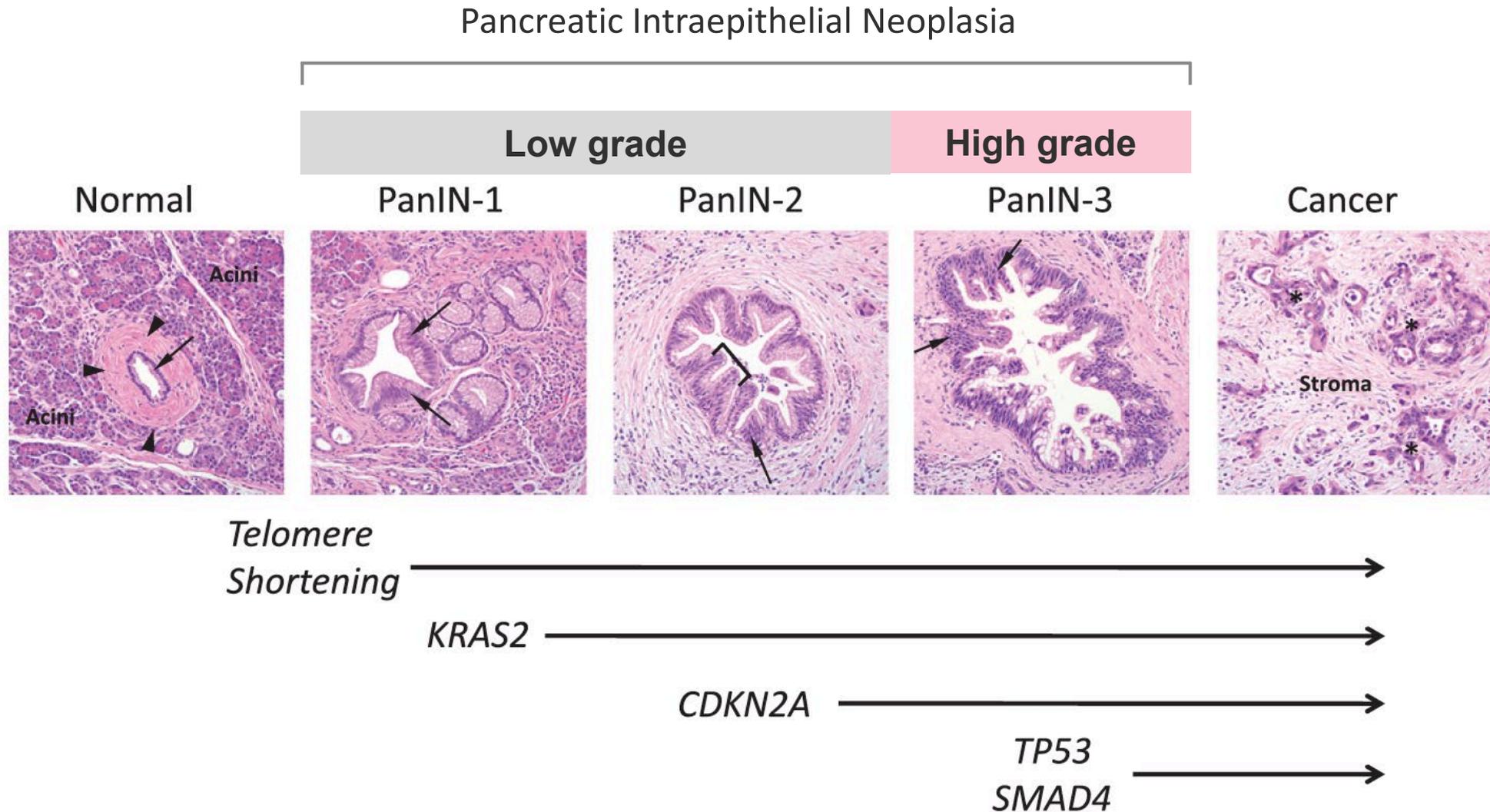
Specificity: 80.2% (95% CI 78-82.3)

Malignant vs Benign Pancreatic Disease

Sensitivity: 78.2%

Specificity: 82.2%

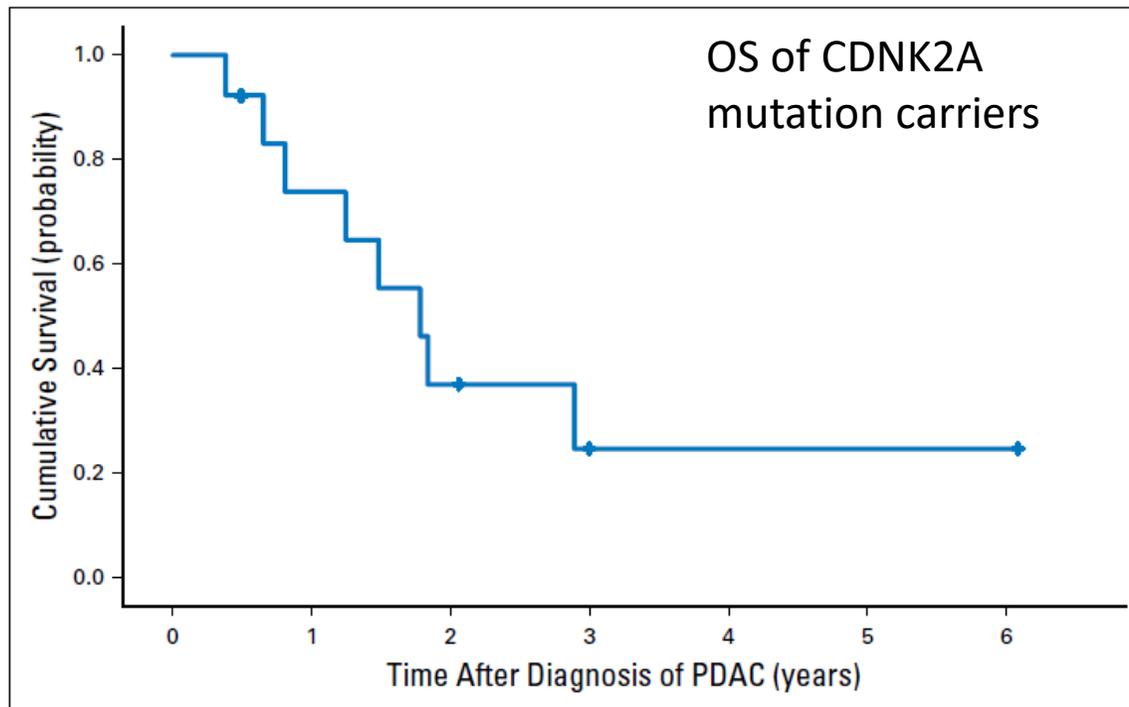
Progression Model of Pancreatic Carcinogenesis



Active surveillance in high risk patients

“Although large studies confirming mortality benefit of pancreatic screening are lacking, emerging data suggest screening in individuals with high risk is associated with downstaging of incident cancers.”

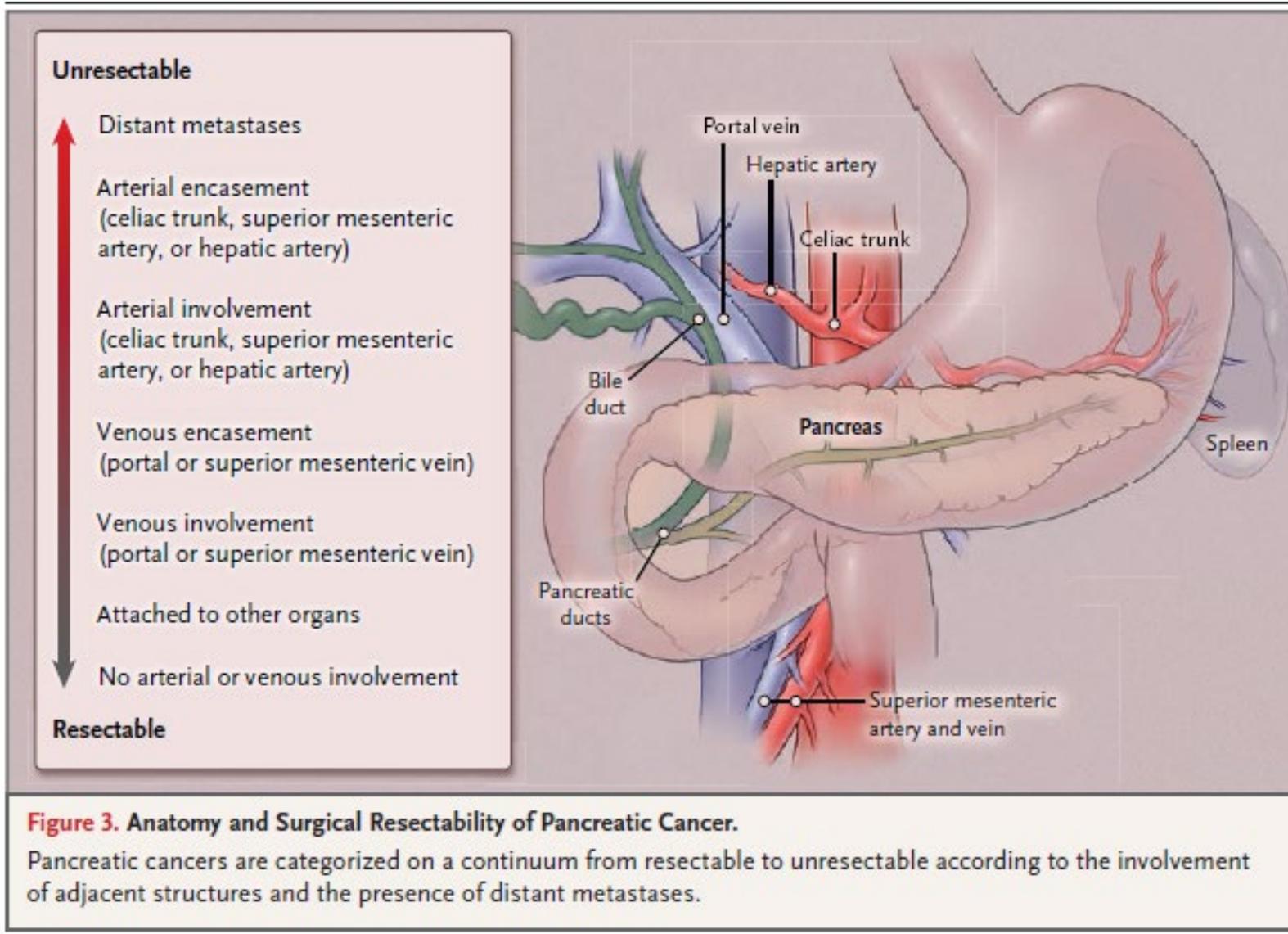
...2019 ASCO Guidelines



Vasen et al, JCO 2016

- Refer patients with familial pancreatic cancer or known germline mutations to centers with established surveillance programs
- Effective methods:
 - Pancreatic protocol MRI or MRCP
 - Endoscopic ultrasound (EUS)
- Ineffective:
 - CT scan
 - Tumor markers

Resectable Disease



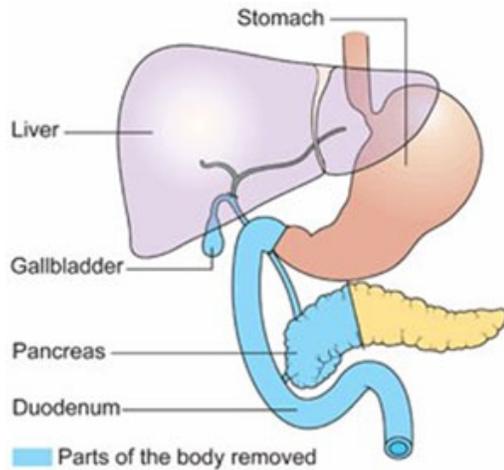
Surgical resectability is defined by:

- Degree of vascular involvement
- Surgeon who evaluates the case

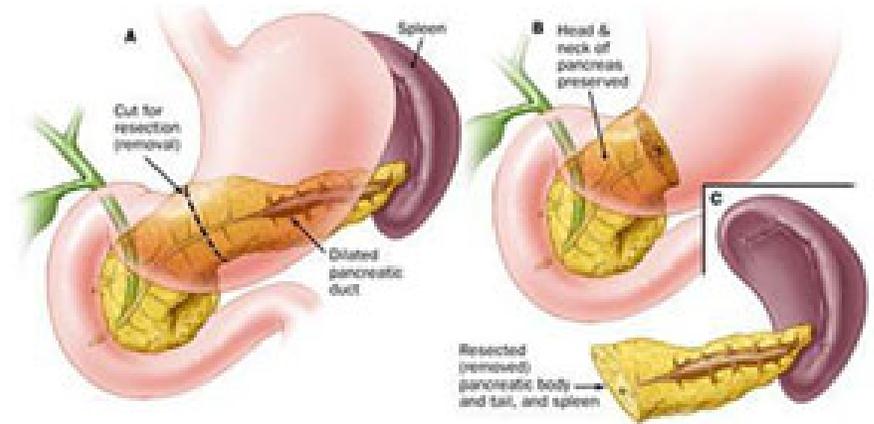
Early Stage Disease: Surgery + Chemotherapy

• 1. Whipple

- For tumors in pancreatic head
- Very complicated procedure
- High morbidity and mortality rate
 - Delayed gastric emptying (21%)
 - Fistula (15%)
 - Wound infection (11%)
 - Bleeding (2%)
 - Chyle leak (1%)
 - Cardiac event (3%)
 - Pneumonia (2%)
- Long recovery period
- Long-term complications



2. Distal Pancreatectomy

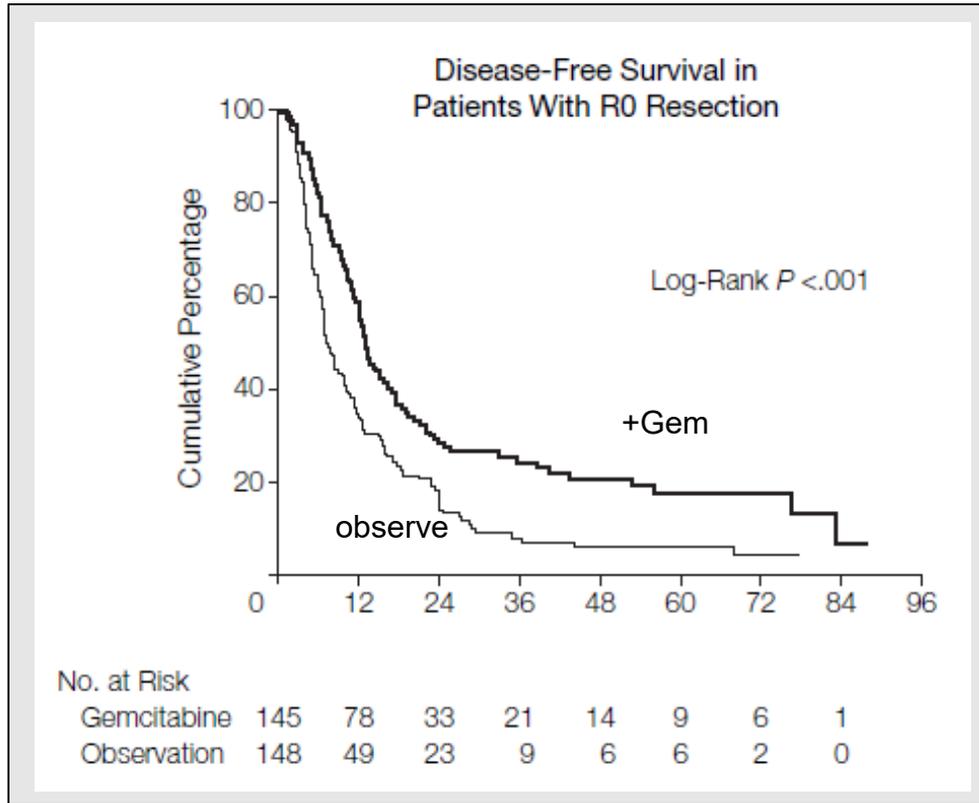


3. Total Pancreatectomy

- Causes insulin dependence

Early Stage Disease: Surgery alone is not enough

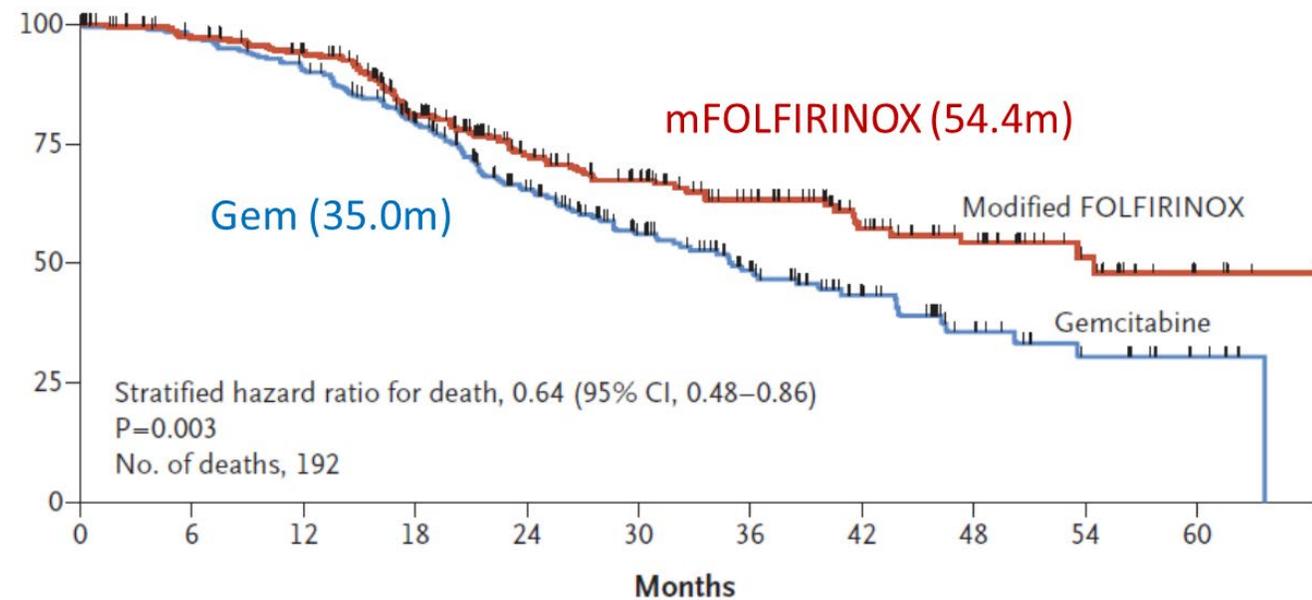
CONKO-001



Oettle et al, *JAMA*, 2007

No. at Risk		0	6	12	18	24	30	36	42	48	54	60
Modified FOLFIRINOX	247	223	210	165	119	91	68	46	32	16	4	
Gemcitabine	246	233	215	171	120	81	55	33	18	9	4	

PRODIGE/ ACCORD



Conroy et al, *NEJM*, 2018

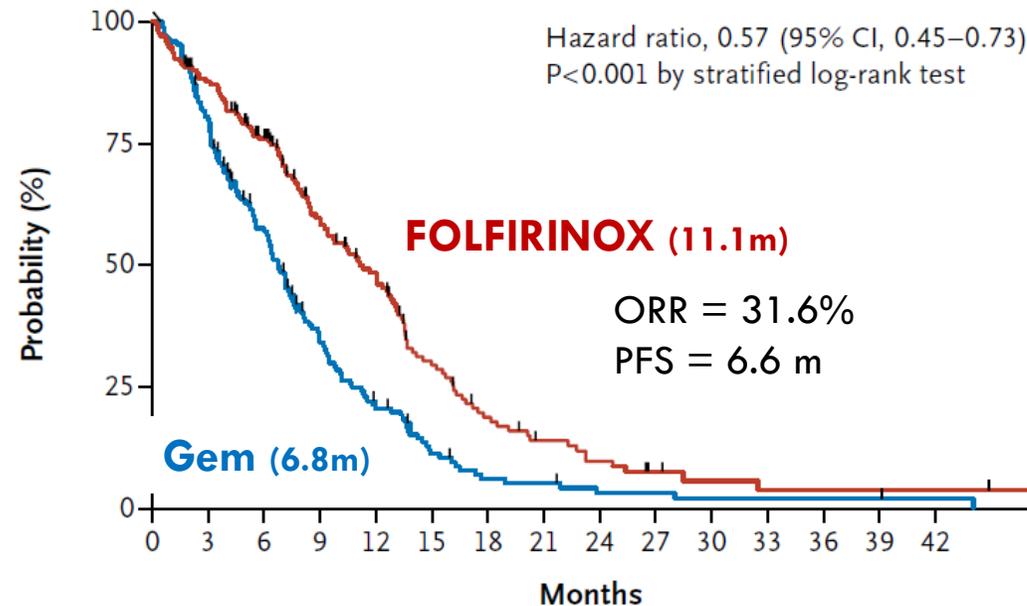
Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer

Vinod P. Balachandran^{1,2,3}, Marta Łuksza⁴, Julia N. Zhao^{1,2,3}, Vladimir Makarov^{5,6}, John Alec Mora^{1,2,3}, Romain Remark⁷, Brian Herbst², Gokce Askan^{2,8}, Umesh Bhanot⁸, Yasin Senbabaoglu⁹, Daniel K. Wells¹⁰, Charles Ian Ormsby Cary¹⁰, Olivera Grbovic-Huezo², Marc Attiyeh^{1,2}, Benjamin Medina¹, Jennifer Zhang¹, Jennifer Loo¹, Joseph Saglimbeni², Mohsen Abu-Akeel⁹, Roberta Zappasodi⁹, Nadeem Riaz^{6,11}, Martin Smoragiewicz¹², Z. Larkin Kelley^{13,14}, Olca Basturk⁸, Australian Pancreatic Cancer Genome Initiative*, Mithat Gönen¹⁵, Arnold J. Levine⁴, Peter J. Allen^{1,2}, Douglas T. Fearon^{13,14}, Miriam Merad⁷, Sacha Gnjjatic⁷, 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. Greenbaum¹⁹, 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

STANDARD TREATMENTS FOR ADVANCED DISEASE

Overall Survival



No. at Risk

Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2

Conroy et al, *NEJM*, 2011

1. Gem-based 2. Fluorouracil-based

First-line

- FOLFIRINOX
- Gemcitabine + nab-paclitaxel
- Gemcitabine
- Gemcitabine + erlotinib
- Fluorouracil (5-FU or cape)
- Hospice

Second-line

- 5-FU + nal-iri
- Or another above

Pick your myelosuppressive poison

FOLFIRINOX

- 5-FU (bolus + infusional)
 - Cardiac ischemia
 - Hand foot syndrome
 - Alopecia
- Leucovorin
- Irinotecan
 - Diarrhea
- Oxaliplatin
 - Irreversible neuropathy
 - Reversible cold neuropathy

GEM/ nab-paclitaxel

- Gem
 - Extremity edema
 - Pneumonitis
- Nab-P
 - Cumulative (reversible) peripheral neuropathy
 - Myalgia
 - Alopecia

Combination chemotherapy for pancreas cancer is very toxic yet...

FOLFIRINOX improves patient QOL

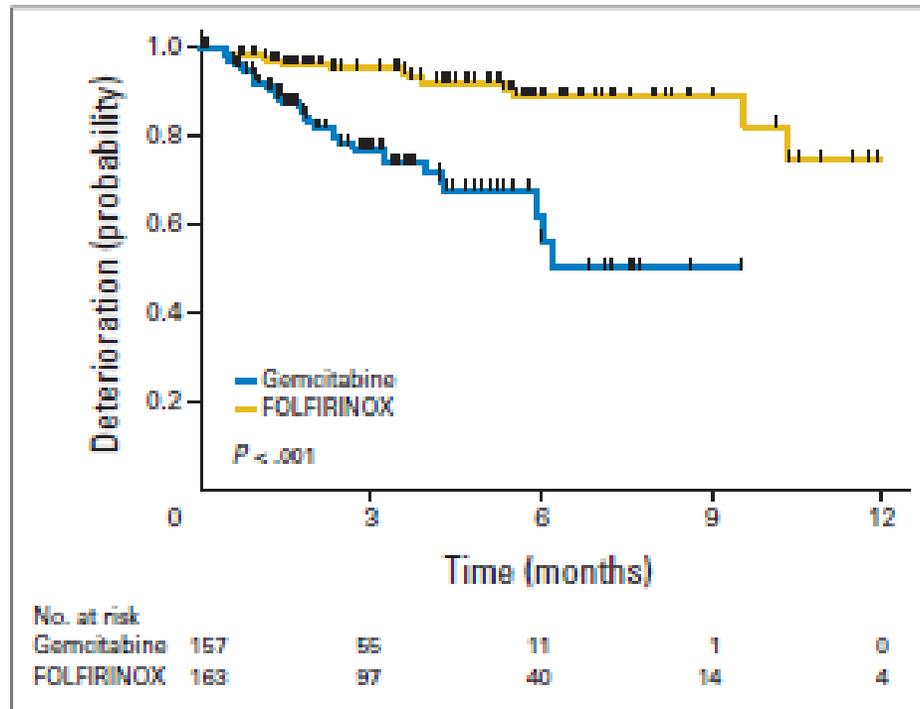


Fig 2. Kaplan-Meier plot for time until definitive deterioration more than 20 points for European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30 global health status/quality of life. FOLFIRINOX, oxaliplatin/irinotecan/fluorouracil/leucovorin.

Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.*

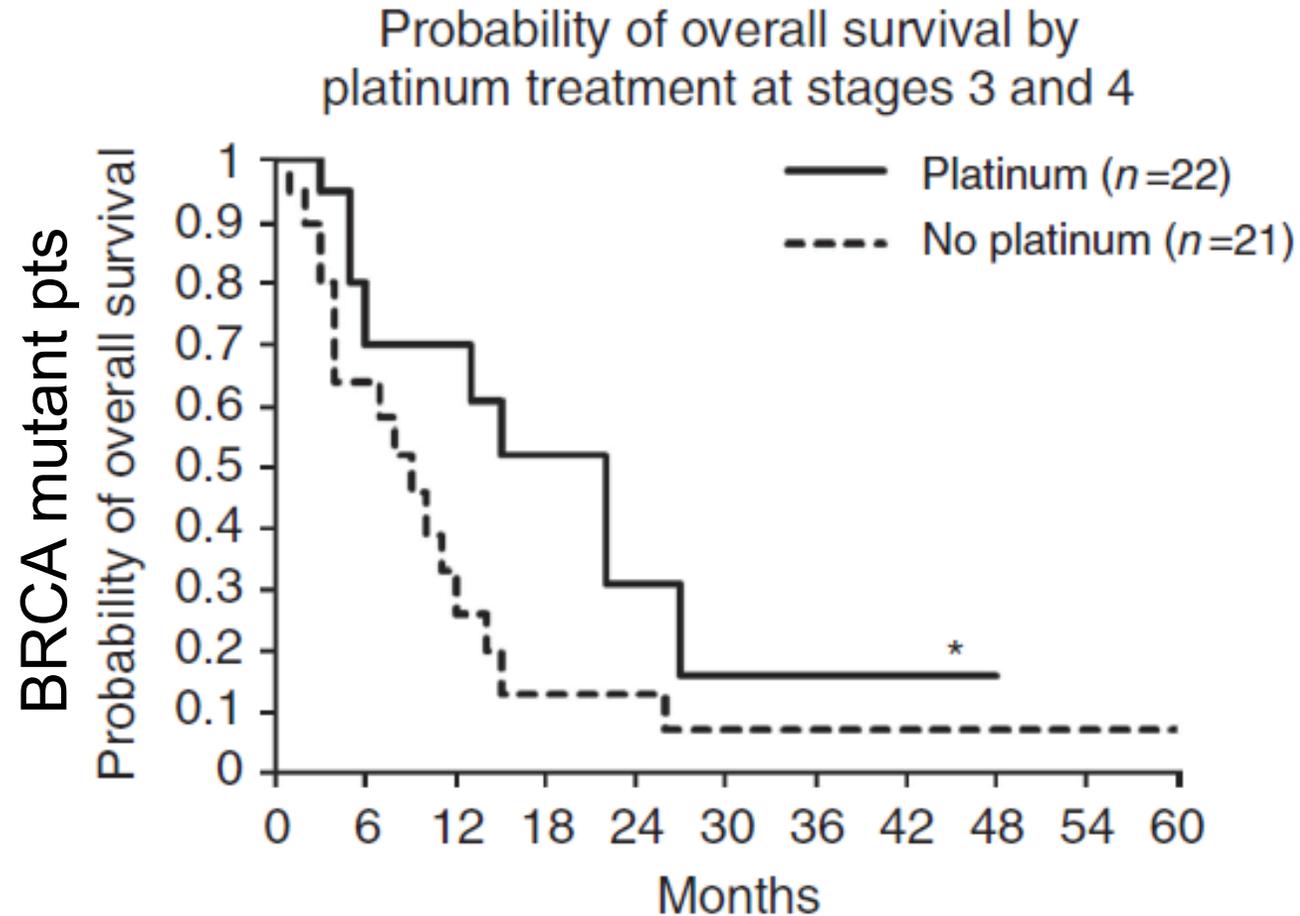
Event	FOLFIRINOX (N=171) <i>no. of patients/total no. (%)</i>	Gemcitabine (N=171) <i>no. of patients/total no. (%)</i>	P Value
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

* Events listed are those that occurred in more than 5% of patients in either group. NS denotes not significant.

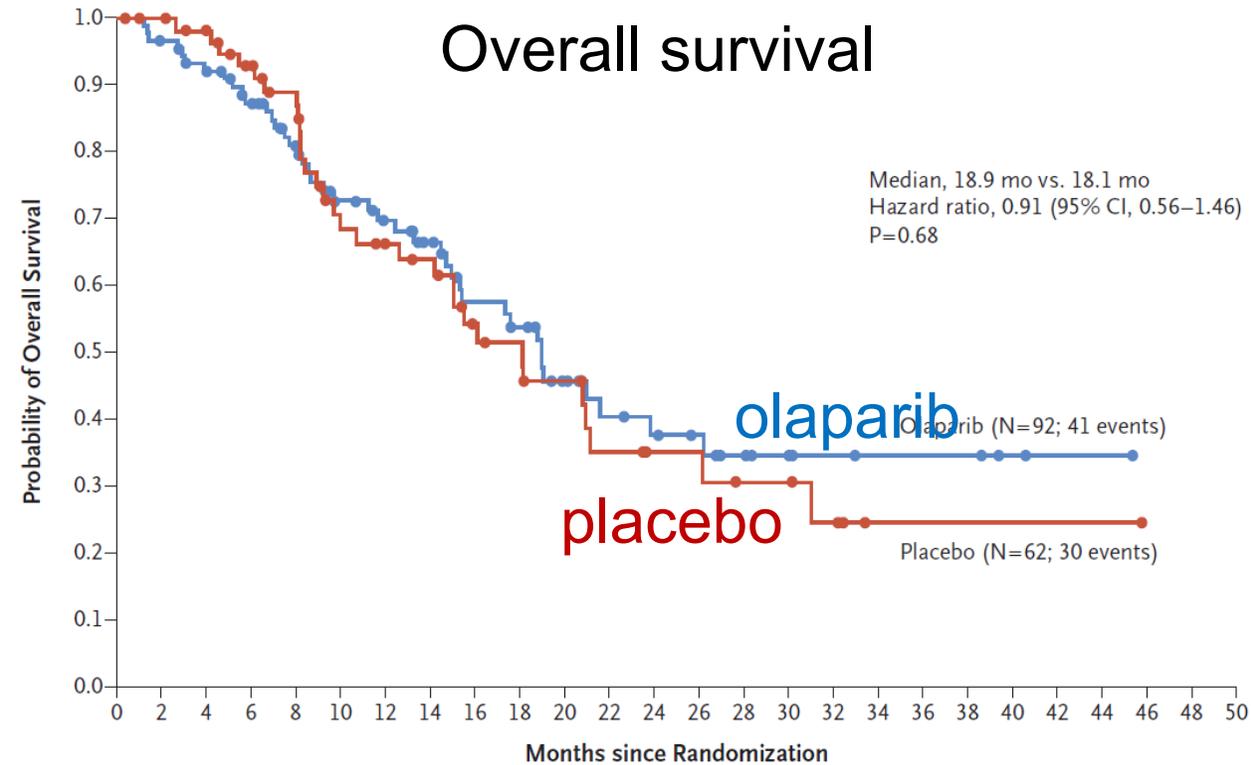
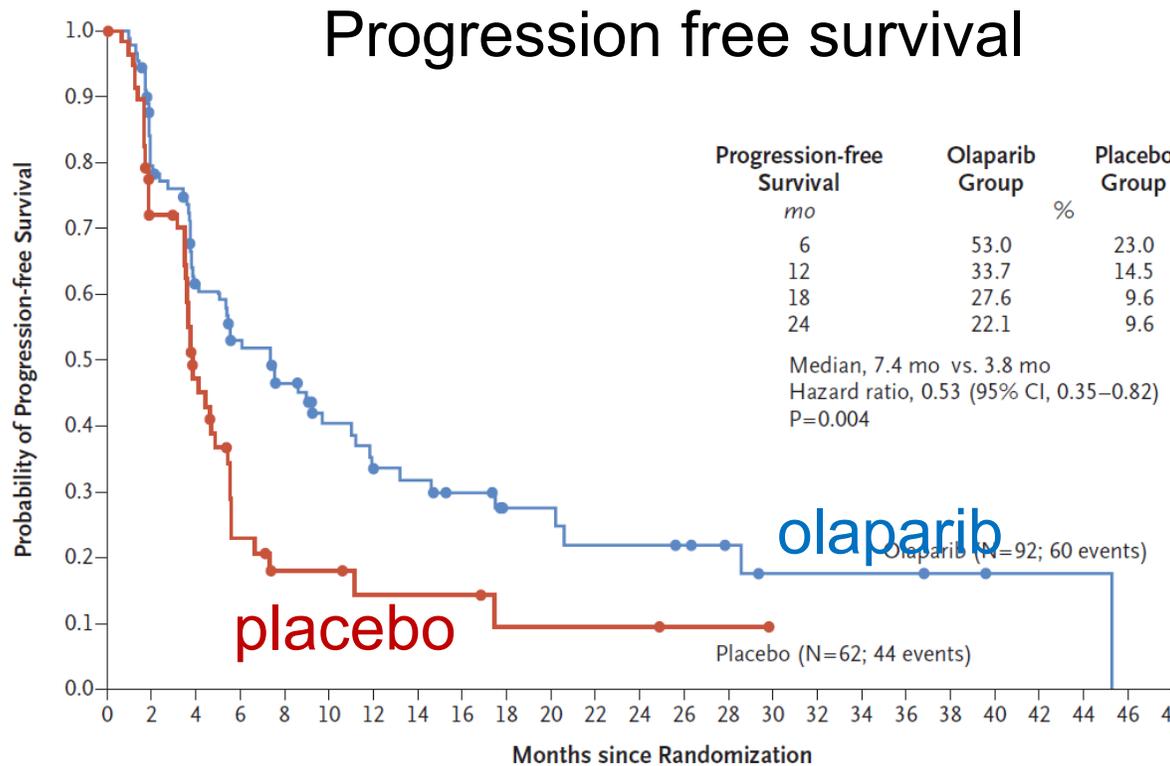
Precision medicine in PDAC: a difficult landscape



Give platinum to patients with BRCA mutation (and probably other DNA repair pathway mutations too)



PARP inhibitors work in platinum-sensitive pts



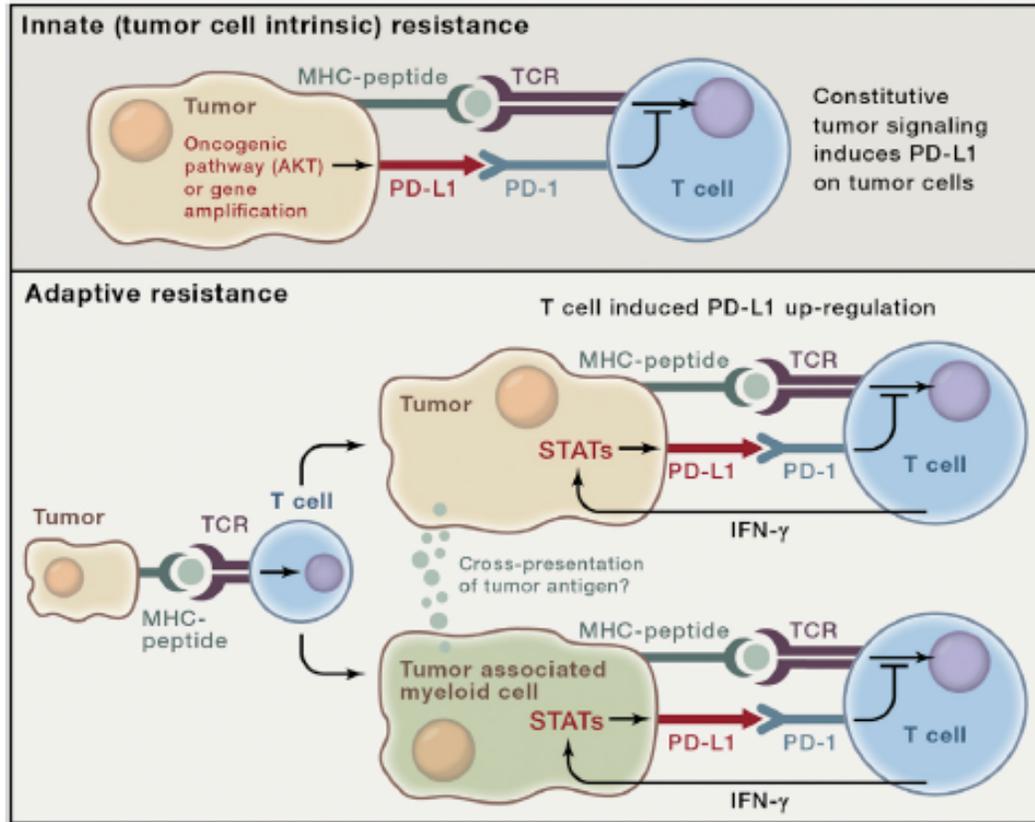
No. at Risk

Olaparib	92	69	50	41	34	24	18	17	14	10	10	8	8	7	5	3	3	3	3	2	1	1	1	0
Placebo	62	39	23	10	6	6	4	4	4	2	2	2	2	1	1	0								

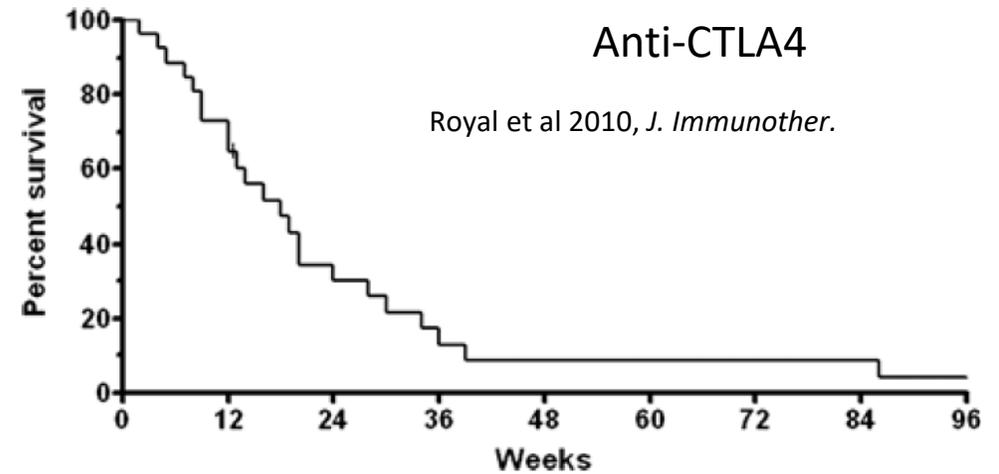
No. at Risk

Olaparib	92	87	80	71	61	51	46	39	31	28	20	16	14	12	9	6	5	4	4	4	2	1	1	0
Placebo	62	60	56	50	44	32	29	27	20	18	14	10	8	8	6	6	4	1	1	1	1	1	1	0

What about immunotherapy?



Topalian et al, *Cancer Cell*, 2015



Anti-PD1			ORR	mPFS	mOS
Cohort-Tumor Type	N*	%	(mo)	(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	

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

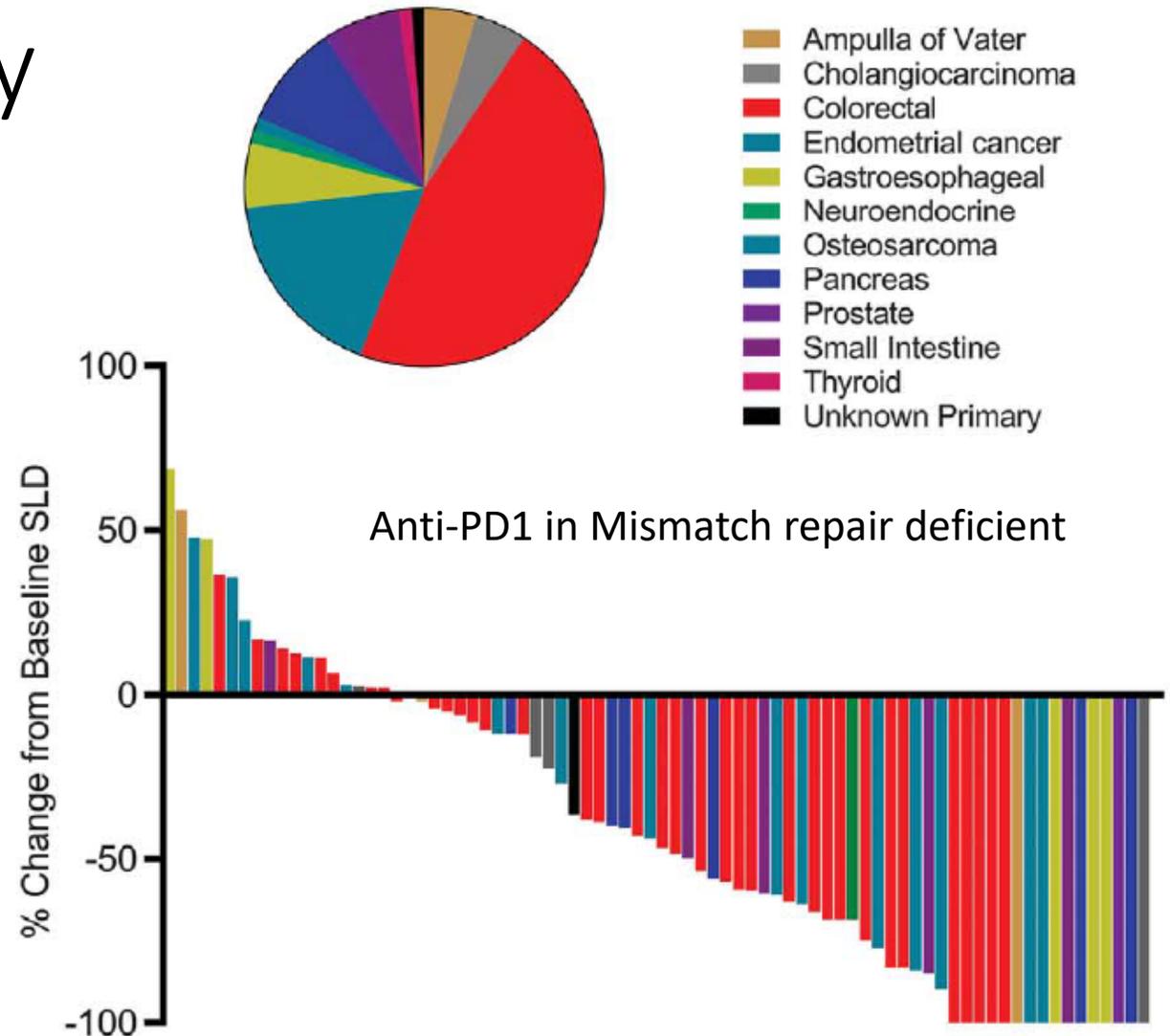
Novel immunotherapies- an active area of investigation

- Make “cold” tumor hot by combining with agents that stimulate immune response
 - Radiation
 - Tumor vaccine
 - Oncolytic virus
 - Chemotherapy
- CSF-1R inhibitor: block cytokine signaling to relocate immunosuppressive macrophages
- CD40 agonist: reprogram poorly functioning ADC's
- Block other checkpoints

Precision Medicine: Microsatellite instability (MSI)

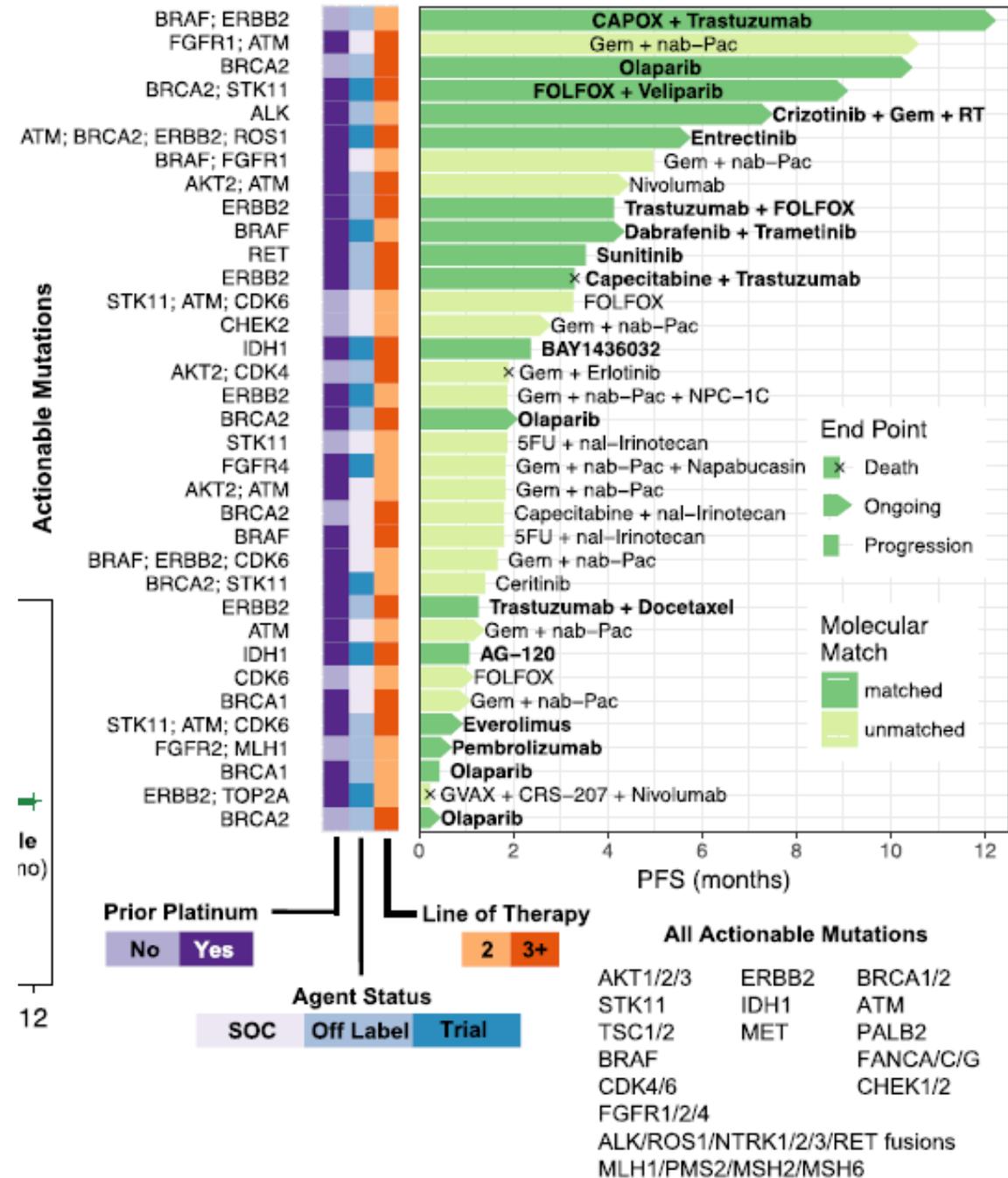
- Lynch syndrome or sporadic
- Causes specific DNA mutations
- Clinical tests available:
 - IHC
 - PCR
 - Genomic testing
- <1% of pancreas cancer patients

Le et al 2017, *Science*

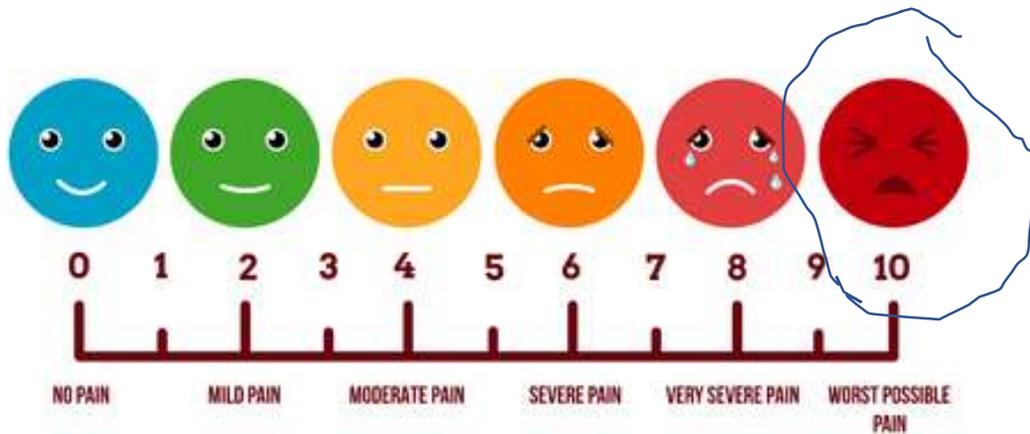


Know Your Tumor: Precision Medicine for PDAC

- 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)



Palliating symptoms of Pancreatic Cancer



- Pain

- Epigastric radiating to the midback
 - Classic for head of the pancreas tumor
 - Celiac plexus
- RUQ pain from liver capsule stretch
- Generalized abdominal pain
- Treatments
 - Narcotic pain medications
 - (resistance not infrequent)
 - Ibuprofen/ Tylenol
 - Neuropathic
 - Celiac plexus block
 - Radiation or effective chemotherapy

Pancreas cancer causes obstruction

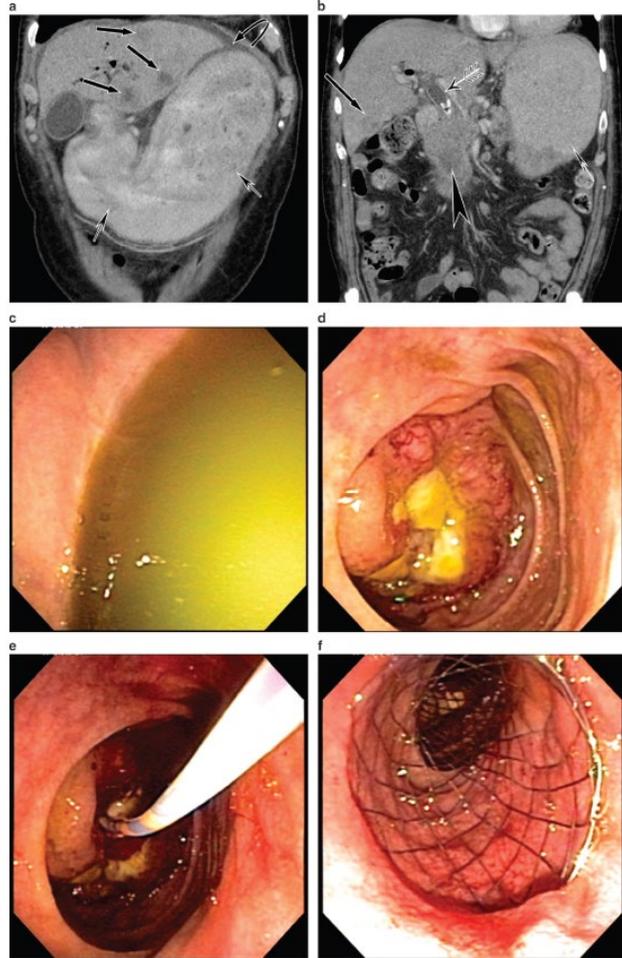


Figure 8. This patient with metastatic pancreas cancer presents with nausea and vomiting. (a) Computed tomography (CT) scan reveals liver metastases and a distended stomach. (b) CT scan reveals the pancreas mass, a dilated bile duct with stent in place, liver metastasis, and a distended fluid-filled stomach. (c) Endoscopic image of the fluid-filled stomach. (d) Duodenal obstruction by tumor. (e) Catheter and guidewire passage beyond the obstruction. (f) Duodenal stent placed.

- Biliary Obstruction

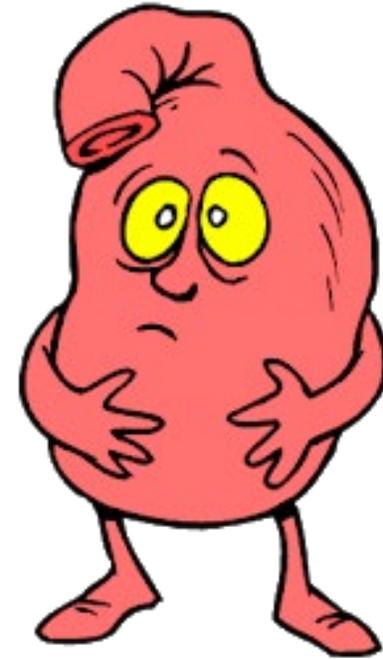
- => jaundice
- Treatments:
 - Effective chemotherapy
 - Endoscopic stent placement
 - Percutaneous drain placement

- Gastric or duodenal obstruction

- => vomiting, poor nutrition
- Treatments:
 - Endoscopic stent placement
 - Effective chemotherapy
 - Radiation

GI Symptoms

- Weight loss and wasting syndrome
 - Profound cachexia
 - Hormonal mediator still undiscovered
- Poor appetite and early satiety
 - “Graze” all day
 - Many small meals
 - High calorie low volume
- Nausea and vomiting
 - Due to obstruction or poor GI motility
 - Anti-emetic medication (prn or standing)



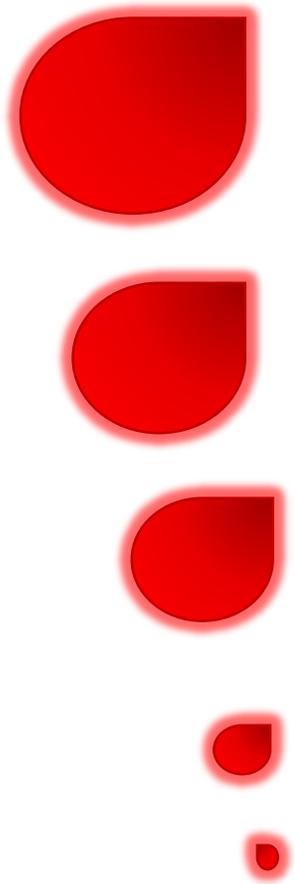


Pancreatic Insufficiency

- Endocrine insufficiency => diabetes
 - 50% of pancreatic cancer patients are diabetic
 - Long-term diabetes is risk for pancreas cancer
 - Paraneoplastic diabetes
 - Effect of pancreas surgery
 - Pancreatogenic diabetes (Type 3c)
 - Frequently insulin-dependent
- Exocrine insufficiency => fat soluble vitamin deficiency
 - Low levels of vitamins AEDK
 - Poor fat digestion causes
 - Bloating
 - Post-prandial pain
 - Diarrhea
 - Pale stools that float
 - Supplement with pancreatic enzymes
 - Teach patients how to correctly take

Blood clots

- 30% of pancreas cancer patients
- Both venous and arterial clots possible
 - DVT and PE
 - Portal vein and splenic vein thrombosis
 - Trousseau's syndrome
- Highest risk with
 - Metastatic or advanced disease
 - Growing disease
 - When starting new systemic treatment
- Prophylactic anti-coagulation now recommended in all patients receiving systemic therapy without significant bleeding risk (ASCO guidelines 2019)





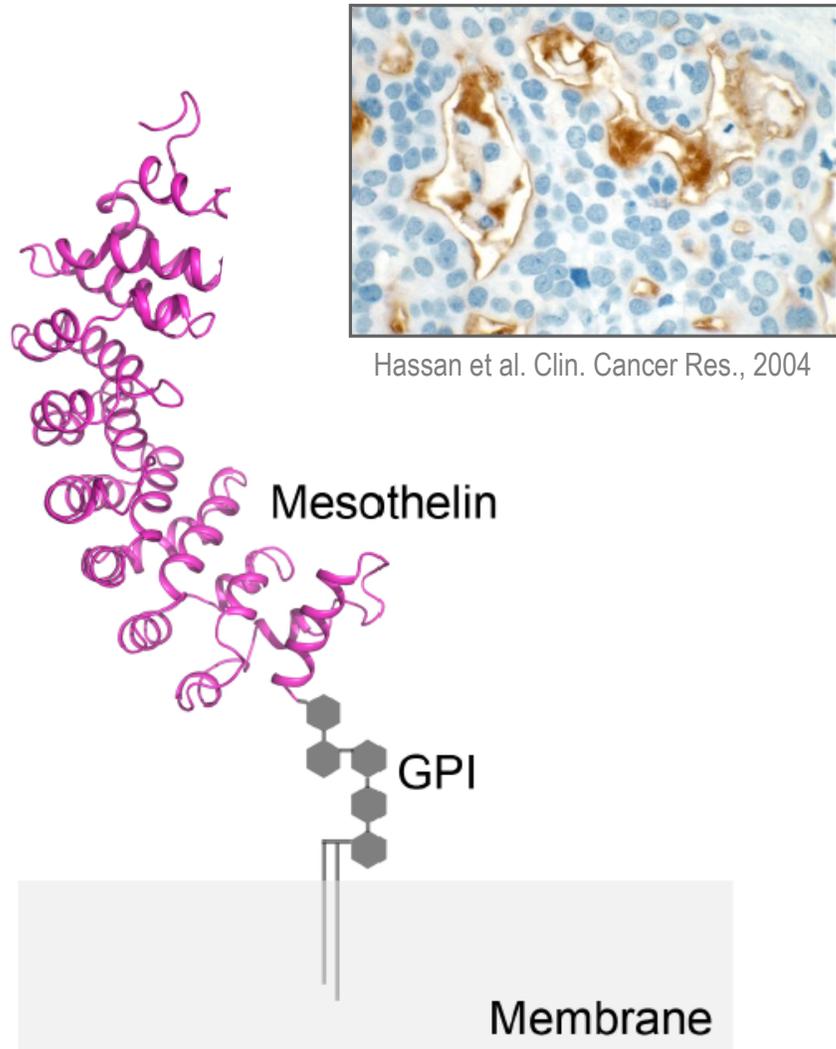
Summary of Pancreatic Cancer

- 3rd leading cause of cancer death in United States because
 - Many patients are diagnosed at a late stage
 - Treatments for early stage disease less effective than those for other tumor types
- Early diagnosis is difficult
- Pancreatic cancer surgeries are very tough
- Available drug treatments are relatively ineffective
- Many new treatments are currently under investigation
- Side effects of pancreatic cancer and its current treatments have significant impact on patient quality of life



Questions?

My Research: Mesothelin-Targeted Therapy for Pancreatic Cancer



Hassan et al. Clin. Cancer Res., 2004

Mesothelin

GPI

Membrane

Ma et al, J. Biol. Chem., 2012

CANCER

- Cancer-specific surface antigen expressed by many solid tumors
 - Mesothelioma
 - **Pancreatic**
 - Ovarian
 - NSCLC
 - Gastric
- Endometrial*
Cervical
Thymic carcinoma
Cholangiocarcinoma

NORMAL

- Normal expression limited to mesothelial cells
- No expression parenchyma of vital organs
- No phenotype in MSLN KO mice

MSLN expression in pancreas ductal adenocarcinoma (PDA)

(C) Pancreatic ductal adenocarcinoma (5B2 antibody)

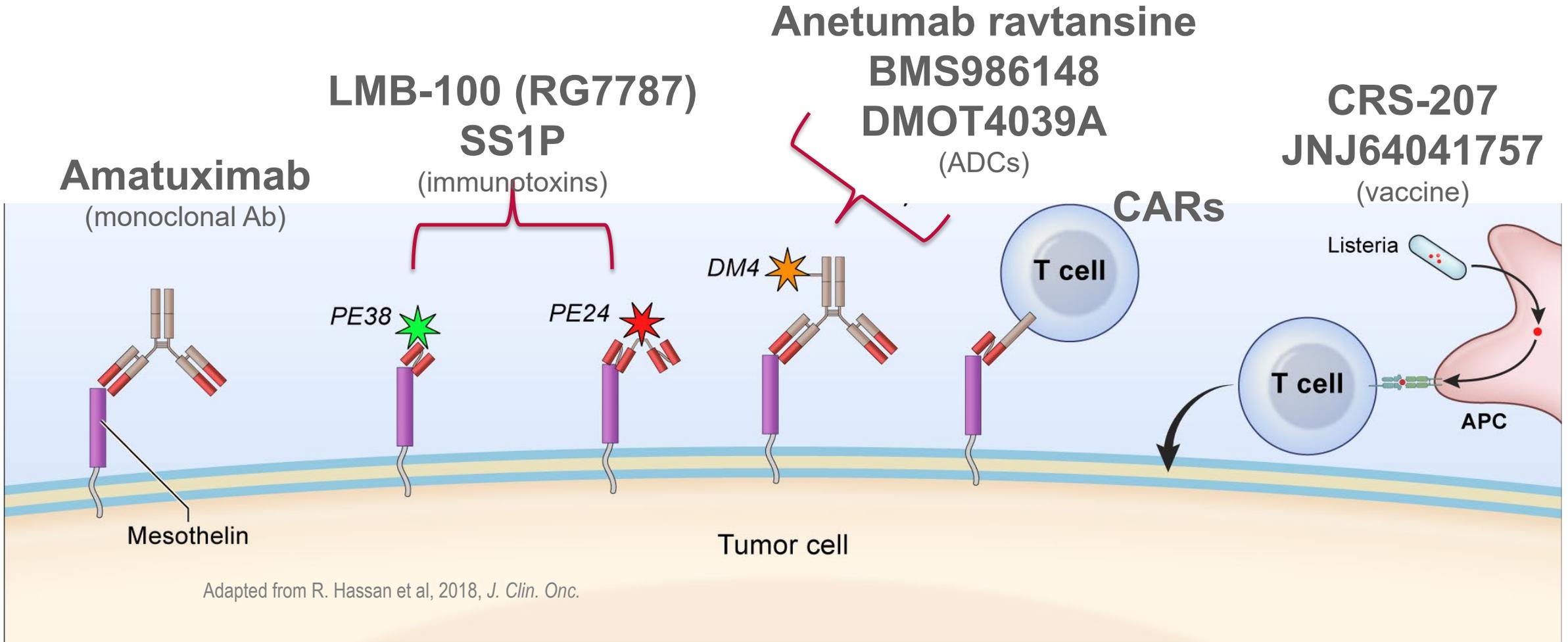
Negative	1+ (1-25% cells) ^{\$}	2+ (26-50% cells)	3+ (>50% cells)	Total	Reference
0/60	10/60	50/60		60/60 (100%)	Argani <i>et al.</i> (5) [*]
0/14	3/14	5/14	6/14	14/14 (100%)	Frierson <i>et al.</i> (2) ^{*, \$}
1/11	0/11	2/11	8/11	10/11 (91%)	Ordonez (6) [*]
2/14	0/14	3/14	9/14	12/14 (86%)	Ordonez (1) [*]
7/68	22/68	39/68		61/68 (90%)	Swierczynski <i>et al.</i> (7) ^{*, #}
0/18	2/18	1/18	15/18	18/18 (100%)	Hassan <i>et al.</i> (8) [*]
10/185 (5.4%)	37/185 (20%)	138/185 (75%)		175/185 (95%)	Total prevalence

5%
Neg

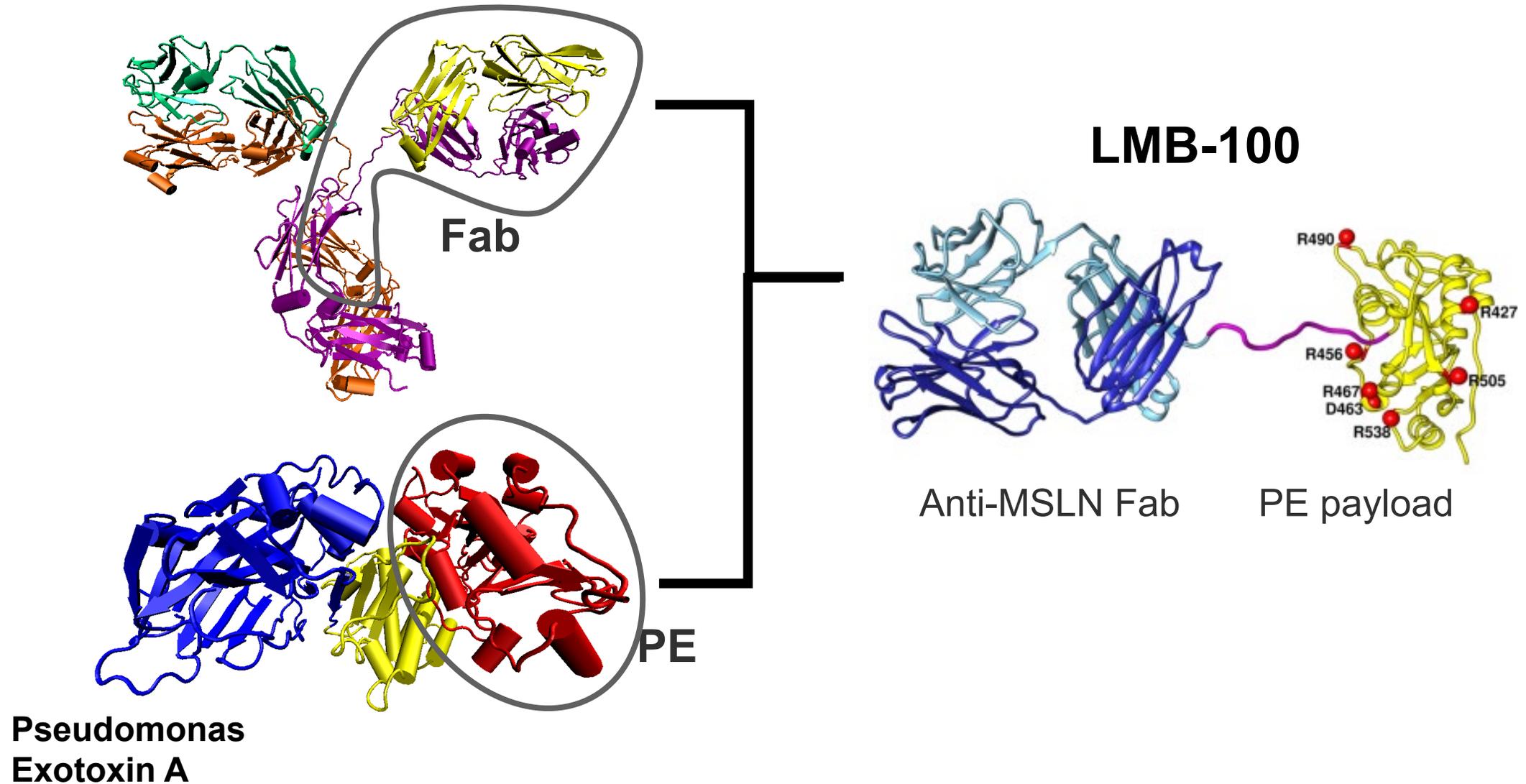
20%
Low

75%
Strong

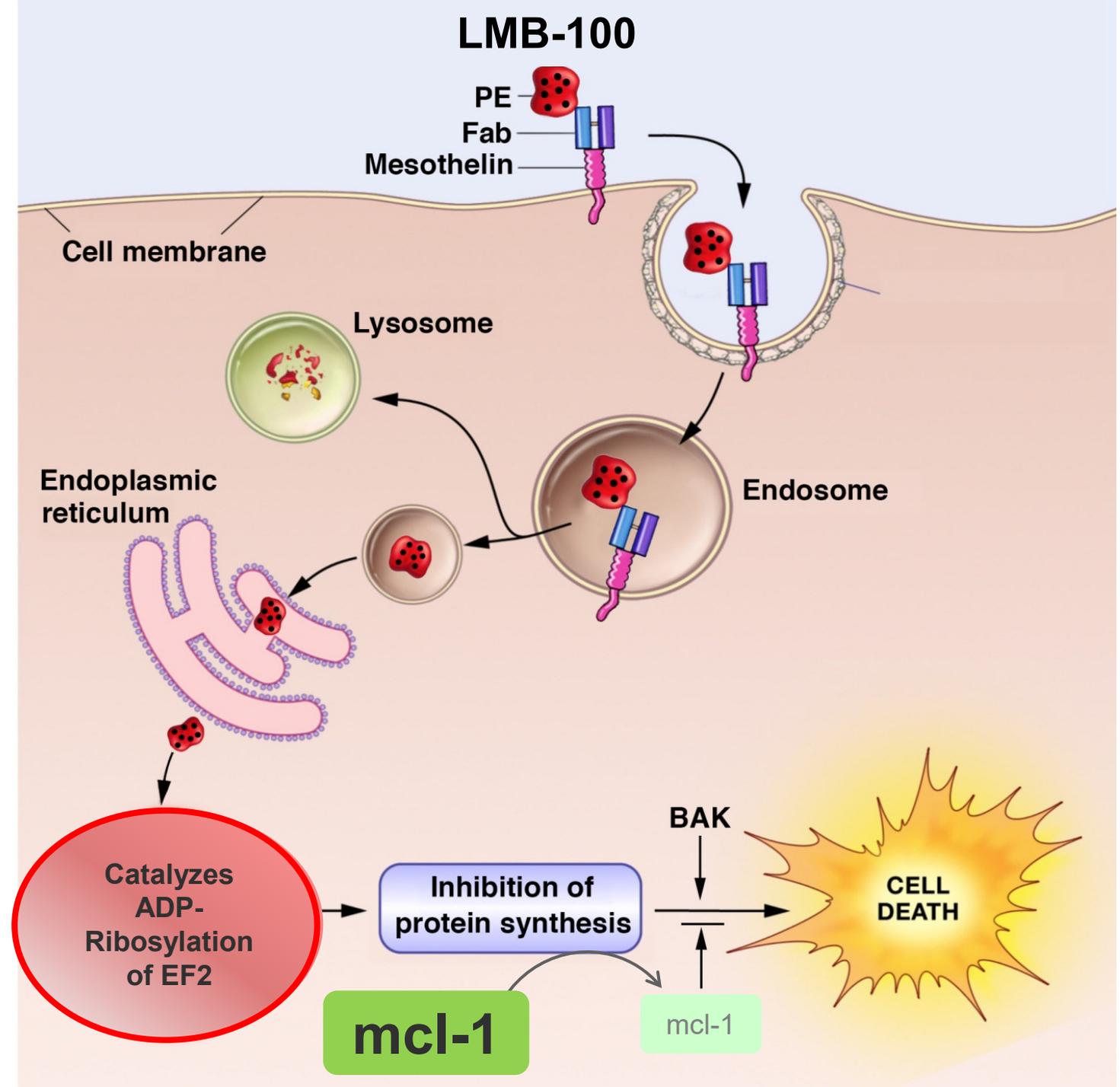
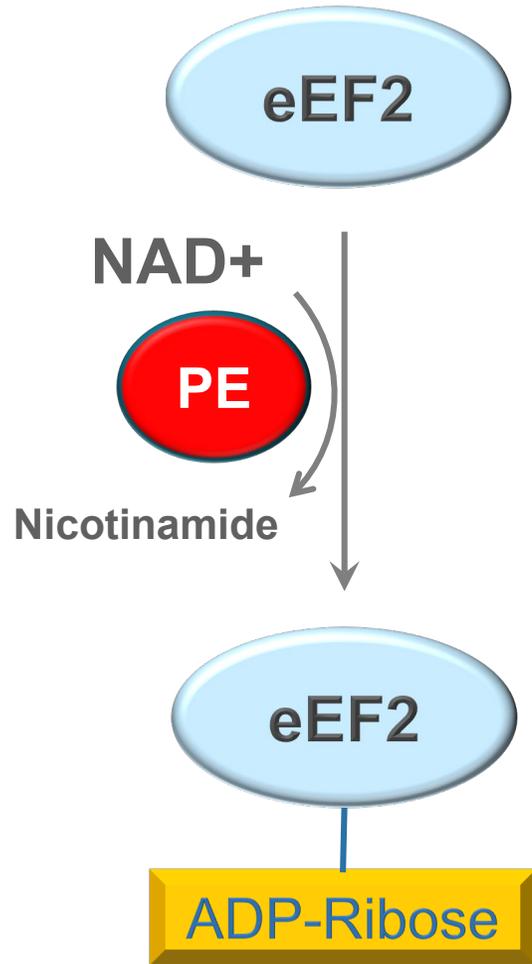
MSLN-targeted therapeutics in the clinic



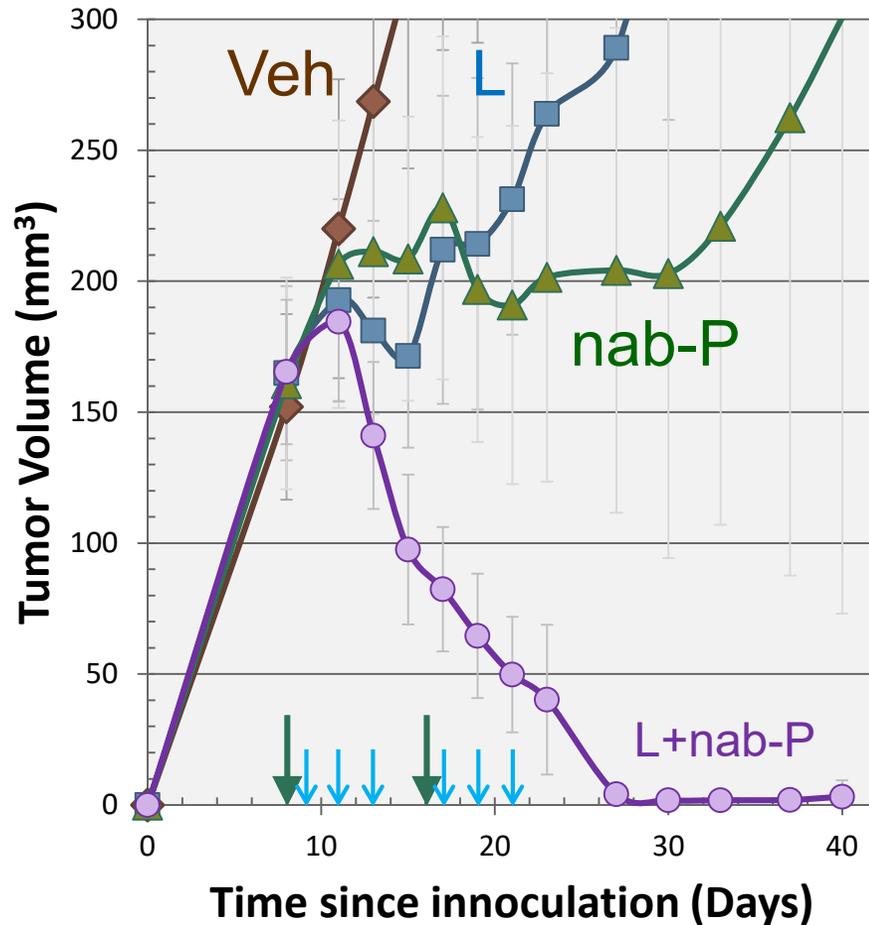
Recombinant Immunotoxin (iTox)



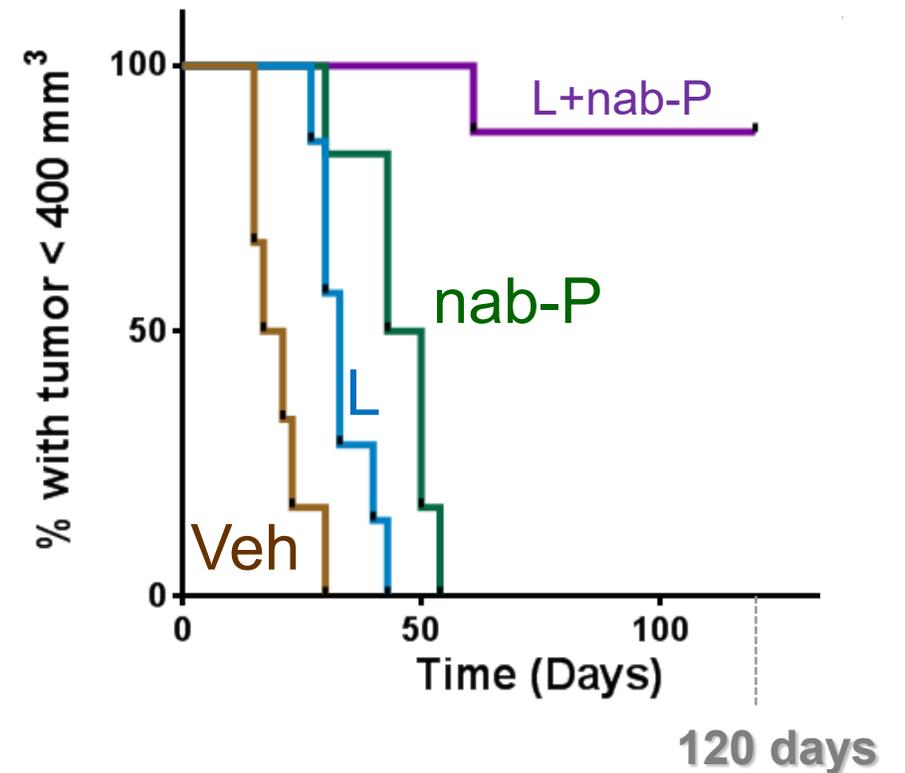
Mechanism of Action



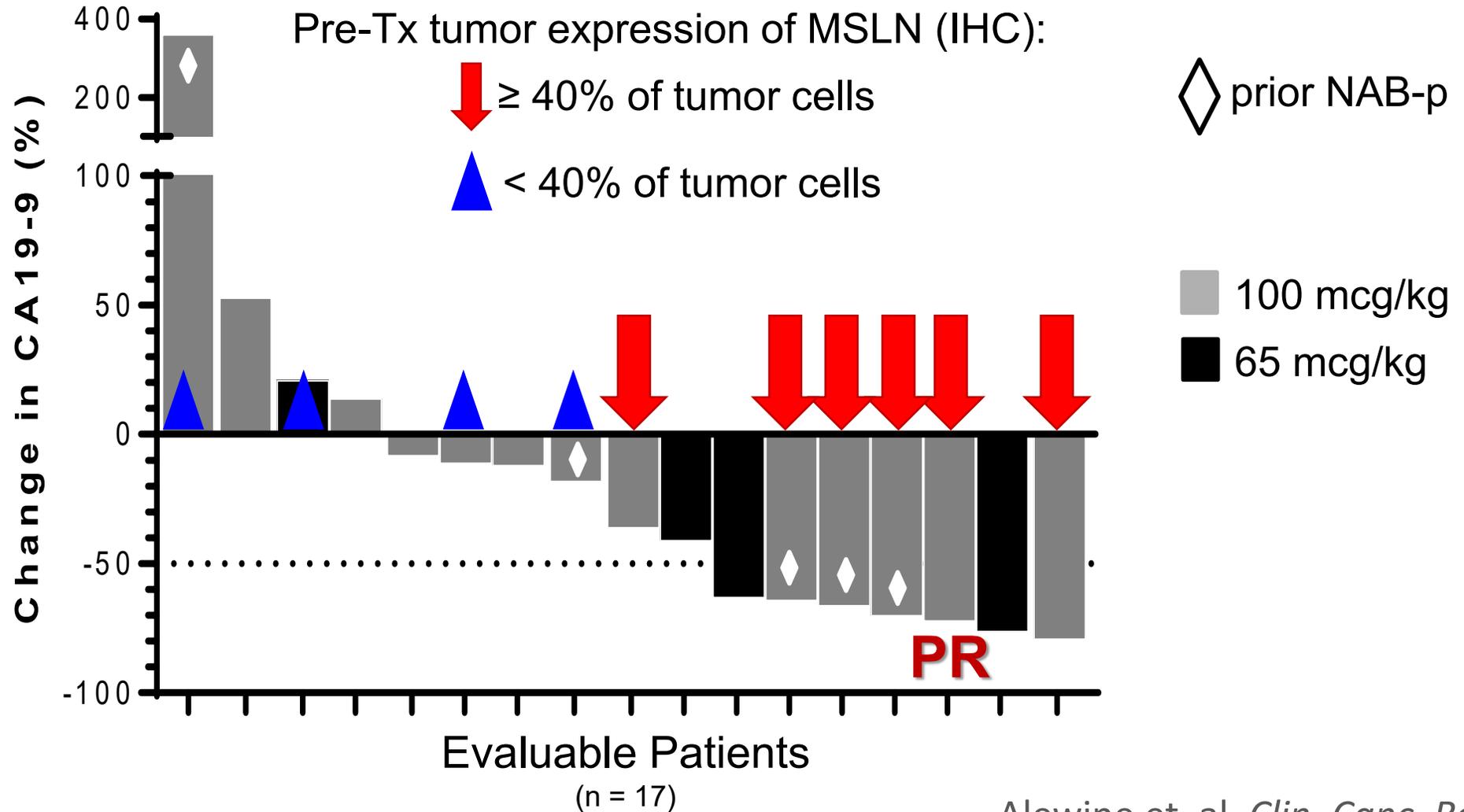
LMB-100 works with nab-paclitaxel to eliminate PDAC tumors



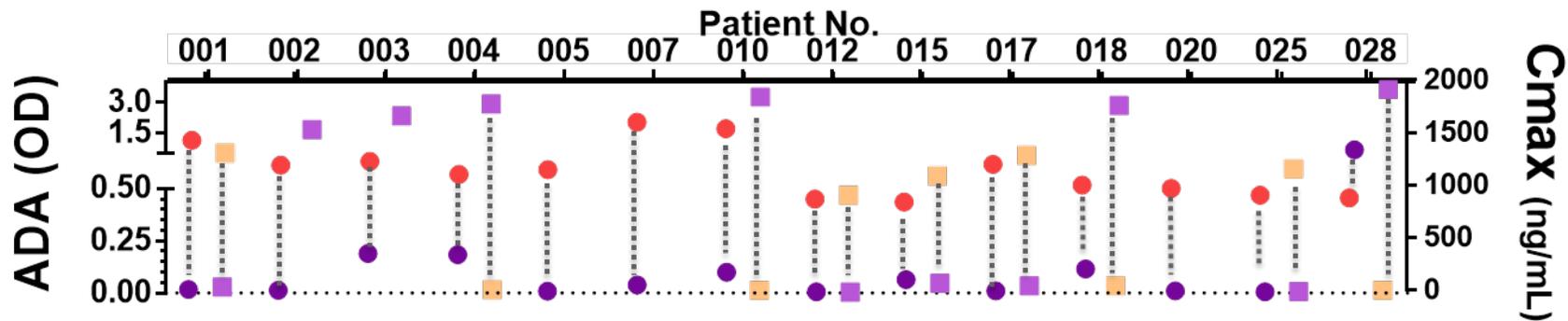
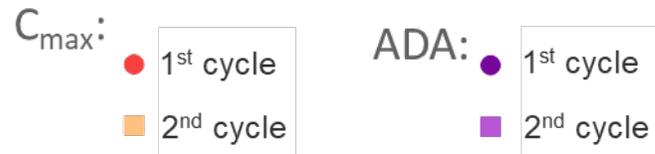
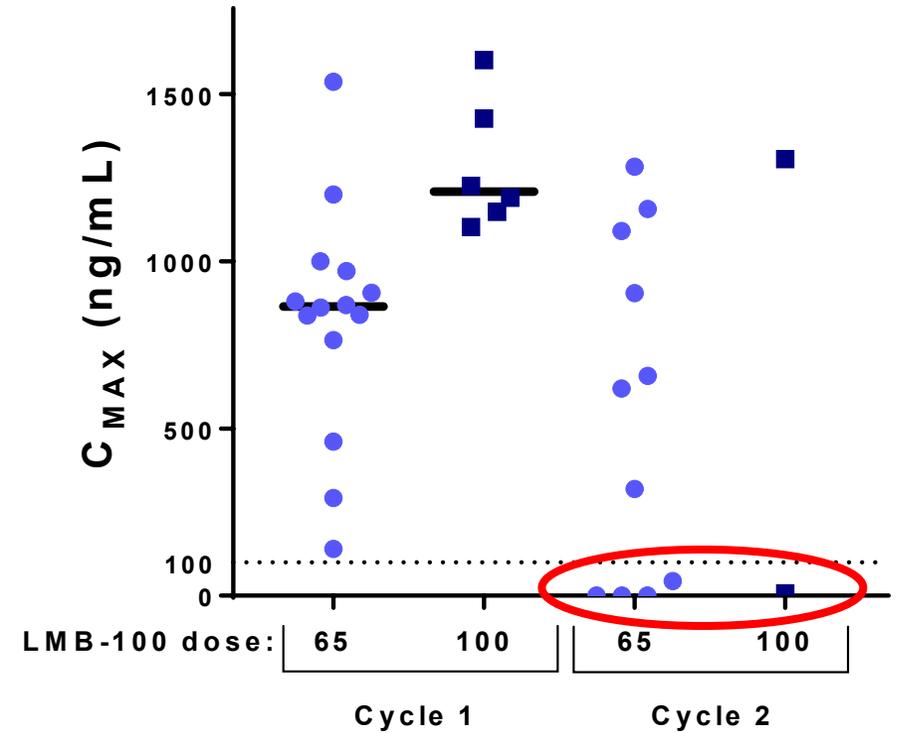
L = LMB-100 (2.5 mg/kg)



LMB-100 + nab-paclitaxel is an active regimen

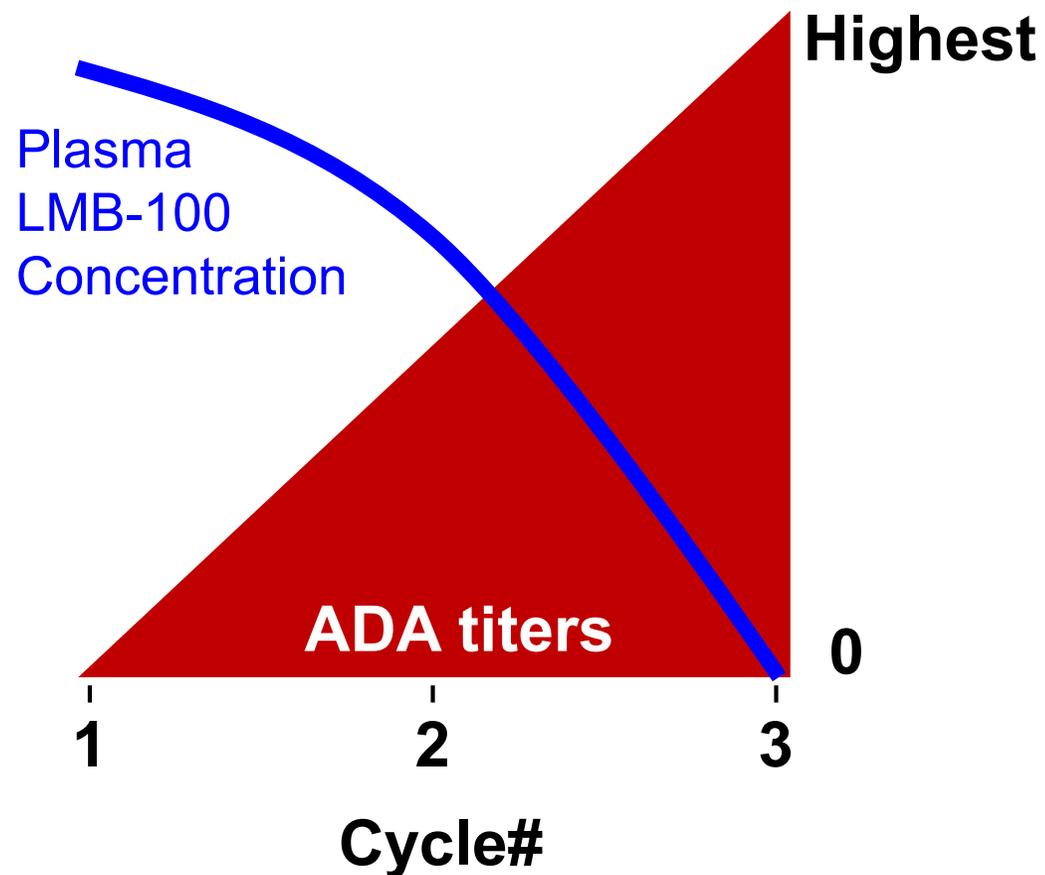


Peak serum levels of LMB-100 are limited by anti-drug antibody formation beginning with Cycle 2



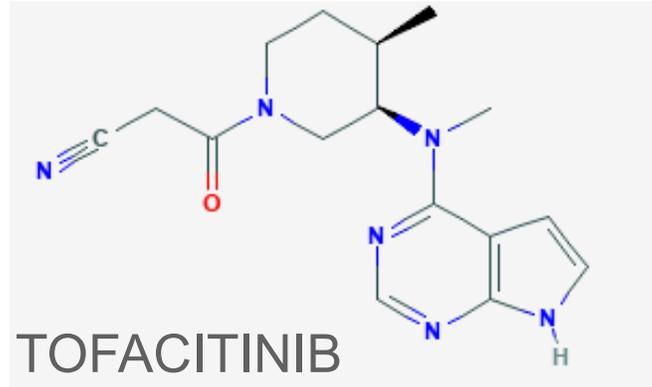
Anti-drug antibodies (ADAs) are a barrier to treatment efficacy

- ADA titers rise with each cycle of LMB-100
- High-titer ADAs are associated with low or undetectable plasma LMB-100 concentration
- Drug levels fall to 0 in most patients by Cycle 3

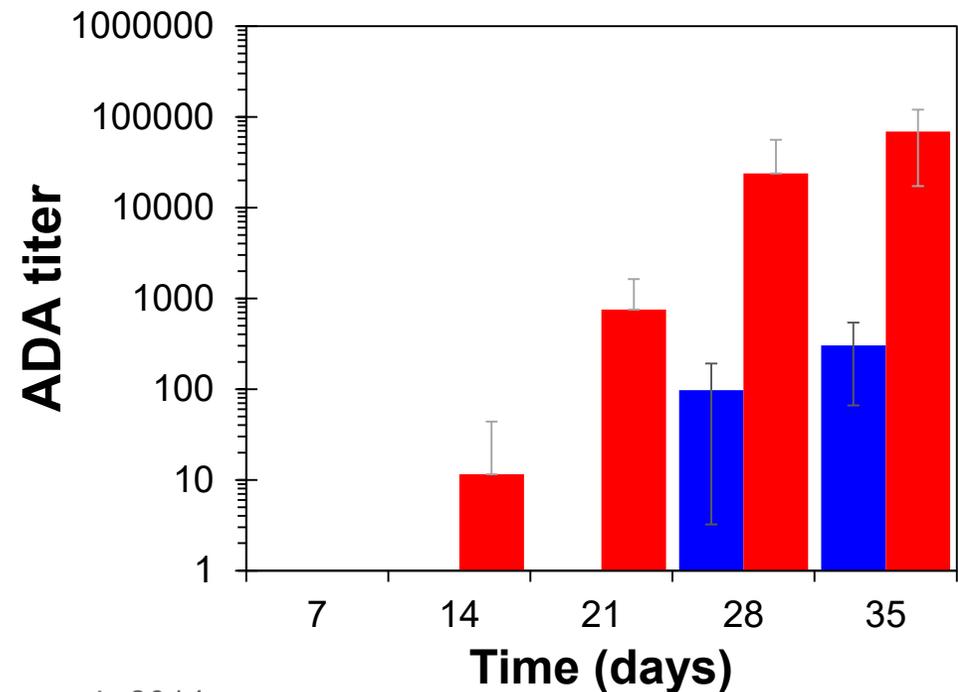
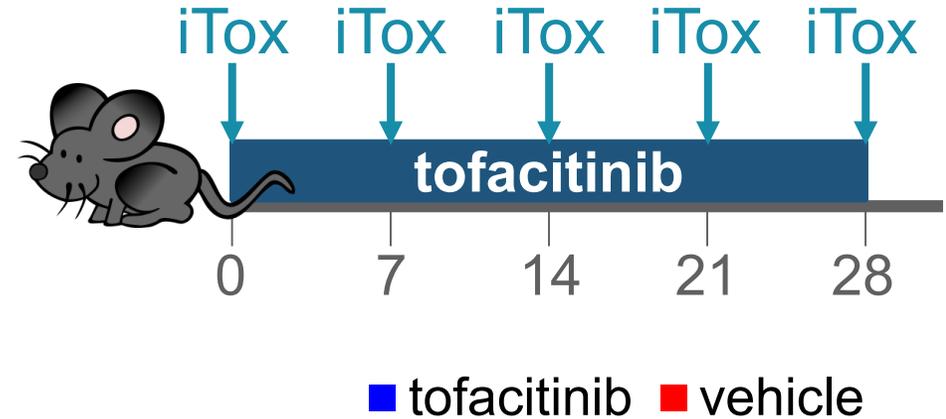


Must prevent or delay ADA formation for LMB-100 to be a viable therapy

Decreasing ADA formation with tofacitinib



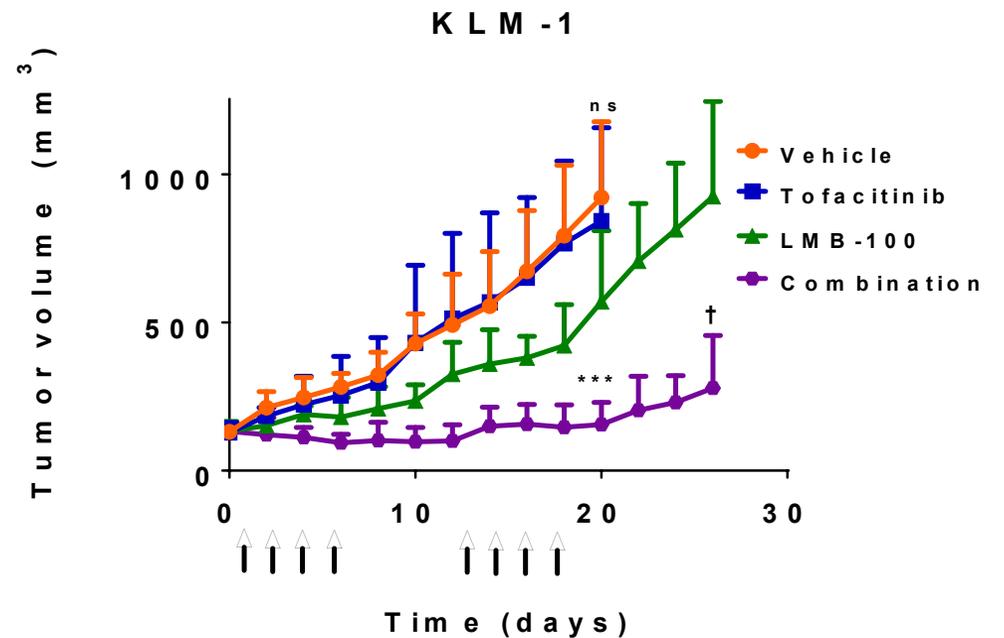
- Janus kinase (JAK) inhibitor
- Inhibits lymphocyte signaling
- FDA approved for treatment of autoimmune diseases
- Limits formation of ADAs against iTox in mice



Additional effect of tofacitinib: increased anti-tumor efficacy through stromal modulation

Tofacitinib treatment

- Reduces macrophage population in tumors
 - Less non-specific uptake of iTox in tumor by macrophages
- => Increases iTox serum half-life
- => Increases iTox delivery to tumor



Simon et al, *JCI Insight*, 2019

Phase I: tofacitinib + LMB-100

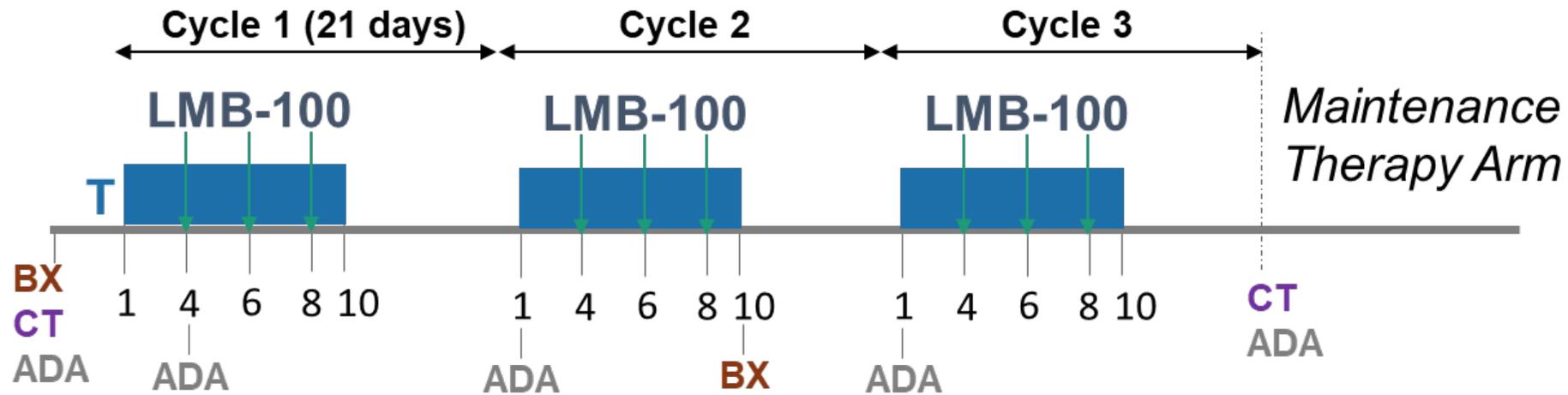
Now accruing!

1. **Dose escalation** to determine maximum tolerated dose

- MSLN(+) solid tumors

2. **Expansion phase** to assess impact on ADA formation

- Pancreatic adenocarcinoma
- extrahepatic cholangiocarcinoma



Tofacitinib (T) 10 mg PO, BID
LMB-100 as per dose escalation

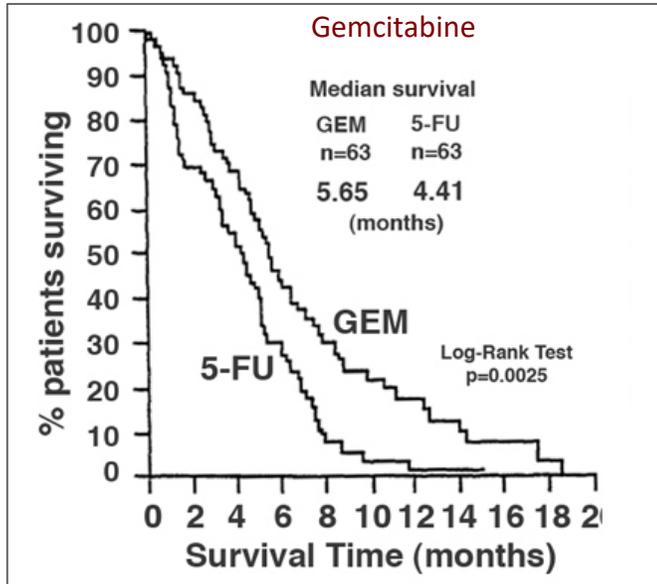
CT = imaging
BX = optional tumor biopsy
ADA = anti-drug antibody titer



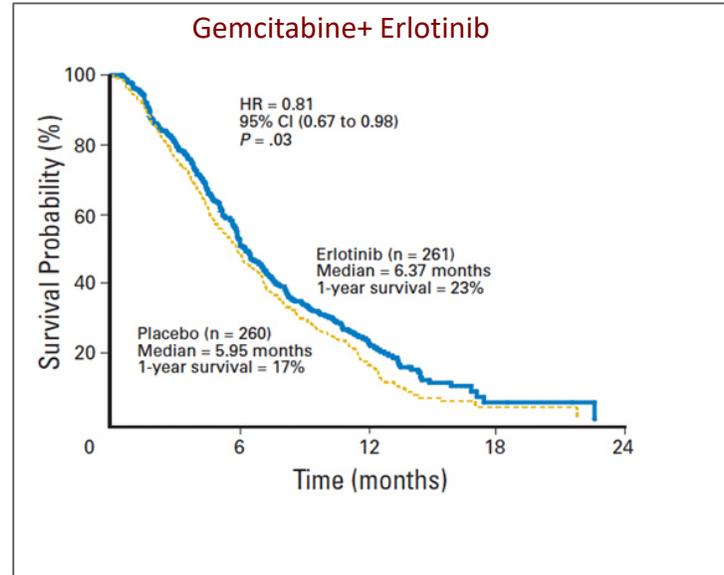
Questions?

Progress in the Treatment of Advanced Pancreatic Cancer

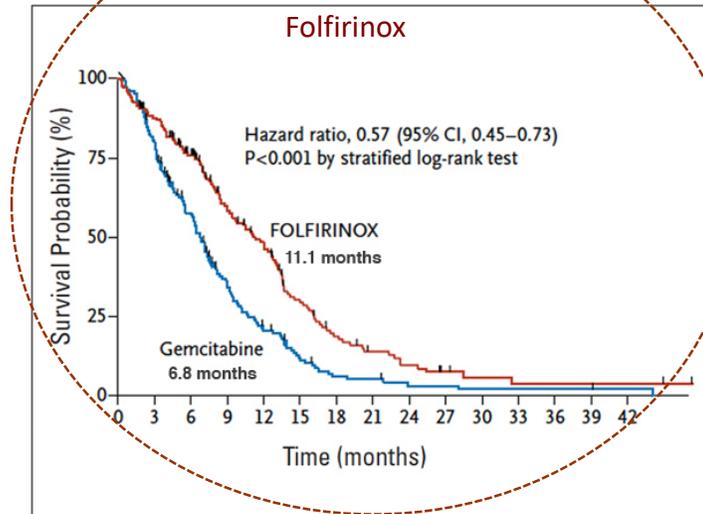
Burris et. al., J. Clin. Oncol., 15, 1997



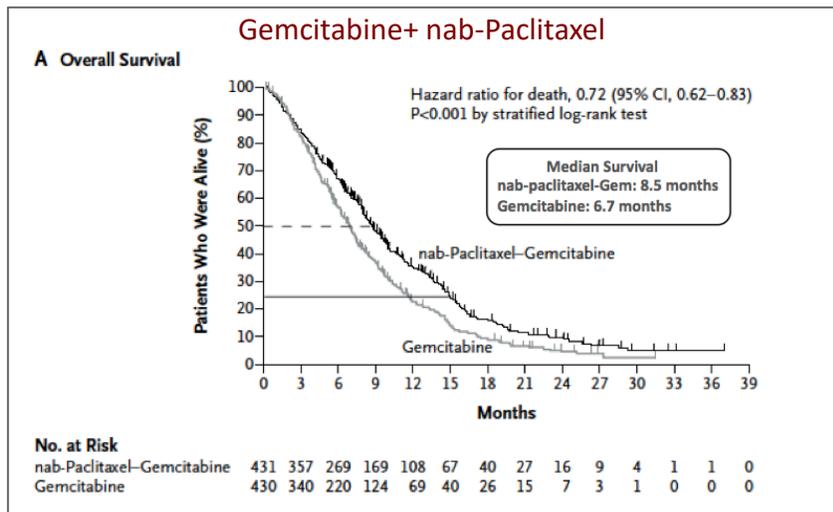
Moore et. al., J. Clin. Oncol. 25, 2007



Conroy et. al., NEJM, 36, 2011



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



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

