Fred Hutch Cancer Center

Pancreatic Cancer

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Disclosure of Financial Relationships

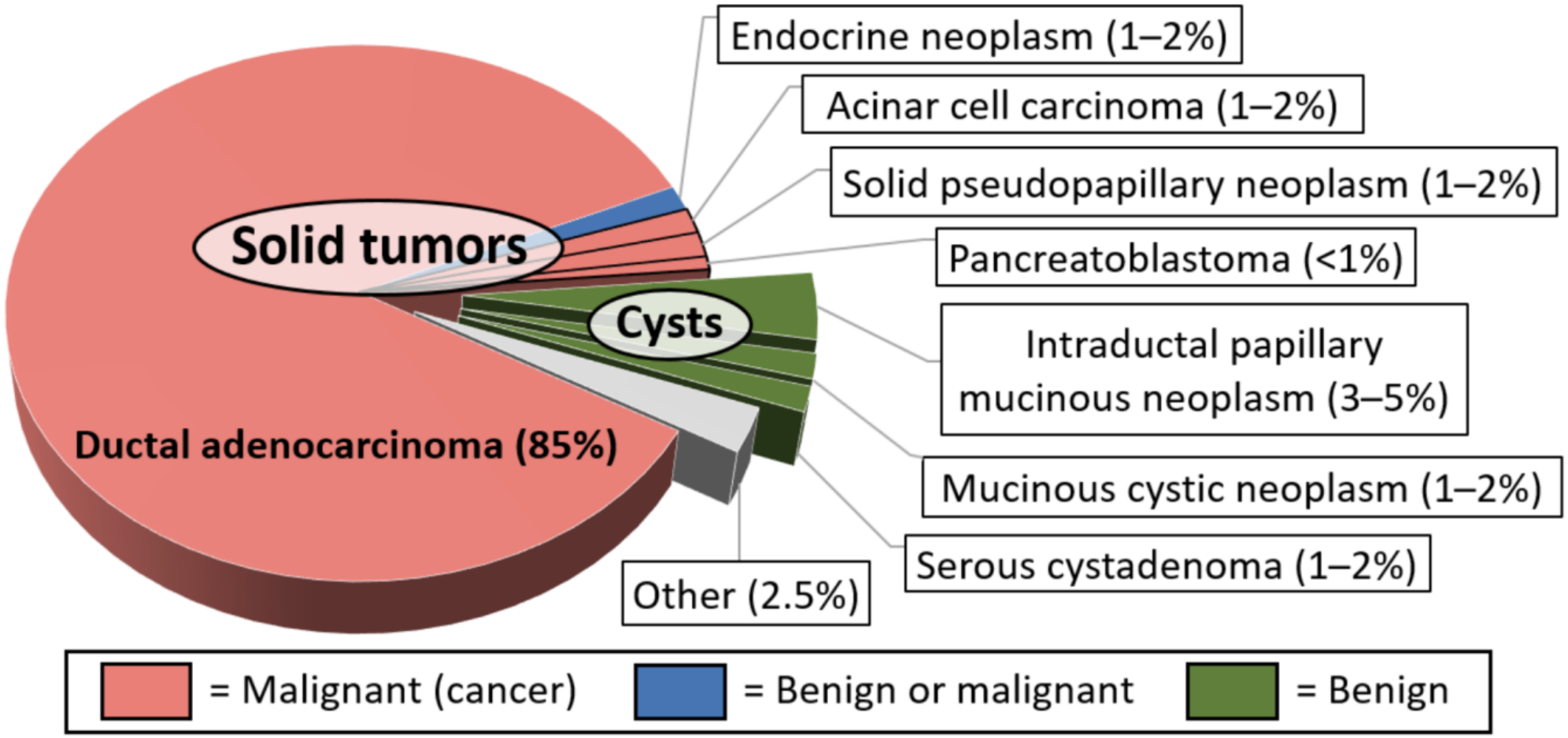
- **I have been a consultant for the following companies**: Guardant Health, Ipsen, Agenus

- **I (via the institution) receive research funding from the following companies**: Exelixis, Replimune, Verastem, Amgen, J&J

Agenda

1. Epidemiology, Pathogenesis, abd Risk Factors
2. Clinical Presentation, Diagnostic Testing, and Staging
3. Treatment of Localized PDAC
4. How We Treat Advanced Pancreatic Cancer Today
5. Importance of Supportive care in PDAC Management

Pancreatic Cancers are *Overwhelming But Not Always* Ductal Adenocarcinomas



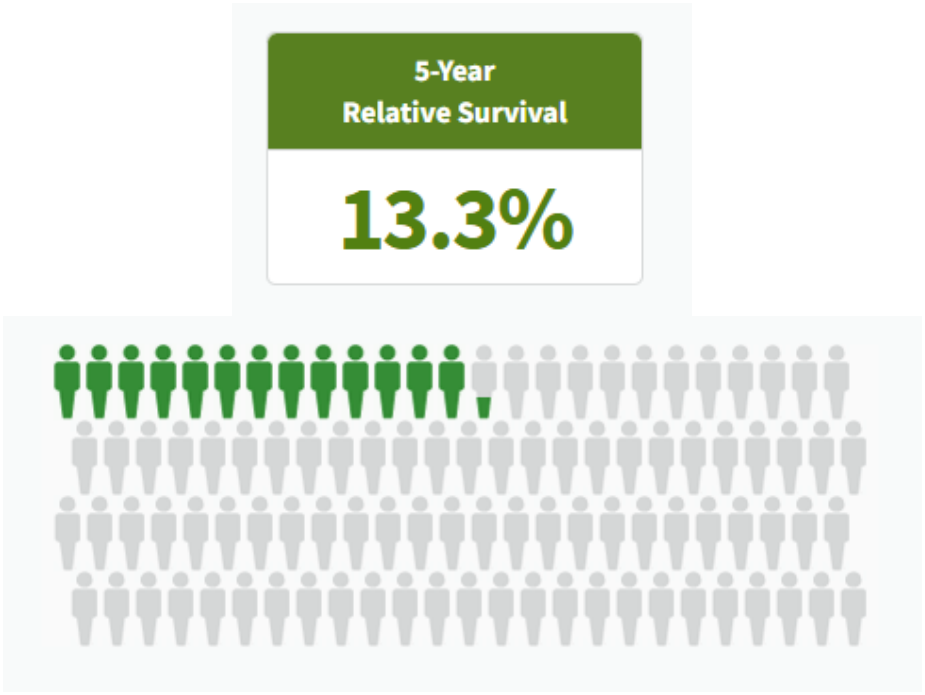
Wang Y *Radiographics* 2011

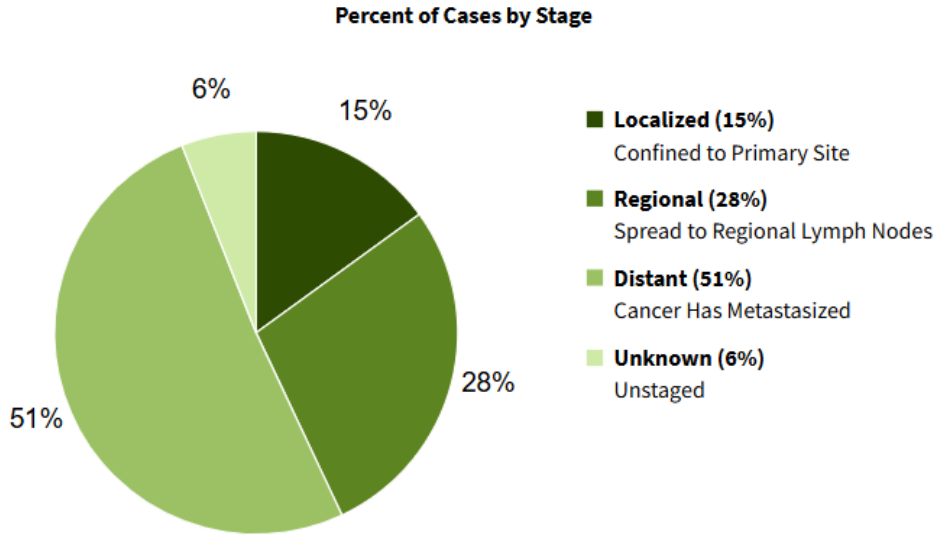
Epidemiology: Summary Statistics
Pancreatic Cancer 2025

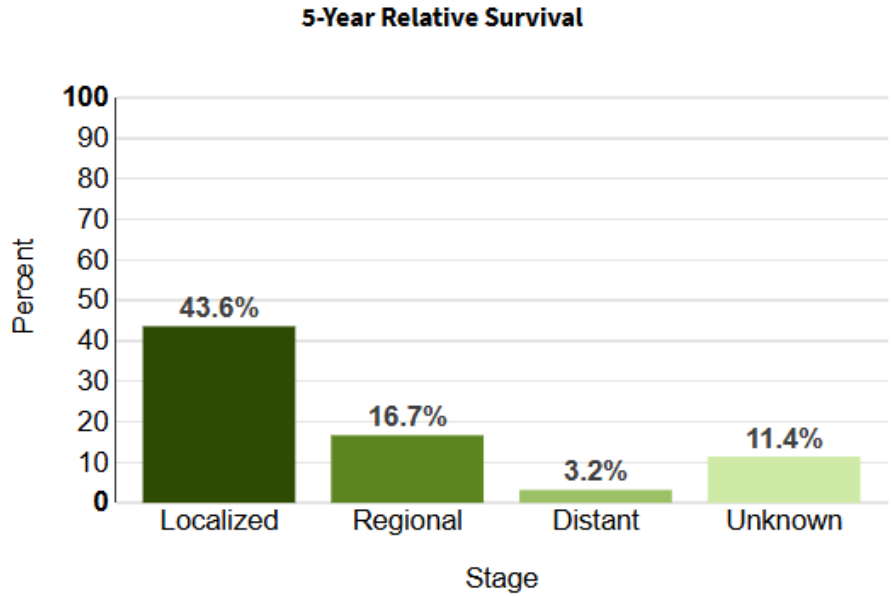
- New diagnoses in the US (2025): 67,4440
- 8th-10th most common cancer in the US (3% of new cancers)
- Increasing incidence ~1% per year
- GLOBOCAN (2002): #12 incidence with 510,992

American Cancer Society, 2024, Siegel R, www.cancer.org; SEER Cancer Statistics Review, 1975-2006. NCI. www.surveillance.cancer.gov

Late Stage at Diagnosis Impacts 5-Year Survival Rate

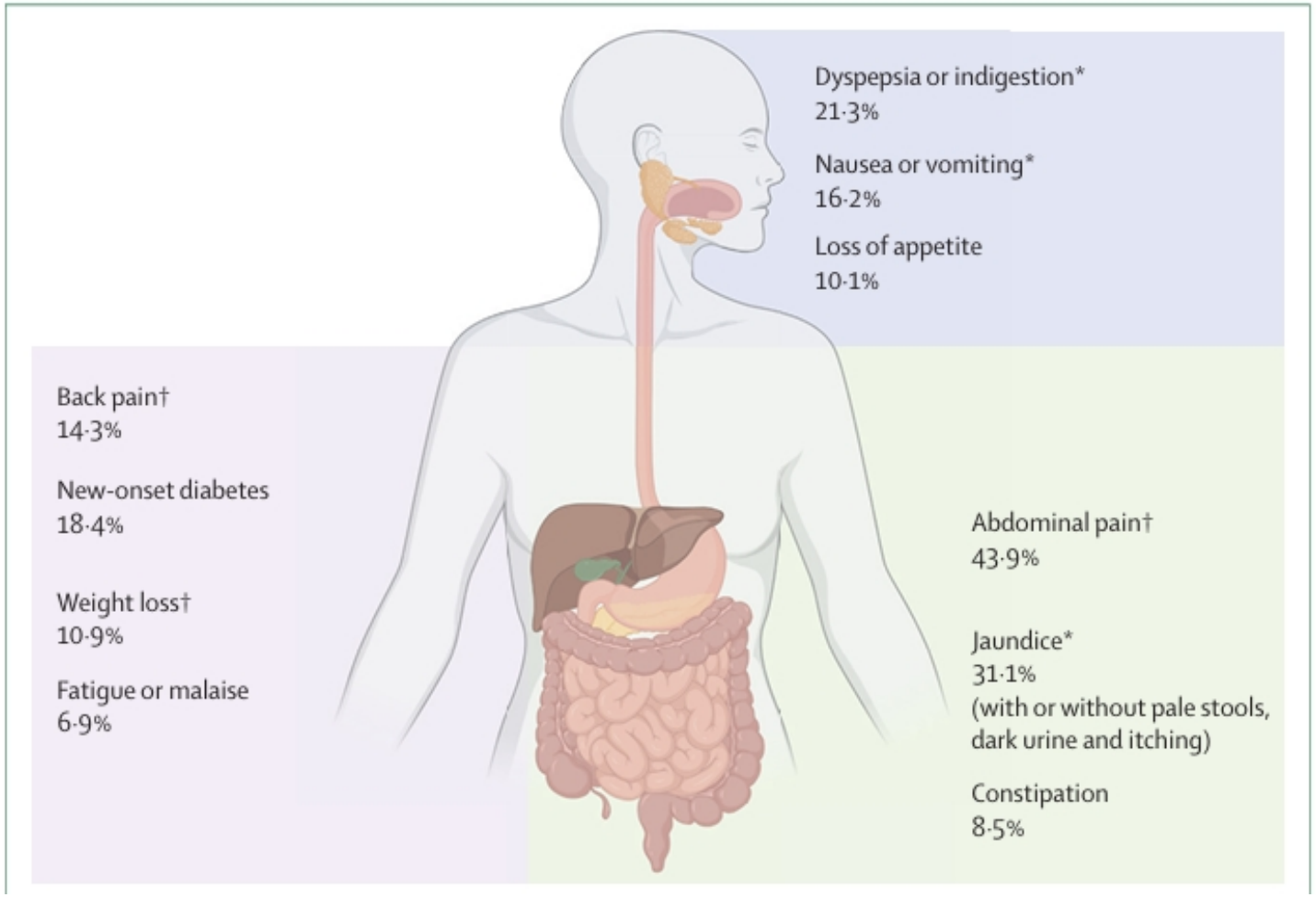






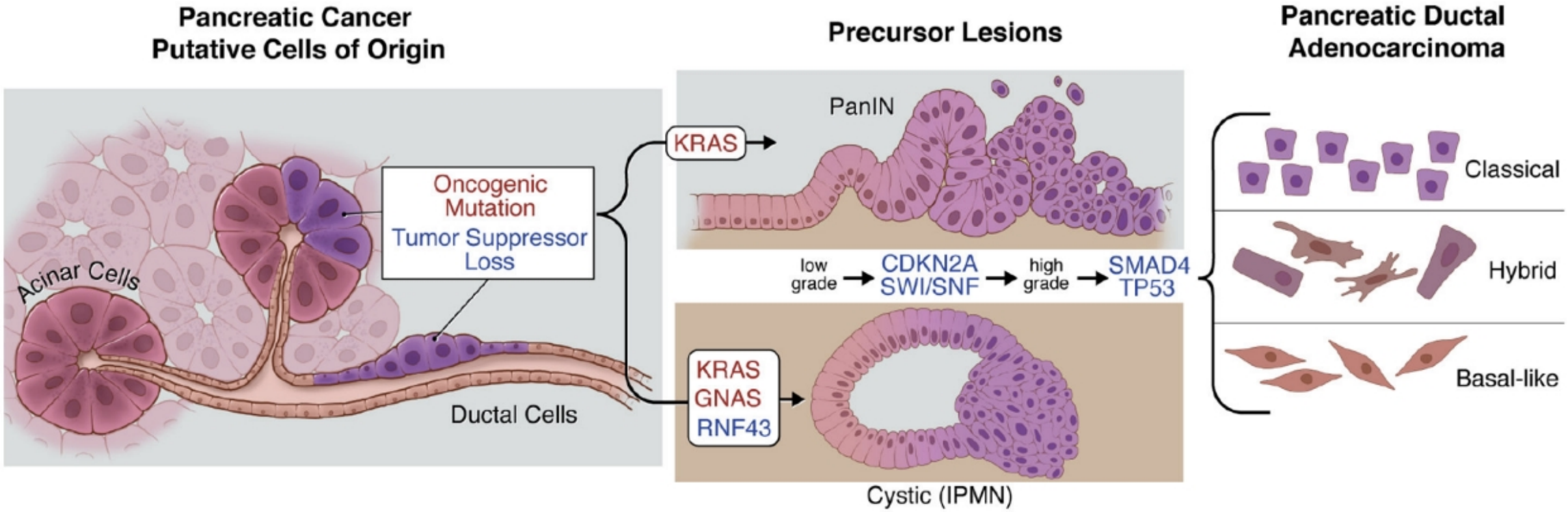
www.seer.cancer.gov/statfacts/html/pancreas.html

Symptoms at Diagnosis are Often Vague & Nonspecific



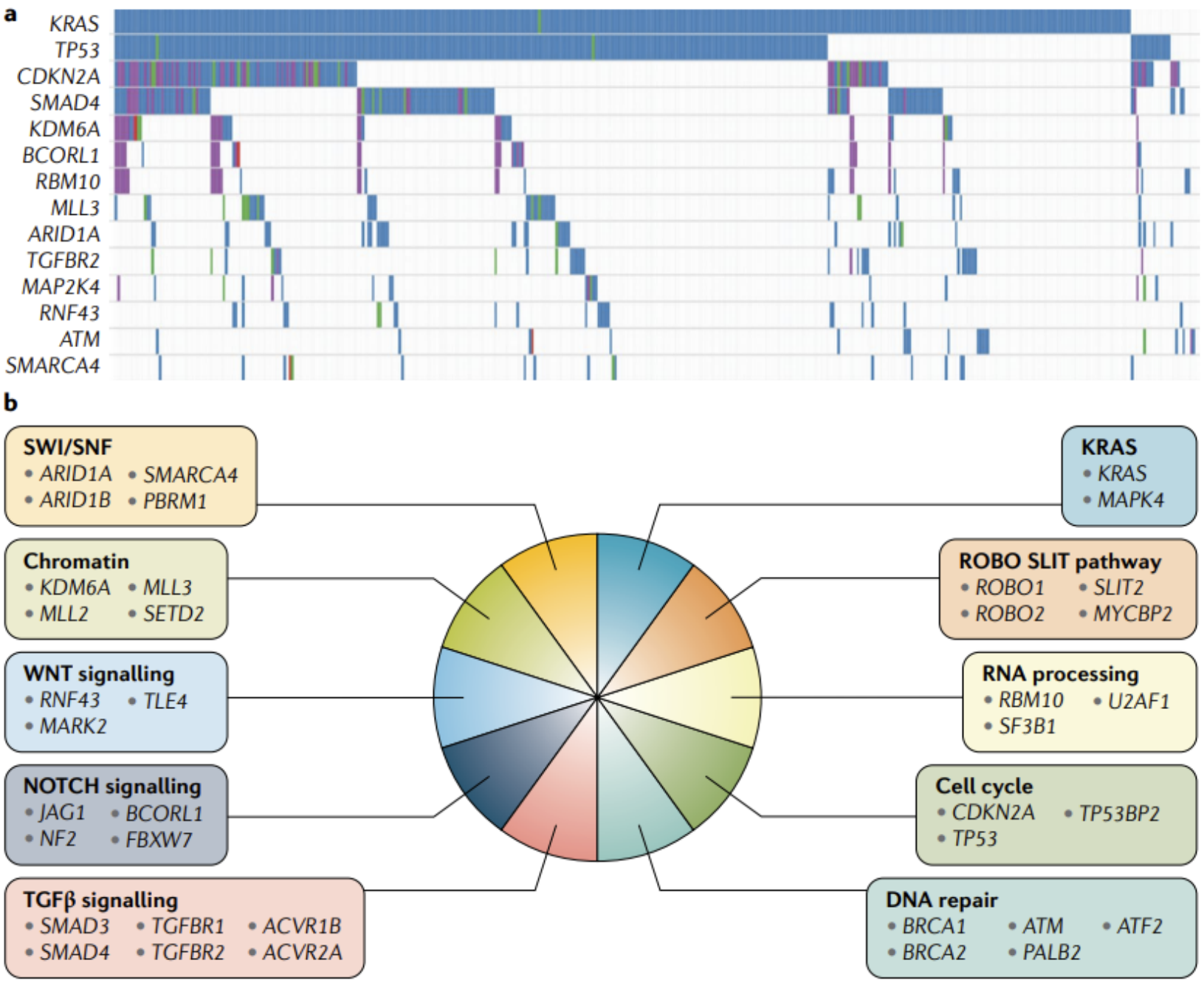
Stoop TF, *Lancet* 2025

Pathogenesis: Initiation and Progression of Pancreatic Cancer



Halbrook CJ, *Cell* 2023

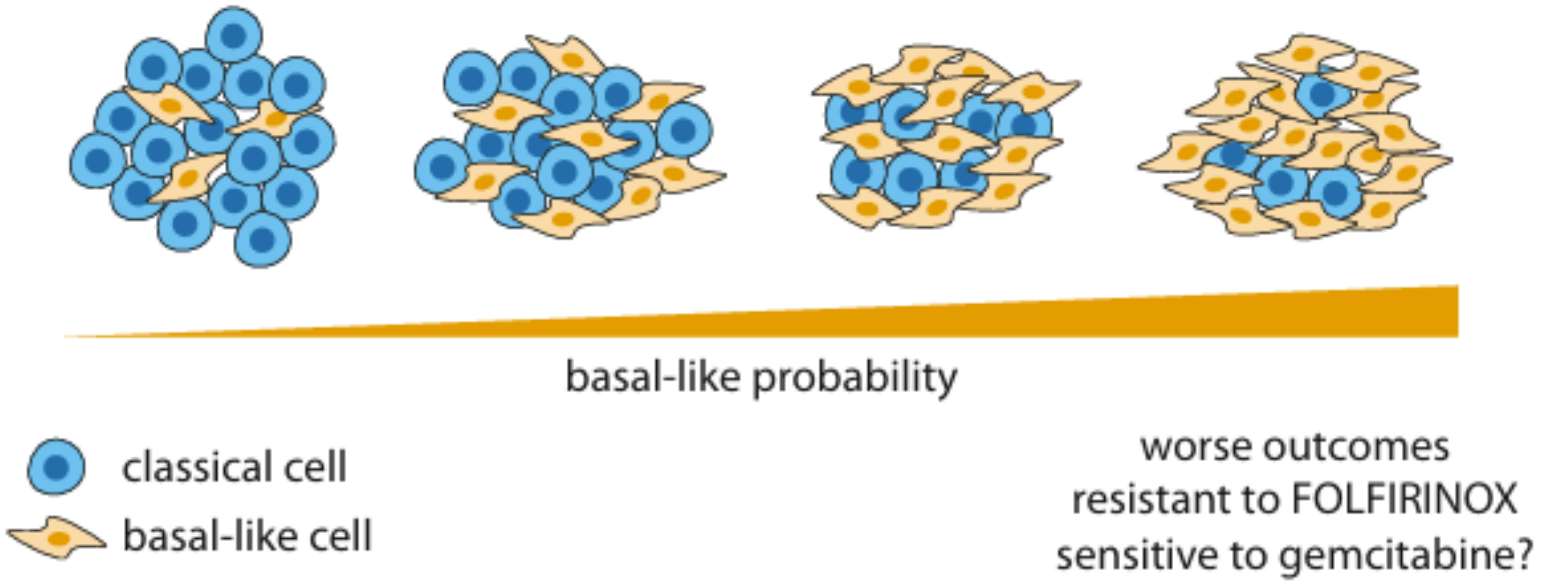
Genomic Aberrations Characteristic of Pancreatic Cancer



Collison EA, *Nat Rev Gastroenterol Hepatol* 2019

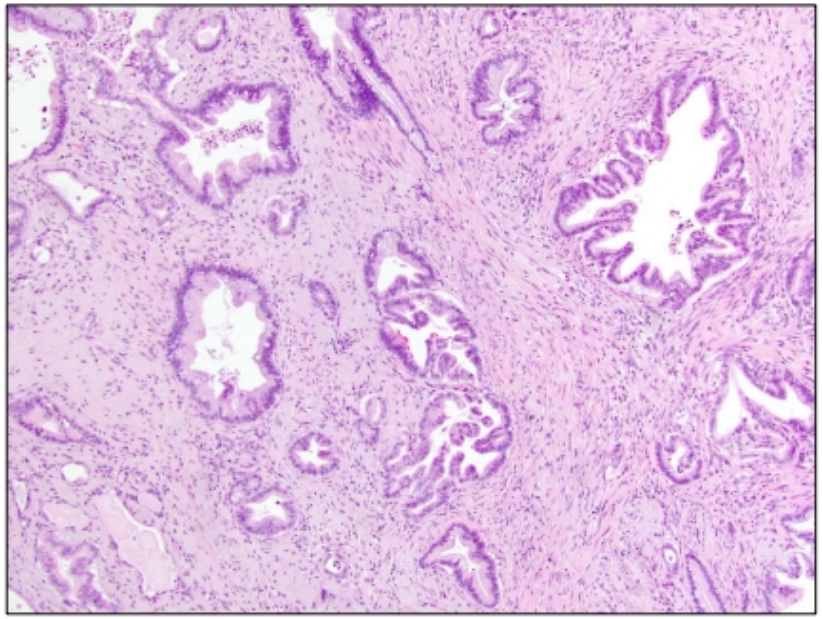
Tumors With Classical and Basal-Like Subtypes Have Distinct Biology

- Transcriptomic analyses: basal-like and classical subtypes
  - Basal-like tumors are enriched for epithelial-to-mesenchymal transition, cell cycle progression, and TGF-beta signaling

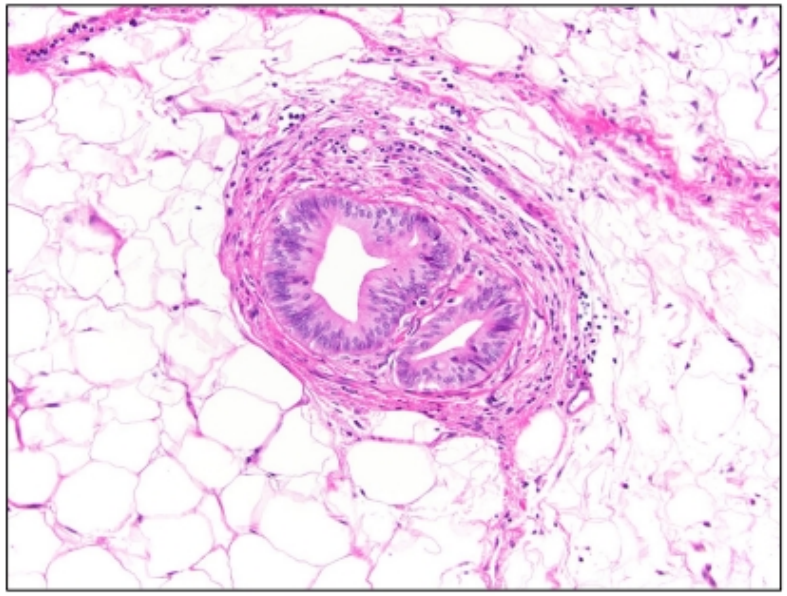


Lee JJ and Yeh JJ, *Surg Clin North Am* 2024

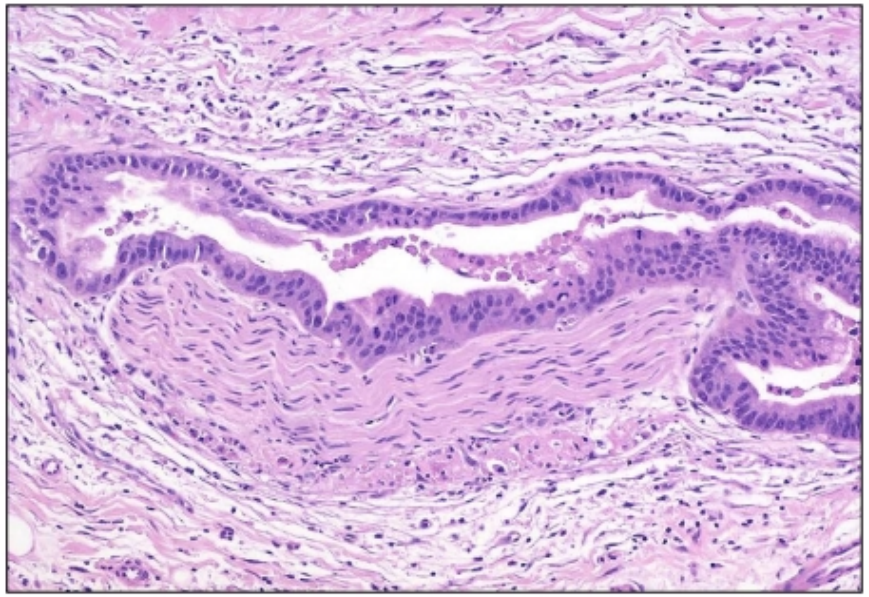
Pancreatic Cancer is Characterized by Desmoplastic Stroma



Ductal Adenocarcinoma



Venous Invasion



Perineural Invasion

Adapted from Anirban Maitra, MBBS (2025 ESMO GI Annual Congress)

Desmoplastic stroma mainly consists of extracellular matrix, vasculature, and cancer-associated fibroblasts

Perineural (~62%) and lymphovascular (~54%) invasion are common and are associated with worse overall survival.

Hosein AN, *Nat Rev Gastroenterol Hepatol* 2020; Kiemen AL, *Nat Methods* 2022; Javed AA, *Ann Surg* Oncol 2024

Modifiable Risk Factors

Risk Factors	Associated Risk of Pancreatic Cancer
Longstanding diabetes	• 1.5-2-fold increased risk for individuals with diabetes >3 years in duration[1-4]
New-onset diabetes	• 5-8-fold increased risk of being diagnosed with pancreatic cancer within 1 to 3 years • <0.3-0.8% of patients with new-onset diabetes develop PDA within 3 years[5-7]
Pancreatitis Acute Chronic	• More likely as first presentation of the disease instead of being a risk factor. • 2 to 3-fold increased risk with long-standing chronic pancreatitis[8-10]
Cigarette smoking	• ~1.8-fold increased risk compared with never smokers[11-14]
Obesity	• ~1.6-fold increased risk in individuals with obesity compared with those with normal weight[15-17]
Physical inactivity	• Inverse association with the risk of pancreatic cancer, most apparent among obese individuals[15]
Diet high in saturated fats	• Relative risk 1.13[18]
Alcohol use	• 1.6-fold increased risk for >6 drinks per day compared with >1 drink per day[19-23]
Allergy	• 25% lower risk of developing PDA[24-27]

[1]Everhart J *JAMA* 1995; [2]Huxley R *Br J Cancer* 2005; [3]Bosetti C *Ann Oncol* 2014; [4]Elena JW *Cancer Causes Control* 2013; [5]Chari ST *Gastroenterology* 2005; [6]Gupta S *Clin Gastroenterol Hepatol* 2006; [7]Munigala S *Clin Transl Gastroenterol* 2015; [8]Yadav D *Gastroenterology* 2013; [9]Duell EJ *Ann Oncol* 2012; [10]Kirkegard J *Gastroenterology* 2018; [11]Iodice S *Langenbecks Arch Surg* 2008; [12]Bosetti A *Ann Oncol* 2012; [13]Lynch SM *Am J Epidemiol* 2009; [14]Koyanagi YN *Cancer Epidemiol Biomarkers Prev* 2019; [15]Michaud DS *JAMA* 2001; [16]Arslan AA *Arch Intern Med* 2010; [17]Stolzenberg-Solomon *Am J Clin Nutr* 2013; [18]Yao X *PLoS One* 2015; [19]Lucenteforte E *Ann Oncol* 2012; [20]Genkinger JM *Cancer Epidemiol Biomarkers Prev* 2009; [21]Jiao L *Am J Epidemiol* 2009; [22]Gapstur SM *Arch Intern Med* 2011; [23]Naudin S *Int J Cancer* 2018; [24]Gandini S *Cancer Epidemiol Biomarkers Prev* 2005; [25]Olson SH *Am J Epidemiol* 2013; [26]Cotterchio M *Cancer Epidemiol Biomarkers Prev* 2014; [27]Gomez-Rubio P *Gut* 2017

Increased Risk if Family History of Pancreatic Cancer

Familial pancreatic cancer, defined as at least 2 first-degree relatives with pancreatic cancer, accounts for only 5-10% of all pancreatic cancer[1-3]

	Increased Risk
1 Relative	2.14-fold (95% CI 0.58-5.49)
Familial Kindred (2 FDR)	6.79 (95% CI 4.94 – 5.75)
3+ Relatives	17.02-fold (95% CI 7.34 – 33.5)

[1]Hruban RH *Adv Surgery* 2010; [2]Permuth-Wey J *Familial Cancer* 2009; [3]Shi C *Arch Pathol Lab Med* 2009

Inherited Risk Factors

Mutated Gene	Syndrome	Prevalence in Pancreatic Cancer Patients (%)	RR/OR for Pancreatic Cancer in Carriers vs Non -Carriers	Associated Cancers
BRCA2	Hereditary breast and ovarian syndrome	2-7	2-10	Breast, ovarian/fallopian tube, prostate
BRCA1	Hereditary breast and ovarian syndrome	0.5-1	2-4	Breast, ovarian/fallopian tube, prostate
PALB2	Hereditary breast cancer	Up to 0.5	>2 fold	Breast (female only)
ATM	Ataxia-telangiectasia	3-4	5-6	Breast (female only)
STK11	Peutz-Jeghers Syndrome	<1	Up to 135	Breast, other GI, lung
CDKN2A, p16	Familial atypical multiple mole melanoma (FAMM) syndrome	<1	12	Melanoma
TP53	Li-Fraumeni syndrome	Up to 0.2	6-7	Breast, sarcoma, adrenocortical, other GI
PRSS1*, SPINK1	Hereditary pancreatitis	<1	Up to 60	
MLH1, MSH2, MSH6, PMS2, EPCAM	Lynch Syndrome	<1	Up to 8 fold	Colorectal, endometrial, ovarian, gastric, small bowel, urothelial, pancreatobiliary

*Unclear whether PRSS1 predisposes to pancreatic cancer in the absence of chronic pancreatitis

Germline Testing in ALL Patients with Pancreatic Cancer

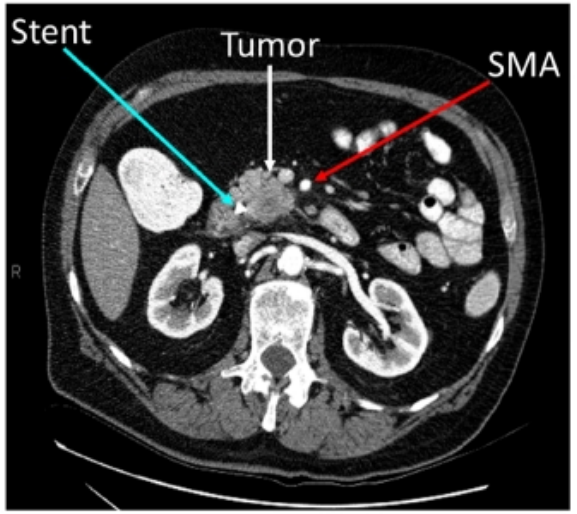
Pathogenic germline alterations may be present in up to 20% of unselected patients.

Tempero MA, Pancreatic Adenocarcinoma, NCCN Guidelines Version 2.2025

Clinical Presentation

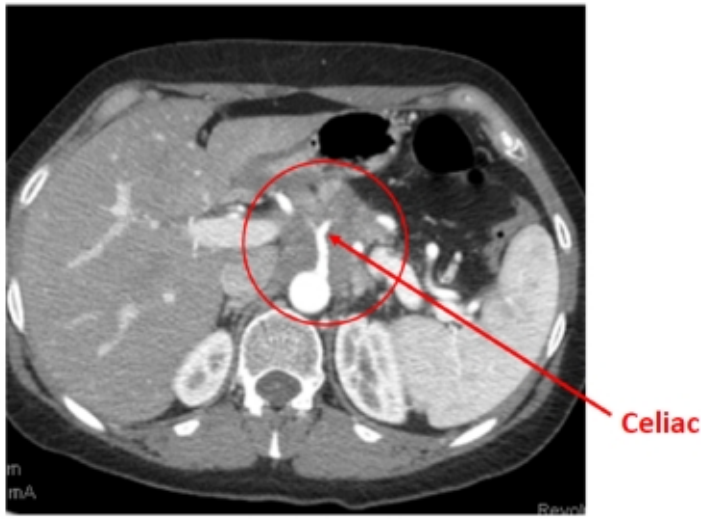
- Often vague and can vary by tumor location in the pancreas

Head of Pancreas



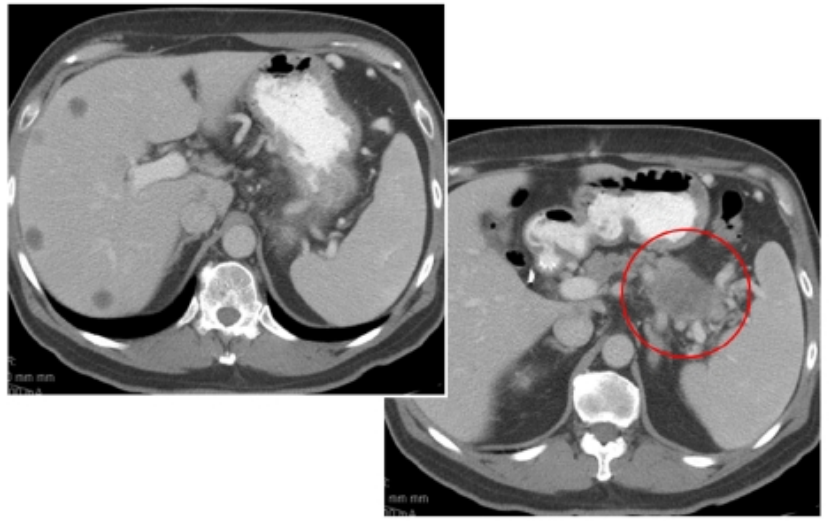
Compression of the bile duct -> jaundice

Head/Body of Pancreas



Compression of splanchnic/mesenteric plexus -> back pain or epigastric pain

Tail of Pancreas



Asymptomatic or constitutional symptoms related to metastatic disease

- New-onset diabetes
- Acute pancreatitis (~5%)

Diagnostic Tests & Staging Studies

- **Multi-phasic pancreatic protocol CT**: visualize arterial and venous structures
- **MRI**: adjunct to CT, particularly to characterize CT-indeterminate liver lesions
- **PET/CT**: not routinely used or recommended but adjunct in high-risk* patients

- **Endoscopic retrograde cholangiopancreatography (ERCP)**: therapeutic intervention for patients who require biliary decompression
- **Endoscopic Ultrasound (EUS)**
  - The role of EUS in staging is complementary to pancreas protocol CT (gold standard)
  - Primary role is to procure tissue for cytologic diagnosis

- **Biopsy**: commonly obtained by EUS-guided biopsy for localized disease
- **Biomarkers (CA 19-9)**: diagnostic marker in symptomatic patients, prognostic, and predictive

- **Diagnostic staging laparoscopy**: used in some institutions for patients (especially for body and tail lesions) prior to surgery or neoadjuvant therapy, or selectively in patients with high-risk* features and indicators of disseminated disease

*Equivocal or indeterminate imaging findings, borderline resectable disease, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes (NCCN Guidelines Version 2.2025)

TNM Staging (AJCC 8th Edition)

Table 1. **Definitions for T, N, M**
American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (8th ed., 2017)

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 cm and <1 cm in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

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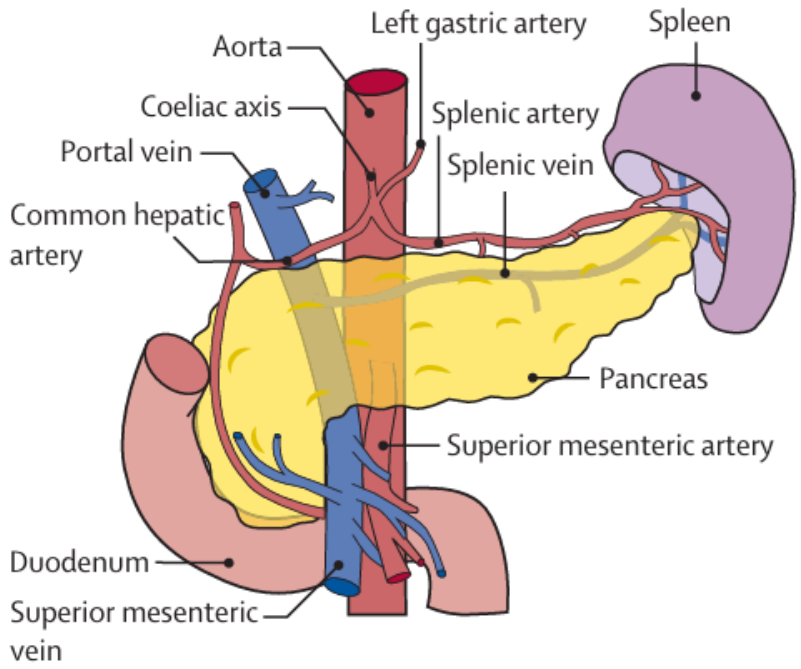
Anatomical Staging: Determining Resectability for Pancreatic Cancer

NCCN Guidelines: All diagnostic and surgical management decisions about resectability should involve multidisciplinary discussion.



	Superior mesenteric artery	Coeliac axis	Common hepatic artery	Portomesenteric venous axis
Resectable	No involvement	No involvement	No involvement	≤180° contact without vein contour irregularity
Borderline resectable	≤180° contact	≤180° contact	Any contact without extension to CA or hepatic artery bifurcation*	≤180° contact with vein contour irregularity OR >180° contact without vein contour irregularity or thrombosis, but reconstructable OR Any contact with inferior vena cava
Locally advanced	>180° contact	>180° contact OR any contact of the CA with aortic involvement	Any contact with extension to CA and/or hepatic artery bifurcation	No reconstructable involvement due to tumour contact or occlusion (either due to tumour or bland thrombus)
Metastatic	Distant metastatic disease, regardless of vascular involvement of the primary tumour			

Stoop TF, *Lancet* 2025

Localized Pancreatic Cancer

Resectable

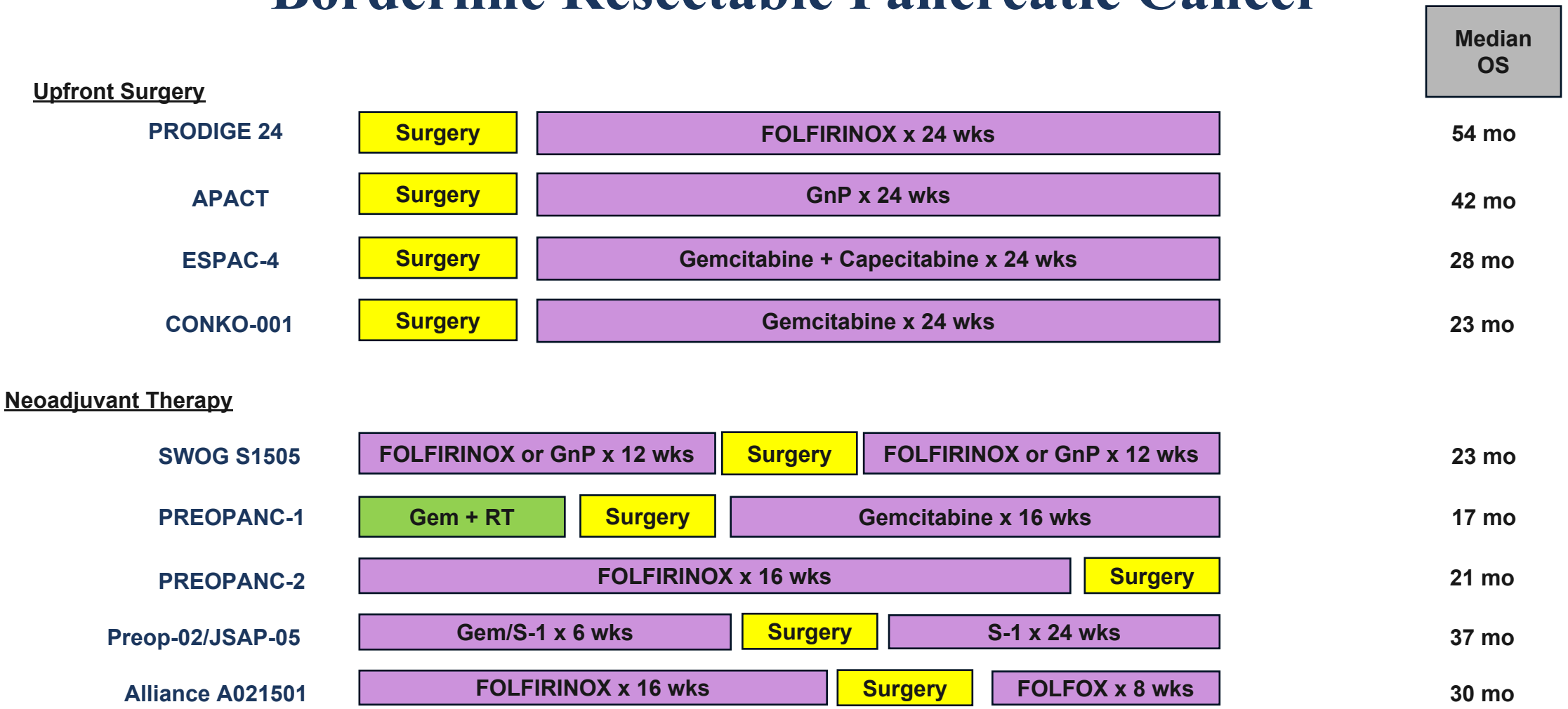
- Definition
  - No arterial tumor contact
  - No tumor contact with the SMV or PV or ≤180-degree contact without vein contour irregularity
- Treatment
  - **Surgery first is still the gold standard**
  - Adjuvant chemotherapy x 6 mo
    - FOLFIRINOX is the standard of care
    - Gemcitabine + capecitabine is an alternative

Borderline Resectable

- Definition: Any tumor not “cleanly resectable” without vascular resection
  - Venous involvement of any degree
  - Focal and non-circumferential involvement of the HA or SMA
- Treatment
  - **Neoadjuvant chemotherapy (FOLFIRINOX preferred vs GnP)**
  - Surgical resection

Tempero MA, Pancreatic Adenocarcinoma, NCCN Guidelines Version 2.2025

Standard of Care Chemotherapy for Resectable / Borderline Resectable Pancreatic Cancer



Neoadjuvant SBRT (Alliance A021501): Role is Limited

Neoadjuvant mFOLFIRINOX alone remains the standard of care.

	Arm A: mFOLFIRINOX	Arm B: mFOLFIRINOX→ RT
18-month OS	66.4%	47.3%
EFS	15 months	10.2 months
Resection Rate	49%	35%
pCR Rate	0%	11%
Pre-op 3+ AE rate	57%	64%
	Efficacious	Did not meet requirements to conclude efficacy

Outcomes were much worse

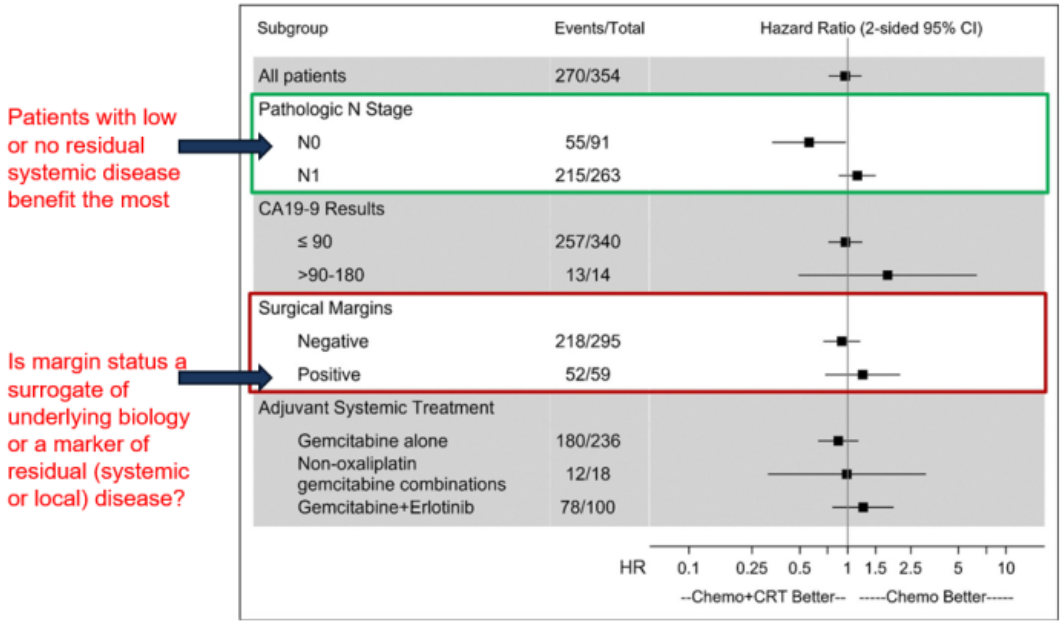
Study **closed early** after an interim analysis demonstrated a **higher R1 resection rate on the FOLFIRINOX + SBRT arm** (unclear why only 19/56 underwent pancreatectomy and only 14/19 had an R0 resection)

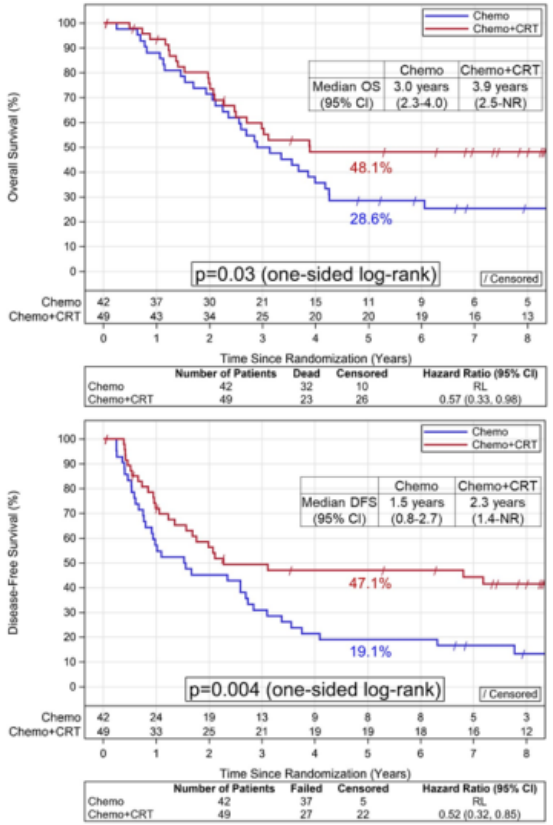
Katz MHG, *JAMA Oncol* 2022

Adjuvant RT: The Jury Remains Undecided

- Radiation is considered in patients at high risk (e.g., positive resection margin) for local recurrence after 6 months of adjuvant systemic therapy (NCCN Guidelines Version 2.2025)
- NRG Oncology / RTOG 0848 (Annual ASCO 2024): Adjuvant chemoradiation following marginally effective systemic treatment significantly improved DFS for all patients but not OS

Improvement in OS and DFS for node negative patients.

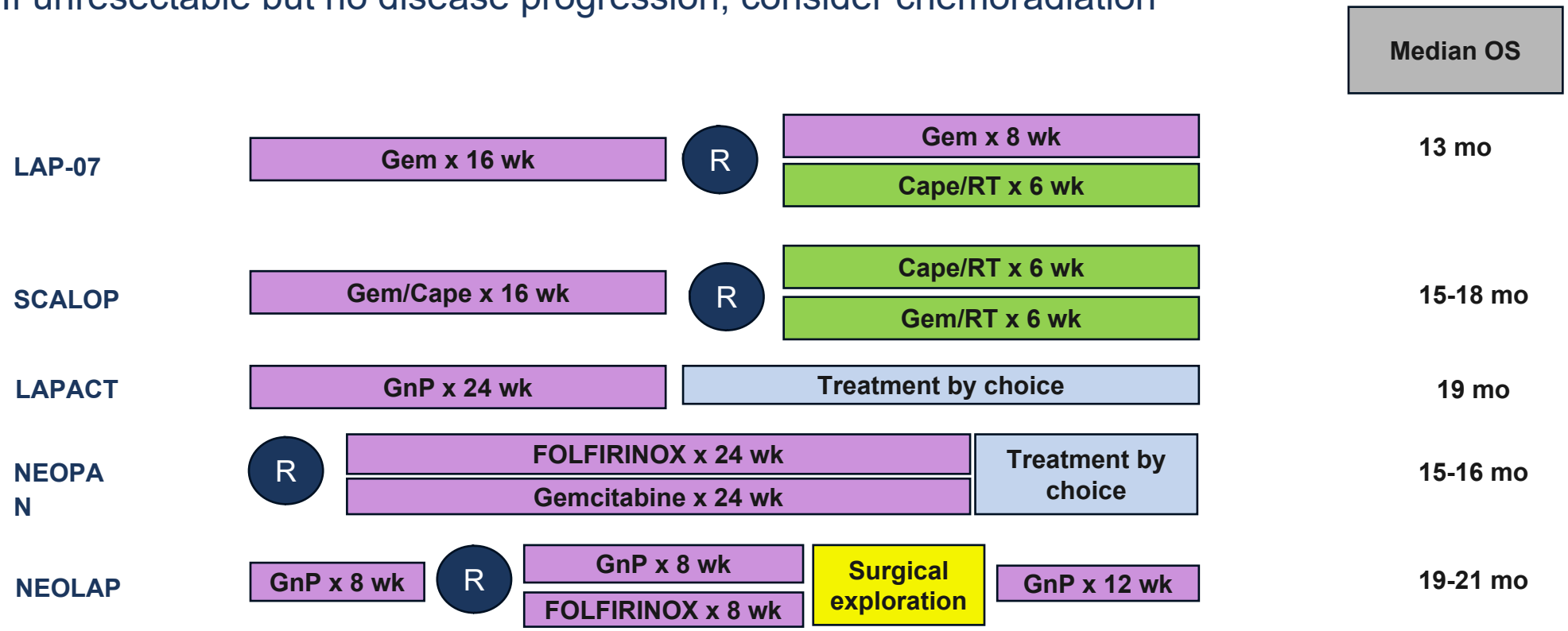




Presented by Goodman KA ASCO 2024

Standard of Care for Locally Advanced Pancreatic Cancer

- Radiographic evidence of vascular encasement (T4) that is not reconstructable
- Treatment: Multiagent chemo (gemcitabine/nab-paclitaxel, FOLFIRINOX) x 6 mo then re-evaluate
  - If resectable → surgical resection
  - If unresectable but no disease progression, consider chemoradiation



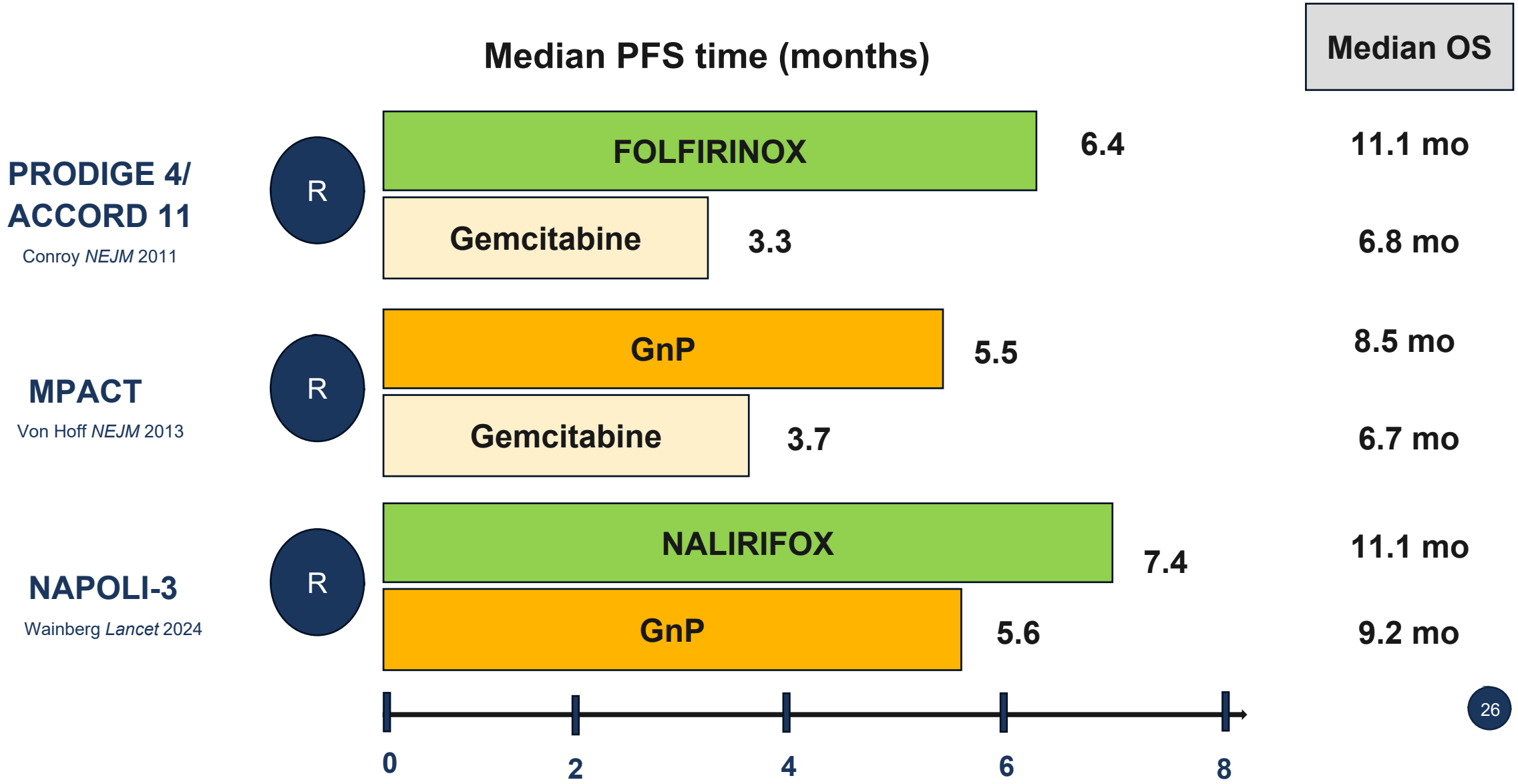
Multiagent Chemotherapy in Advanced Pancreatic Cancer

- Combination chemotherapy remains the backbone of pancreatic cancer treatment
- Outcomes are poor with each regimen
  - Median OS < 1 yr (vs ~4 mo if untreated)
- Apart from *BRCA1/2* and *PALB2* mutations, no routine biomarkers to guide choice of regimen

Metastatic Disease (First-Line Therapy)	
	Preferred Regimens
Good PS 0–1	• **FOLFIRINOX (category 1) or modified FOLFIRINOX[e,5]** • **Gemcitabine + albumin-bound paclitaxel[6] (category 1)** • **NALIRIFOX[f,7] (category 1)** **Only for known *BRCA1/2* or *PALB2* mutations:** • **FOLFIRINOX (category 1) or modified FOLFIRINOX[e,5]** • **Gemcitabine + cisplatin[8,9]**

Tempero MA, Pancreatic Adenocarcinoma, NCCN Guidelines Version 2.2025

Standard of Care 1L for Metastatic Pancreatic Cancer



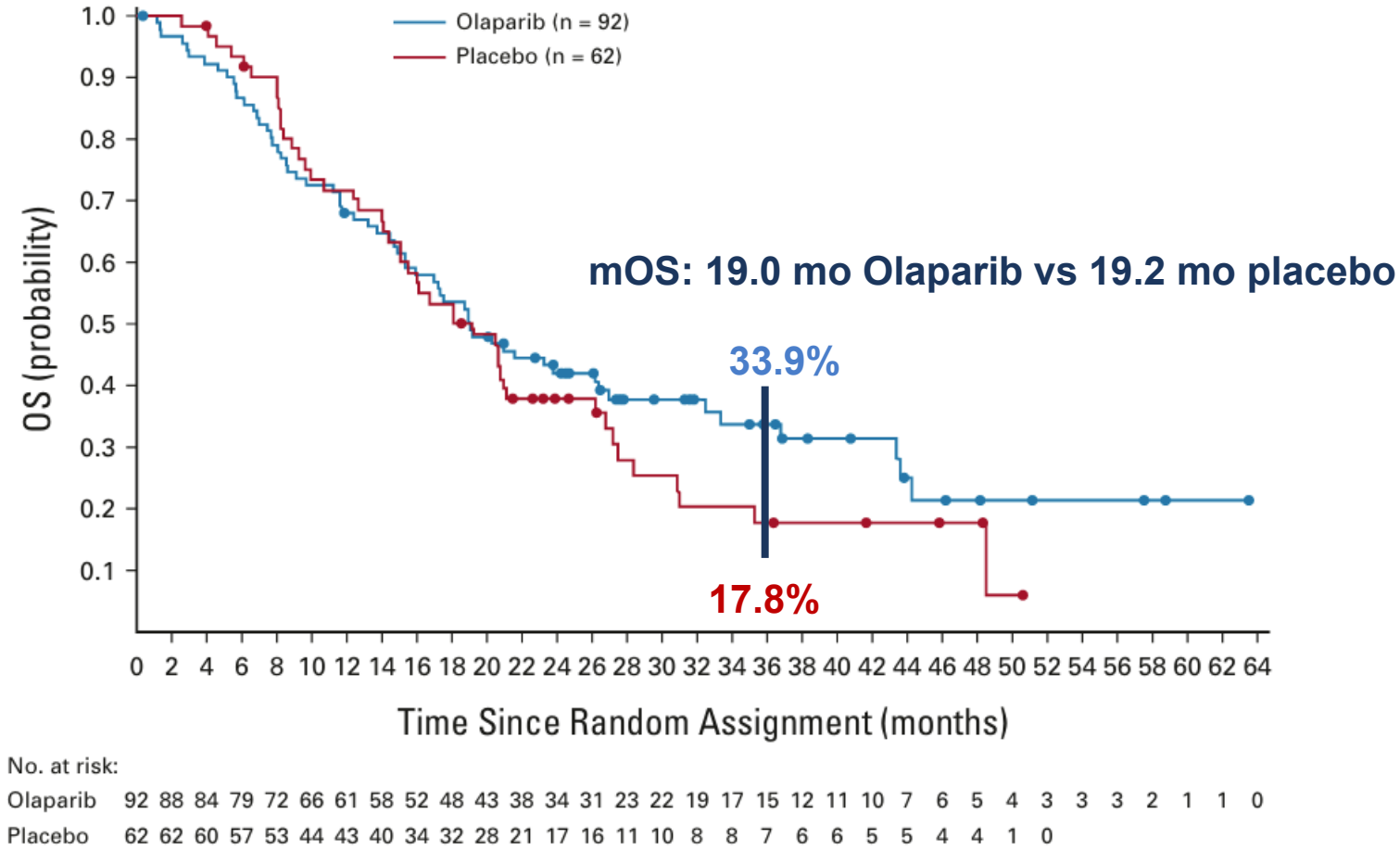
POLO g*BRCA*: Maintenance Olaparib vs Placebo After Platinum-Based Therapy

Metastatic PDAC
Germline *BRCA*
Prior platinum ≥ 4mo
ECOG 0-1; N=145

RANDOMIZE

Olaparib
300 mg PO BID

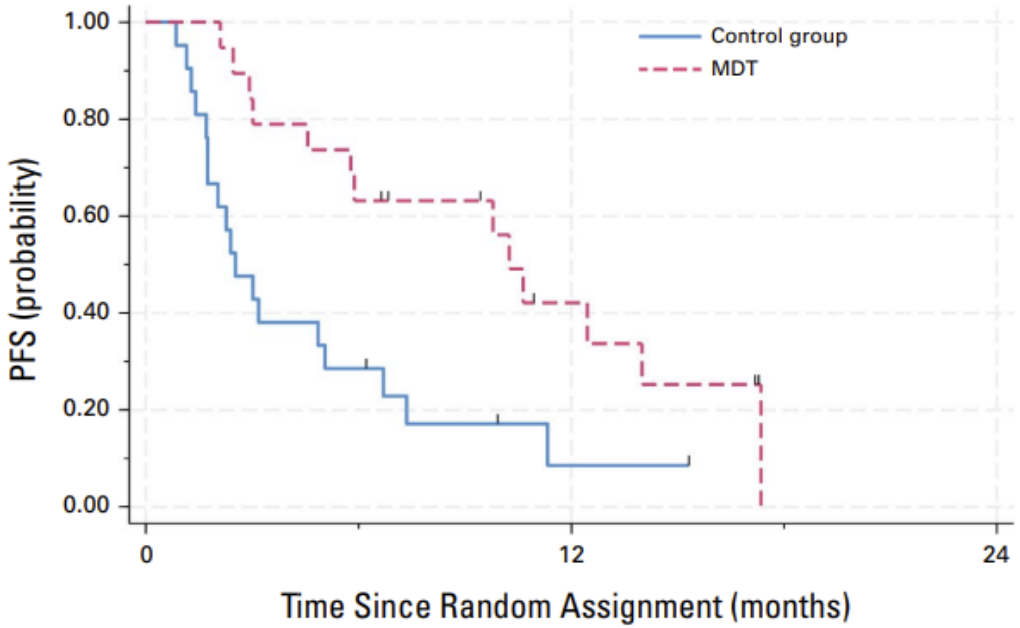
Placebo
300 mg PO BID



Golan T, *N Engl J Med* 2019; Kindler H, *J Clin Oncol* 2022

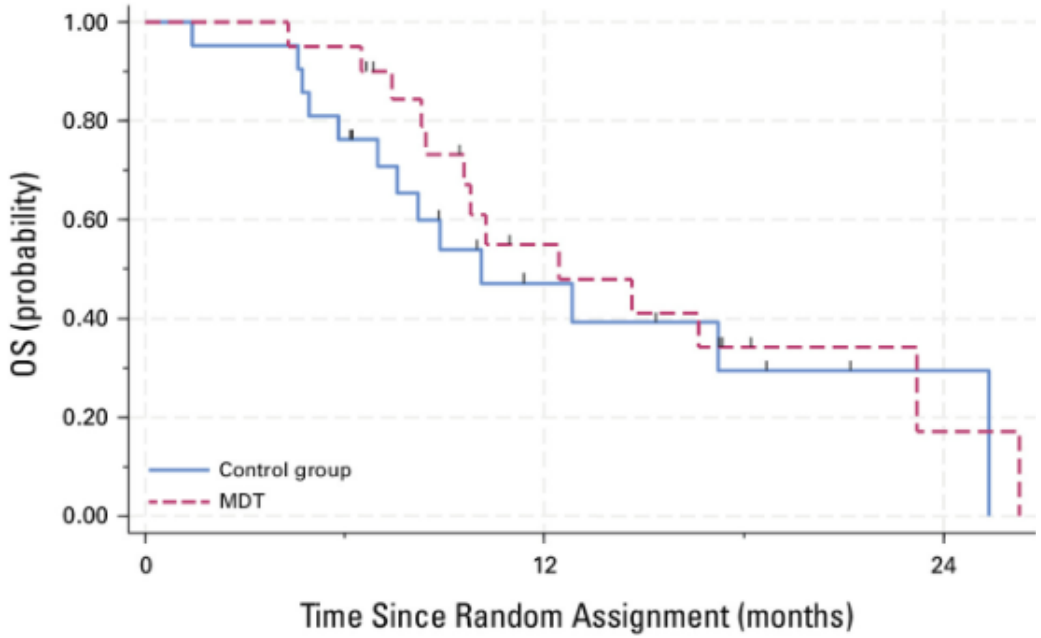
Metastasis-Directed Therapy (MDT) for Select Patients with Oligometastatic PDA: EXTEND Trial

Improvement in mPFS with MDT, 10.3 vs 2.5 mo



No. at risk (events)					
Control group	21	(18)	1	(0)	0
MDT	19	(10)	5	(3)	0

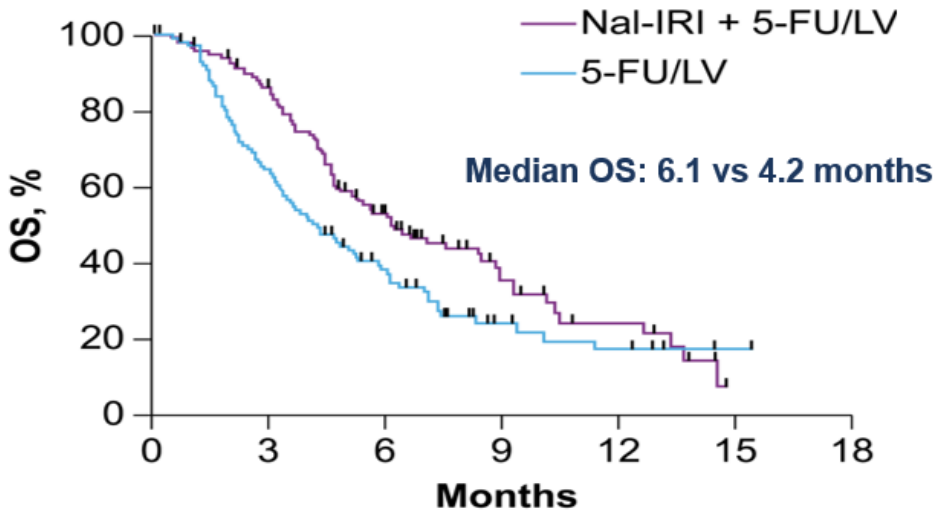
No OS Benefit with MDT

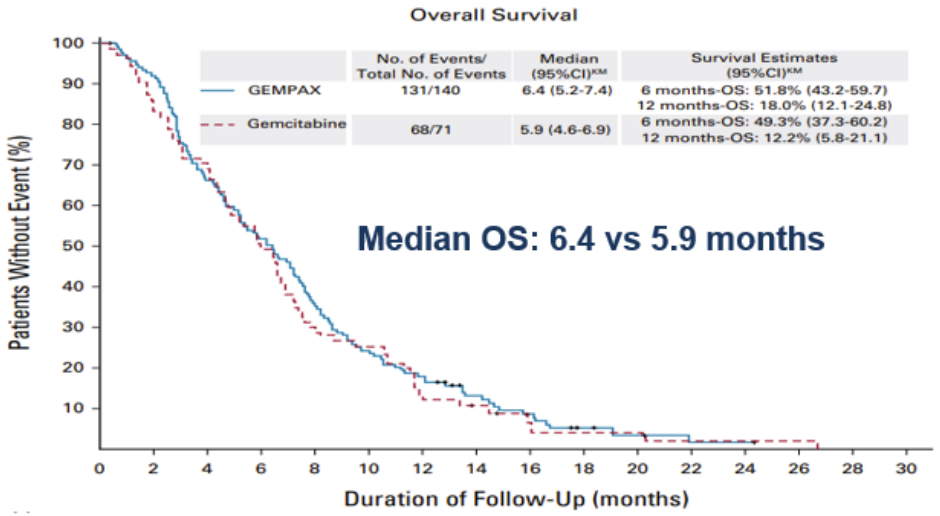


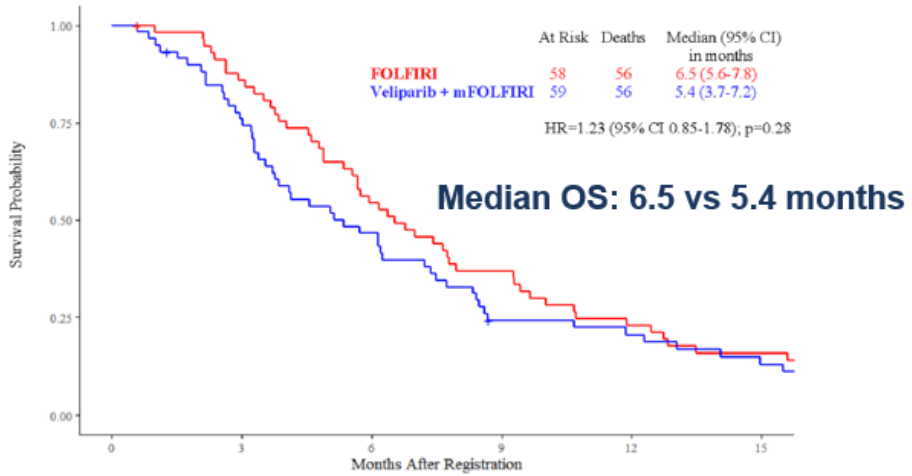
No. at risk (events)					
Control group	21	(10)	6	(2)	1
MDT	20	(8)	8	(4)	1

Ludmir EB *J Clin Oncol* 2024

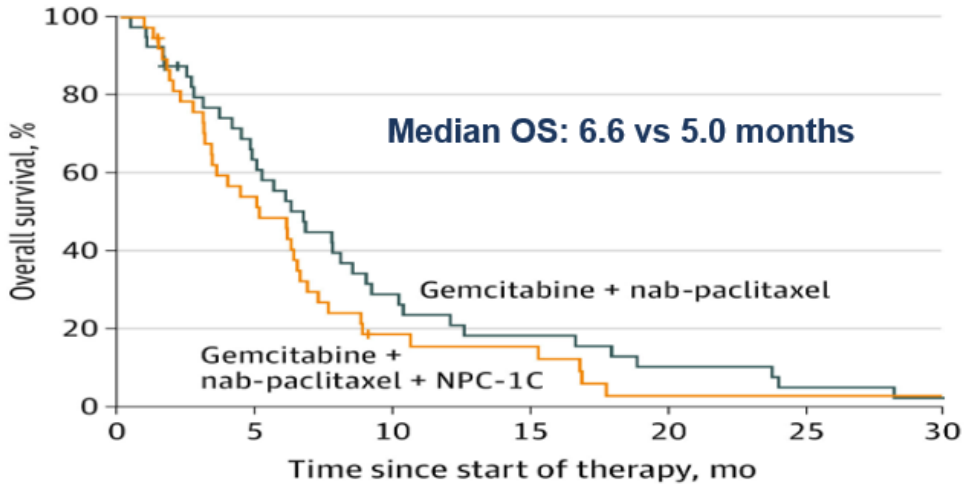
2L Chemo: Median OS ~6 Months







Wang Gillam A, et al. *Lancet* 2016
Chiorean EG, et al. *Clin Cancer Res* 2021



De La Fouchardiere C, et al. *J Clin Oncol* 2024
Huffman BM, et al. *JAMA Netw Open* 2023

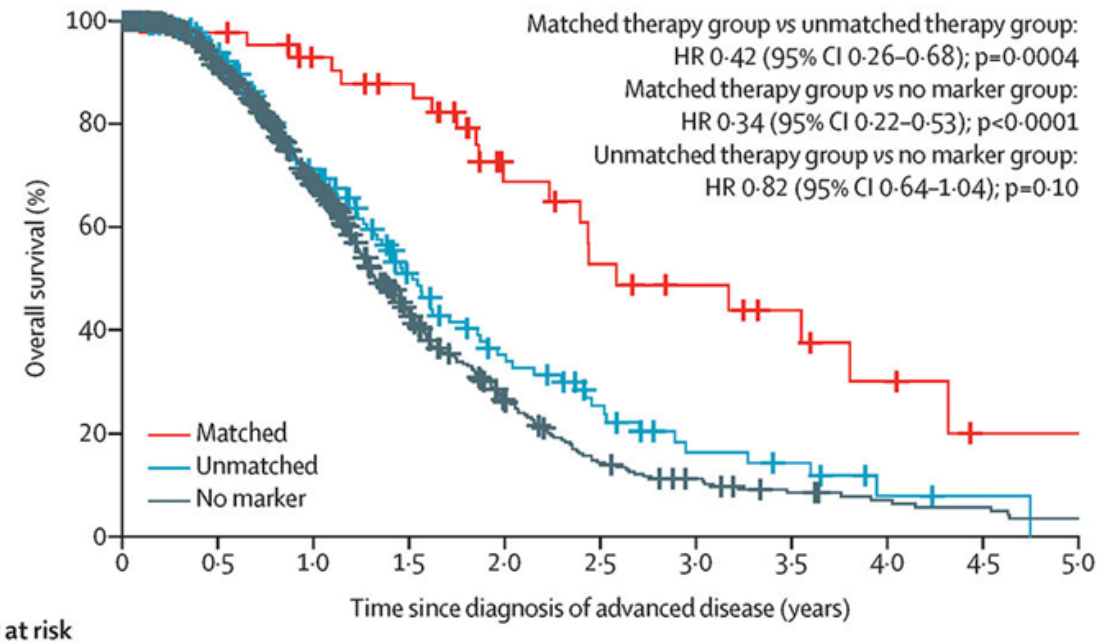
Genomic Profiling Guides the Choice of Molecular Targeted Therapy for Pancreatic Cancer Patients

- Must be done in all patients with locally advanced or metastatic pancreatic cancer
- Testing on tumor tissue is preferred
- Consider liquid biopsy (use of ctDNA) if tissue is not available

Tempero MA, Pancreatic Adenocarcinoma, NCCN Guidelines Version 2.2025

Patients with actionable alterations derive considerable benefit from receiving a matched therapy.

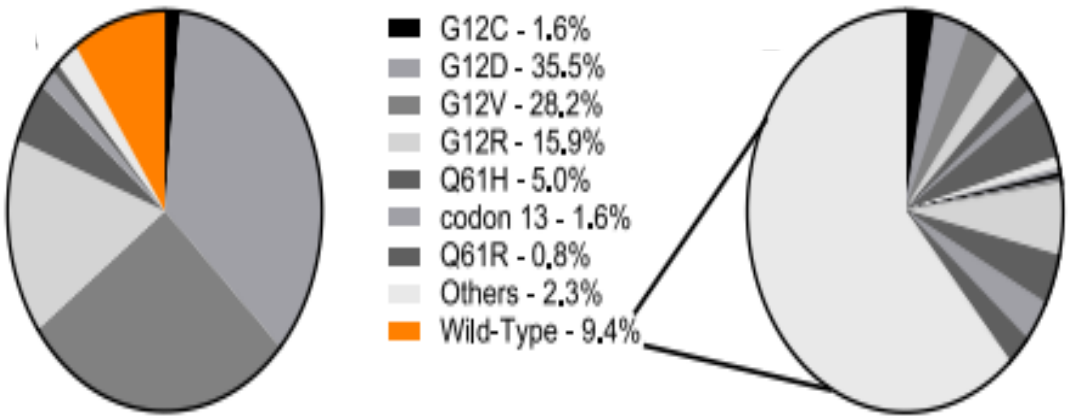
Know Your Tumor Registry



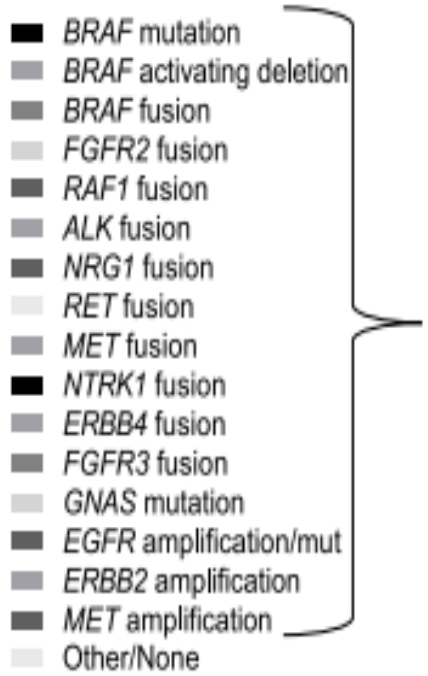
Number at risk (number censored)											
Matched therapy	46	42	36	32	18	13	10	7	4	1	1
	(0)	(3)	(4)	(2)	(8)	(1)	(2)	(2)	(1)	(2)	(0)
Unmatched therapy	143	116	78	44	27	16	8	6	2	1	0
	(0)	(19)	(11)	(15)	(4)	(4)	(3)	(1)	(2)	(1)	(0)
No marker	488	384	241	124	63	33	22	14	10	8	5
	(0)	(66)	(55)	(39)	(15)	(4)	(4)	(3)	(2)	(0)	(0)

Pishvaian MJ *Lancet Oncol* 2020

Enrichment of Actionable Gene Alterations in *KRAS* WT Pancreatic Cancers



KRAS G12C: Adagrasib, Sotorasib



BRAF V600E: Dabrafenib/trametinib

TMB high (≥ 10 mut/Mb): Nivo + IPI

MSI-H, dMMR, or TMB-H: Pembrolizumab

MSI-H, dMMR: Dostarlimab

RET fusion: Selpercatinib

HER2 IHC 3+ or IHC 2+ / FISH +: T-DXd

FGFR2 fusion: Erdafitinib

NRG1 fusion: Zenocutuzumab

NTRK fusion: Entrectinib, larotrectinib, repotrectinib

Lee MS and Pant S, ASCO Educational Book 2021; Philip PA et al *Clin Cancer Res* 2022; Kane GM et al *J Clin Oncol* 2022; NCCN Guidelines 2.2025

Principles of Palliation and Supportive Care

Symptom	Therapy
Biliary obstruction	• Endoscopic biliary metal stent (preferred) • Percutaneous biliary drainage with subsequent internalization • Open biliary-enteric bypass
Gastric outlet/duodenal obstruction	• Gastrojejunostomy (open or laparoscopic) +/- G/J-tube • Enteral stent • Venting PET for gastric decompression
Thromboembolic disease	• LMWH preferred over warfarin • Consider DOACs for patients without luminal tumors
Bleeding from the primary tumor site	• Therapeutic endoscopy, if clinically indicated • RT, if not previously done • Angiography with embolization, if clinically indicated
Ascites	• Therapeutic paracentesis

Tempero MA, Pancreatic Adenocarcinoma, NCCN Guidelines Version 2.2025; Safyan RA *Am Soc Clin Oncol Educ Book* 2024

Principles of Palliation and Supportive Care

Symptom	Therapy
Anorexia	• Daily low-dose olanzapine • Corticosteroids • Megestrol acetate • Synthetic cannabinoids
Exocrine pancreatic insufficiency and nutrition	• Pancreatic enzyme replacement if EPI • Nutritional evaluation with a registered dietician (counseling on high-protein, high-calorie, nutrient-dense food) • Manage co-occurring symptoms: nausea, dysgeusia, depression, constipation, pain
Nausea and vomiting	• 5HT3 receptor antagonists, atypical antipsychotics (e.g., olanzapine) • Adjuvant therapy: benzodiazepines, anticonvulsants, dopamine receptor antagonists, and cannabinoids
Diarrhea	• Antidiarrhea agents • Hydration • Pancreatic enzyme replacement

Tempero MA, Pancreatic Adenocarcinoma, NCCN Guidelines Version 2.2025; Safyan RA *Am Soc Clin Oncol Educ Book* 2024

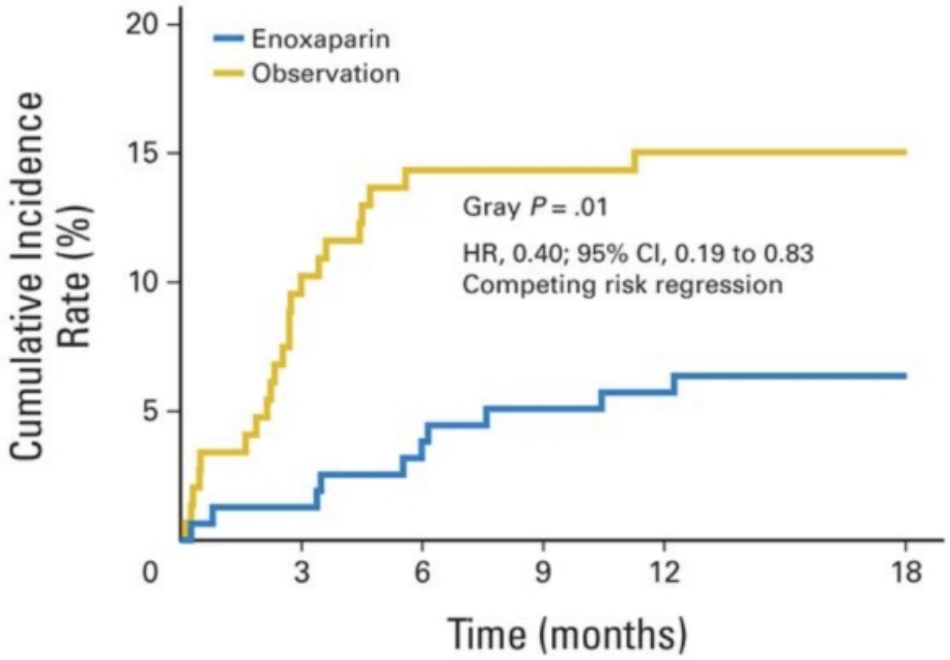
Principles of Palliation and Supportive Care

Symptom	Therapy
Depression, anxiety	• Management of cancer-related pain • Pharmacologic therapy • Counseling • Referral to mental health specialists
Physical activity	• Localized PDAC: prehabilitation with early initiation of an exercise training program • Metastatic PDAC: physical activity in combination with other supportive care
Cancer-related fatigue	• Exercise • Nutrition • Methylphenidate • Corticosteroids
Cancer-related pain	• Acetaminophen and nonsteroidal anti-inflammatory drugs • Complementary approaches (acupuncture, etc) • EUS-guided celiac plexus block • Anti-cancer therapy (chemo, RT) • Opioids

Tempero MA, Pancreatic Adenocarcinoma, NCCN Guidelines Version 2.2025; Safyan RA *Am Soc Clin Oncol Educ Book* 2024

Prophylactic LMWH Decreases VTE but No OS Benefit

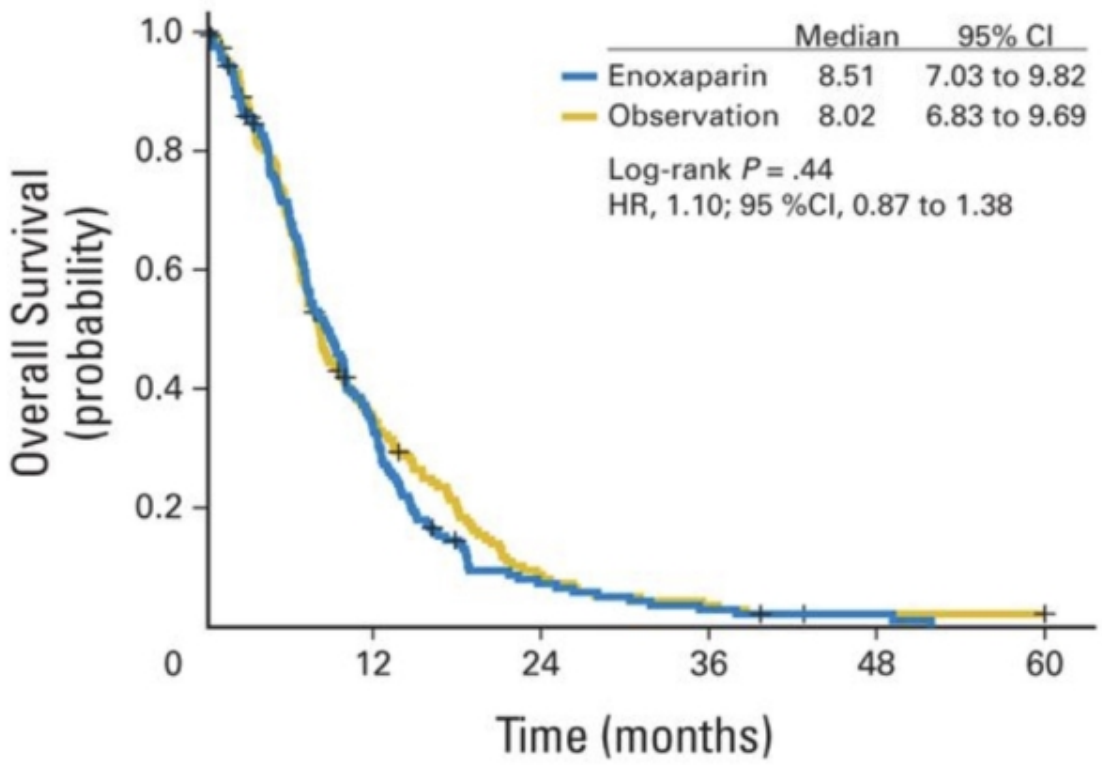
Symptomatic VTE Events



No. at risk						
Enoxaparin	160	102	55	26	12	4
Observation	152	87	47	27	14	5

Incidence rate, %						
Enoxaparin	0	1.3	3.8	5.1	5.7	6.4
Observation	0	10.2	14.4	14.4	15.1	15.1

Overall Survival

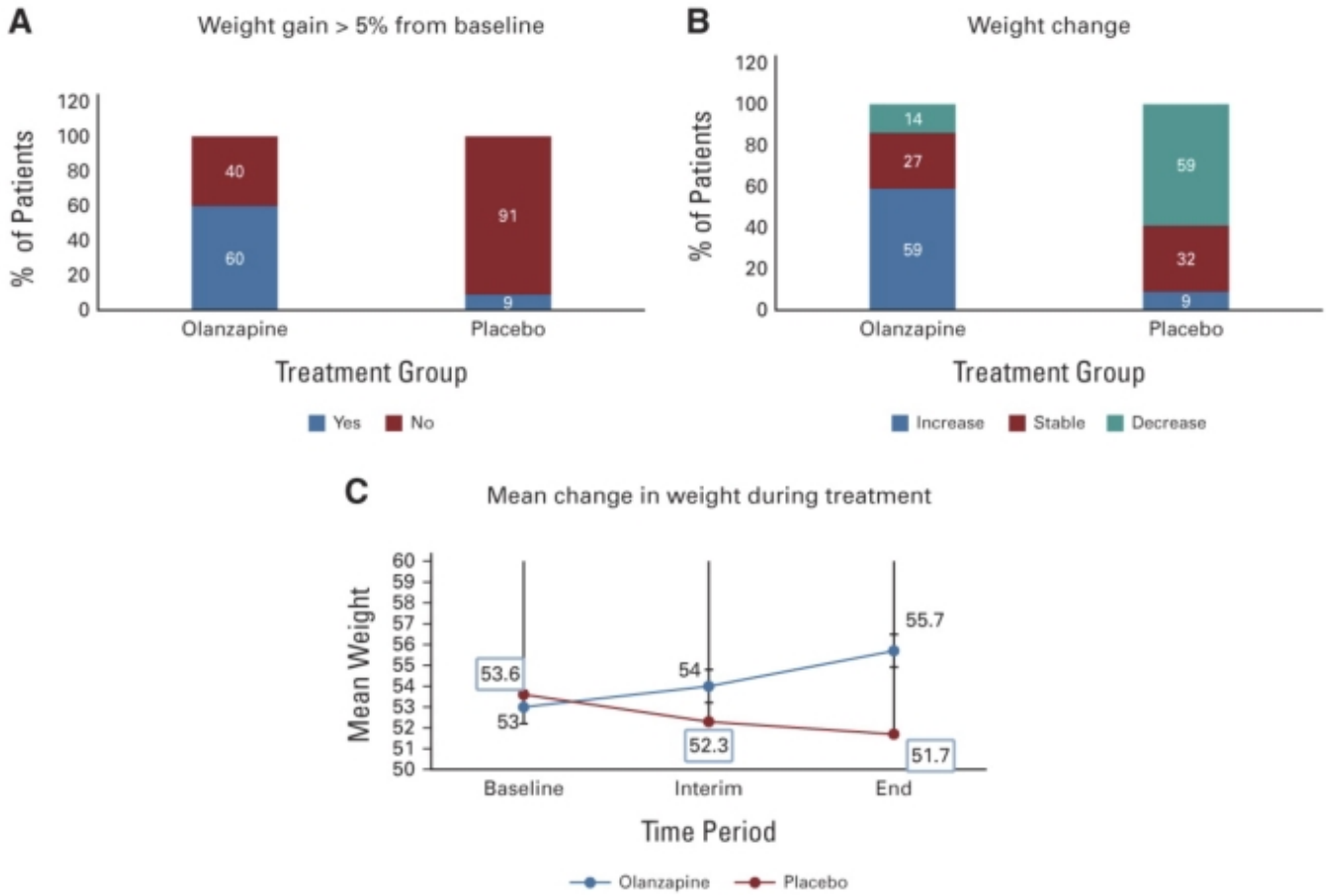


No. at risk						
Enoxaparin	160	49	10	4	2	0
Observation	152	48	11	5	2	2

Pelzer U *J Clin Oncol* 2015

Appetite and Weight: Olanzapine for Cancer Cachexia

- N=124
- Untreated, locally advanced or metastatic
- Gastric, hepatopancreaticobiliary (HPB), and lung cancers
- Randomly assigned (double-blind) to olanzapine 2.5 mg daily x 12 weeks vs placebo along with chemotherapy
- Primary endpoints: proportion of patients with weight gain >5% and improvement in appetite



Sandhya L *J Clin Oncol* 2023

For the Boards

PDAC is the most common histology, with a poor prognosis and rising incidence; most patients present with advanced disease due to nonspecific symptoms and lack of effecting screening

Surgical resection is the only potential curative treatment, but only 10-20% of patients are resectable at diagnosis

For locally advanced or metastatic disease, multiagent chemo (FOLFIRINOX or GnP) is standard of care 1L treatment if good PS

Germline and somatic molecular profiling is now standard of care for ALL patients with advanced disease to identify actionable alterations

Mutli-D management, supportive care, and early integration of palliative care are essential throughout the disease course

Fred Hutch Cancer Center

Thank You!

Clinical Case #1

- 66 year-old woman, ECOG performance status 0-1
- No family history of malignancy. Ashkenazi Jewish descent.
- Locally advanced mass in the head of the pancreas with bilobar liver metastases. Biopsy of a liver lesion confirmed moderately differentiated adenocarcinoma.
- CA 19-9 = 52,174
- Germline testing: loss-of-function BRCA2 mutation.
- Received mFOLFIRINOX x 6 months with good minimal side effects.
- RECIST response. CA 19-9 = 32 U/mL.

Question #1

True or False

Early germline genetic testing for all patients with pancreatic cancer with a multigene panel is standard practice.

Answer: True

- Depending on geographic region, 10-20% of pancreatic cancer cases are hereditary, with mutations in BRCA1 and BRCA2 being the most common.
- Clinical risk factors such as family history of cancer and young age of onset are not reliable predictors for which patients may carry one of these predisposing mutations.
- 2018: NCCN recommended that all pancreatic cancer patients should receive germline testing, regardless of family history.

Question #2

Next plan of care?

A. Continue FOLFIRINOX until progression/toxicity
B. 5-FU-based maintenance therapy
C. Biomarker-directed maintenance therapy with Olaparib
D. Treatment break/observation

Answer: C

- For patients with a germline *BRCA1/2* mutation, after at least 16 weeks of initial platinum-based chemotherapy, for those without disease progression, discontinue chemotherapy and initiate maintenance therapy using the PARP inhibitor Olaparib (POLO trial).
- The optimal timing of Olaparib in this setting is not established.
- PARP activity is essential for the repair of single-strand DNA breaks via the base excision repair pathway. In the setting of *gBRCA1/2*, cancer cells have defective homologous recombination repair function, and the unrepaired DNA breaks that result after treatment with PARP inhibitors eventually lead to cancer cell death (“synthetic lethality”).
- Maintenance olparib compared with placebo was associated with significant improvement in mPFS, the primary endpoint (7.4 vs 3.8 mo, HR 0.53) and twice as many patients were progression free at 2 years (22 vs 9.6%). Overall survival was similar in both arms.

Case #2

- 62 yo engineer, healthy, presents with epigastric discomfort radiating to the left side.
- Multiphase CT abdomen and pelvis shows a pancreatic body mass encasing the celiac artery and abutting the SMA as well as the SMV.
- CT chest shows no distant metastases.
- CA 19-9 = 63
- ECOG performance status 0

Question

Which of the following choices is the best next step?

A. Upfront surgical resection
B. Chemoradiation followed by surgery then adjuvant mFOLFIRINOX
C. Neoadjuvant mFOLFIRINOX then re-evaluate by a multi-disciplinary team
D. Chemoradiation alone

Answer: C

- Surgical resection offers the only chance of cure for nonmetastatic pancreatic cancer.
- This patient has locally advanced, unresectable disease due to local vascular invasion.
- An initial period of chemotherapy is recommended (rather than radiotherapy or chemoradiotherapy).
- If aggressive medical therapy permits, combination chemotherapy with mFOLFIRINOX is preferred.
- Resectability should be assessed after 4-6 months of neoadjuvant therapy.
- Chemoradiation may be considered to optimize local control in those patients who can no longer tolerate further chemotherapy but who continue to have localized disease, unresectable and maintain a good performance status

Case #3

- 55 year-old woman presents for a 2nd-opinion.
- Diagnosed with a tail of pancreas mass with bilateral lung metastases and extensive intra-abdominal lymphadenopathy.
- CA 19-9 = 94,592
- Tumor next generation sequencing: BRAF V600E mutation, microsatellite stable
- ECOG performance status 1
- Received 1st-line mFOLFIRINOX with good tolerability.
- Stable disease, CA 19-9 nadir 36,814.
- Then disease progression after 6 months.

Question

What treatment plan would you recommend?

A. Gemcitabine + nab-paclitaxel
B. 5FU + nanoliposomal irinotecan
C. Gemcitabine + erlotinib
D. Dabrafenib + trametinib
E. Gemcitabine + cisplatin

Answer: D

- BRAF alterations are observed in approximately 2% of pancreatic cancer patients.

- NCI-MATCH basket trial
  - 35 solid tumors (3 pancreatic cancer) harboring BRAF V600 mutation
  - Treatment: dabrafenib + trametinib
  - 1 pancreatic cancer patient had stable disease as best response.
  - ORR was 35% for all patients
  - PFS and OS rates were 11.4 and 28.6 months, respectively
  - Led to FDA approval of this combination in pretreated cancers with *BRAF V600E* mutations