Fred Hutch Cancer Center

Pancreatic Cancer

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Disclosure of Financial Relationships

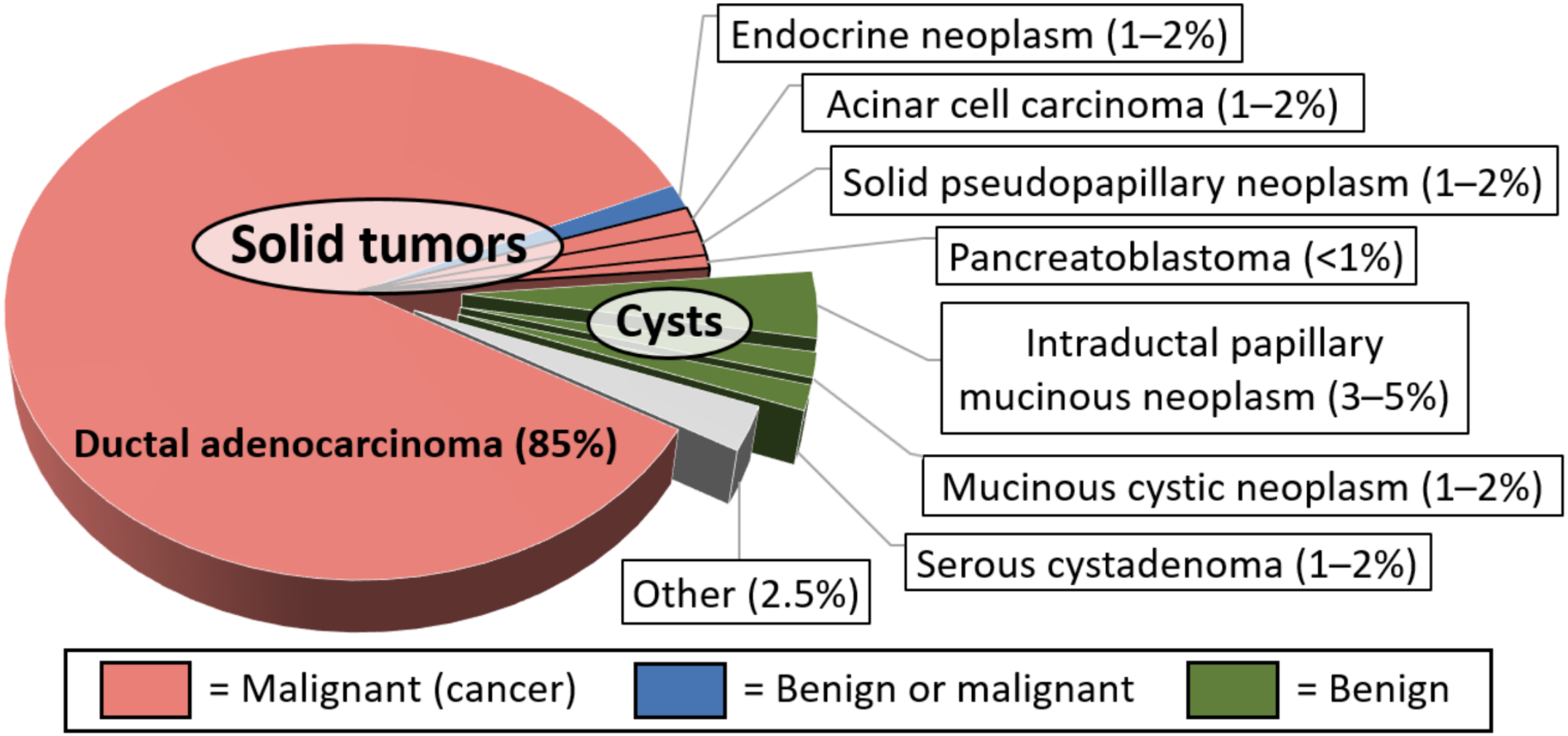
- I have been a consultant to the following companies:
  - Guardant Health
  - Ipsen
  - Agenus

- I receive research funding from the following companies:
  - Exelixis
  - Replimune
  - Verastem

Outline

1. Epidemiology and risk factors
2. Staging
3. Management of resectable, borderline resectable, and locally advanced PDA
4. Treatment options for advanced PDA
5. Molecular profiling and therapeutic opportunities

Types of Pancreas Tumors



Wang Y *Radiographics* 2011

Pancreatic Adenocarcinoma (PDA): General Facts

- Approximately 66,000 diagnoses per year in the US
- Incidence of about 1% over lifetime
- The eighth to tenth leading cause of cancer in the US
- Third to fourth leading cause of cancer-related mortality
- 5-year survival (all-comers), 13%
- Median age at diagnosis, 71 years
- Male/female incidence ratio: 1.3/1.0

Cancer Facts & Figures 2024; Siegel RL *CA Cancer J Clin* 2023

Pancreatic Adenocarcinoma (PDA): General Facts

- No effective screening exists
- Cure is rare and only seen in resected patients
  - 50% of patients present with metastatic disease (AJCC stage IV)
  - 30% of patients present with locally advanced disease (AJCC stage III)
  - 20% of patients present with localized resectable disease (AJCC stage I and II)
- Presenting symptoms are often vague and nonspecific
- Common sites of metastasis: liver, lymph node, lung, and peritoneum
- Rare sites of metastasis: skin, brain, leptomeninges

Siegel RL *CA Cancer J Clin* 2023; Rawla P *World J Oncol* 2019; Lee MS and Pant S, ASCO Educational Book 2021

Lifestyle and 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	• 2 to 3-fold increased risk with long-standing chronic pancreatitis[8-10]
Intraductal pancreatic mucinous neoplasms (IPMN)	• Risk for main duct IPMN is ~70% • Branch-duct IPMN: ~15% evolve to pancreas cancer over 15 years
Cigarette smoking	• ~1.7-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

High-Risk Pancreatic Cancer Susceptibility Genes

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

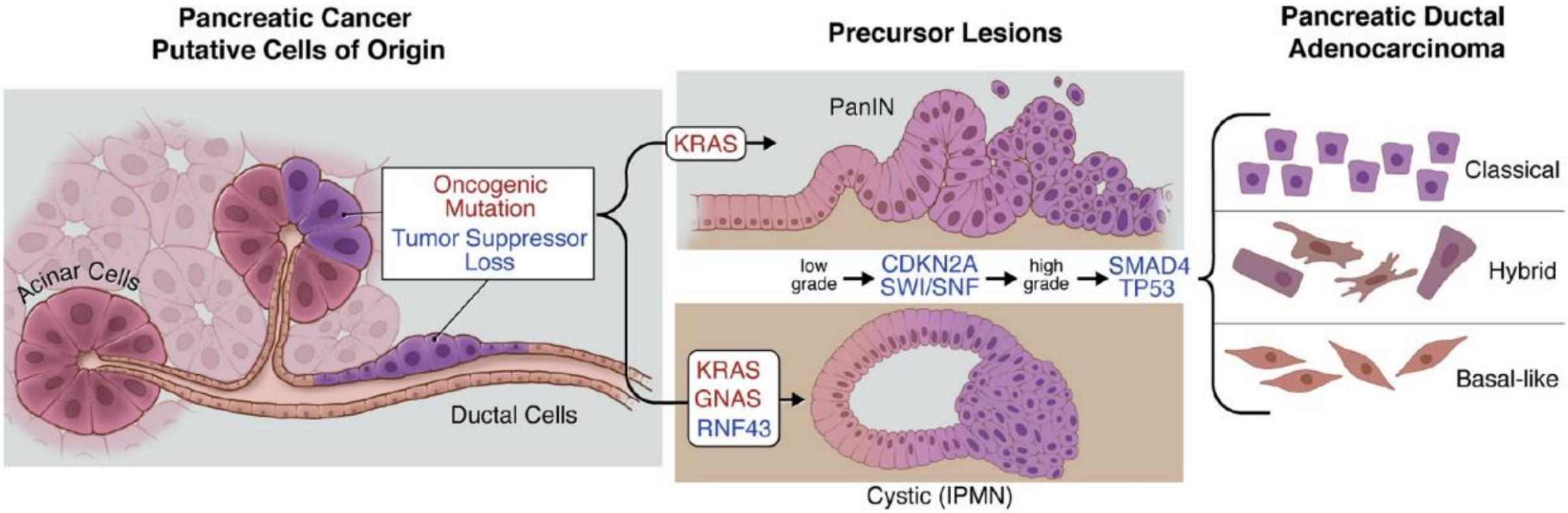
*Unclear whether PRSS1 predisposes to pancreatic cancer in the absence of chronic pancreatitis

Germline Testing in ALL Patients with Pancreatic Cancer

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

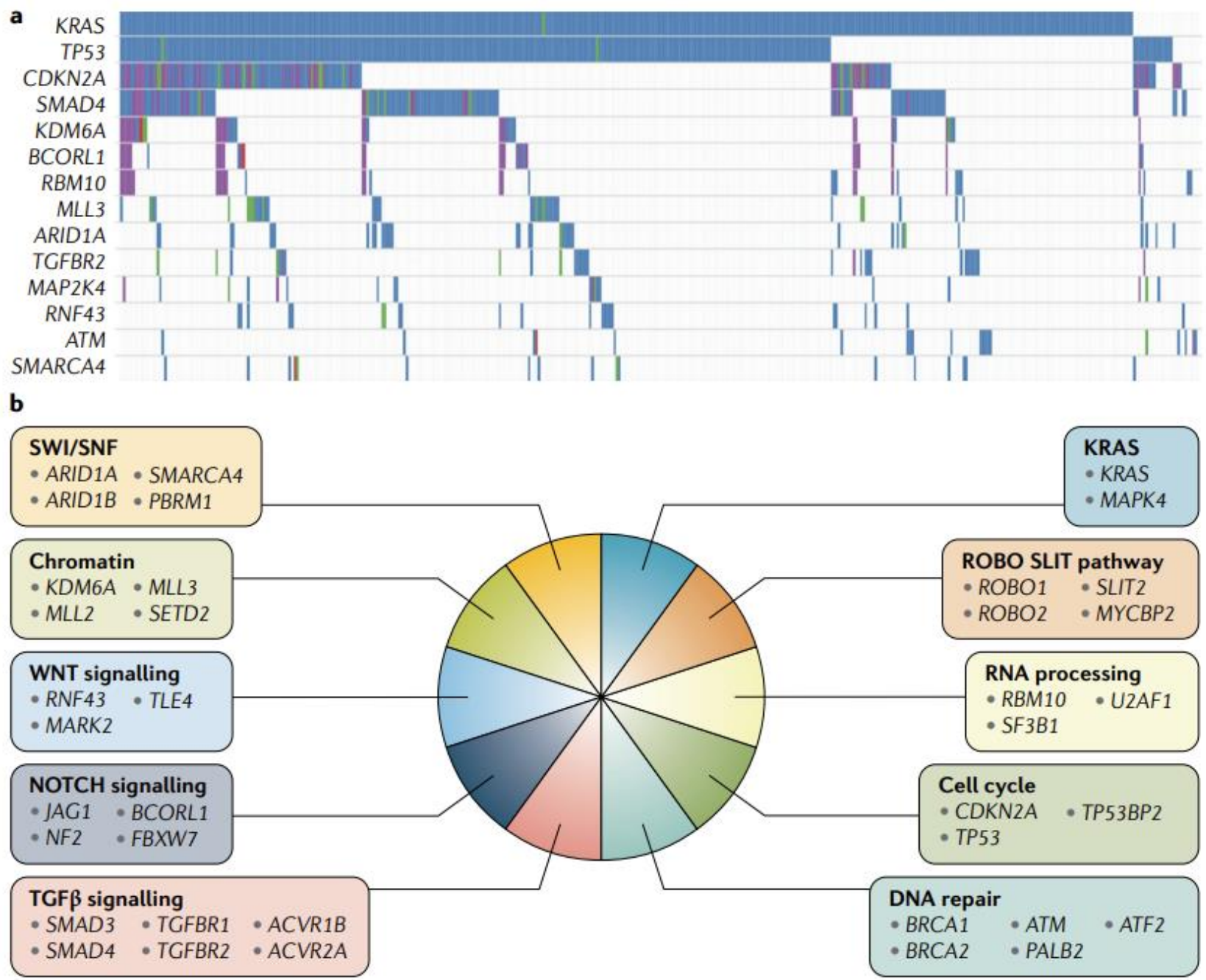
NCCN Guidelines Version 3.2024

Initiation and Progression of Pancreatic Cancer



Halbrook CJ *Cell* 2023

Genomic Aberrations Characteristic of Pancreatic Cancer

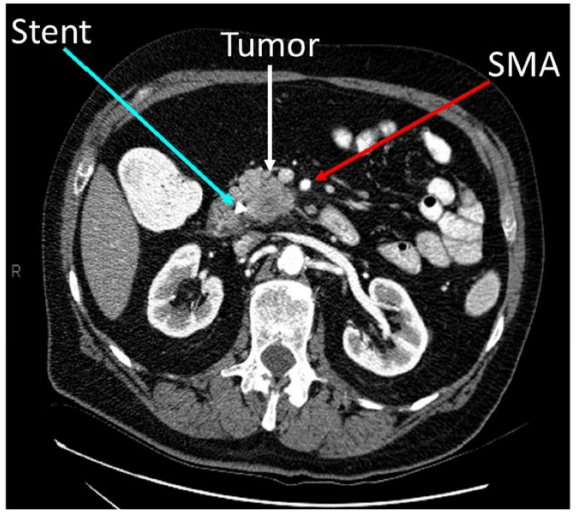


Collison EA, *Nat Rev Gastroenterol Hepatol* 2019

Clinical Presentation

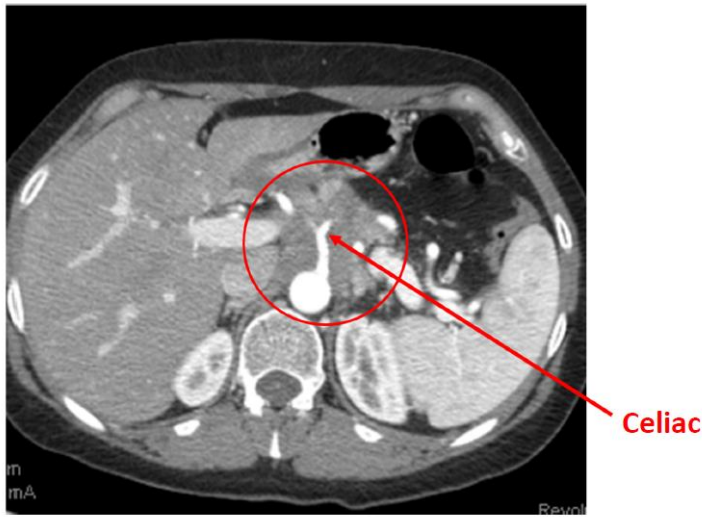
- Often vague and can vary by tumor location in the pancreas

Head of Pancreas



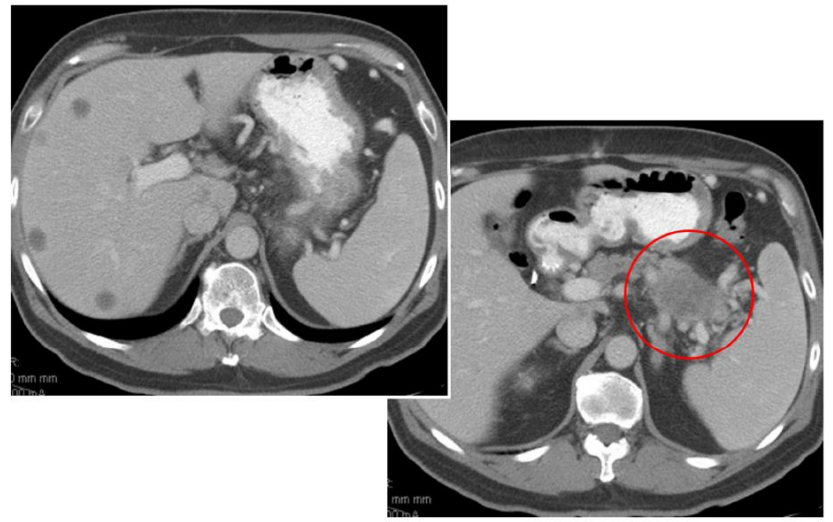
Compression of the bile duct -> jaundice

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 3.2024)

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

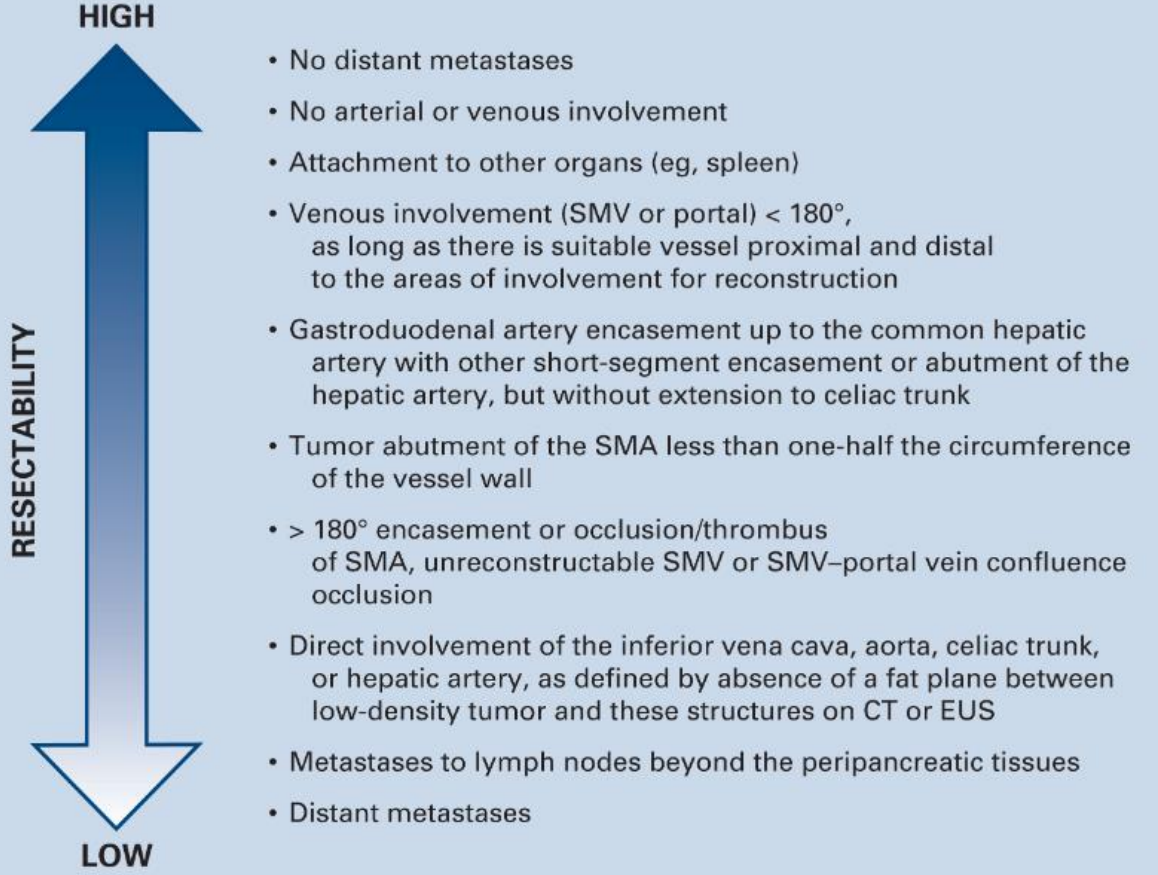
Table 2. **AJCC Prognostic Groups**

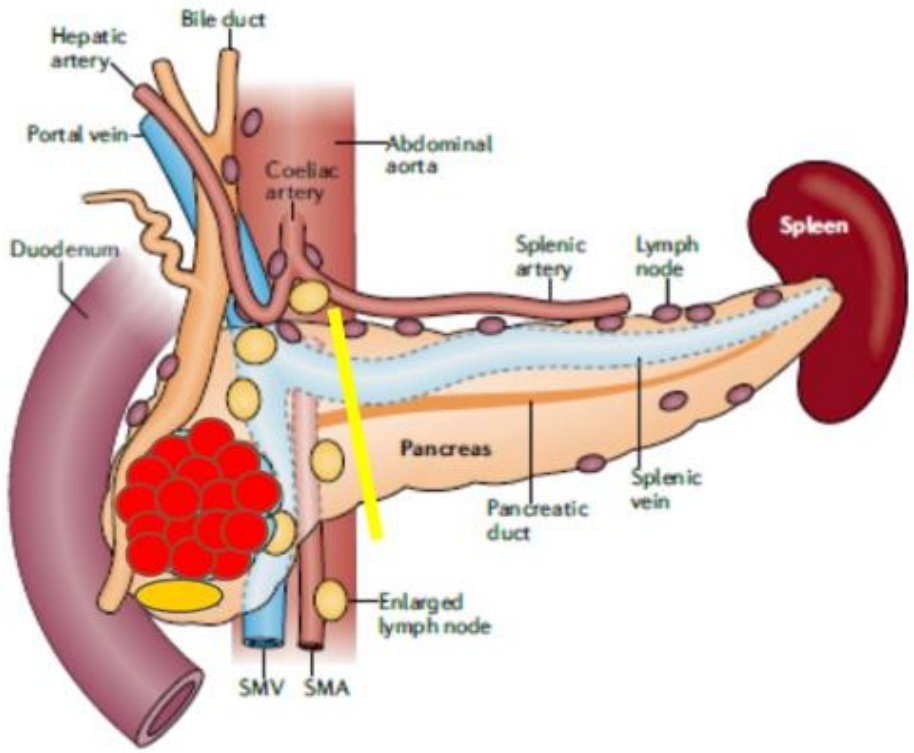
	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

NCCN Guidelines Version 3.2024

Determining Resectability for Pancreatic Cancer

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





Adapted from UpToDate 2019

Criteria Defining Resectability

• Decisions about resectability status should be made in consensus at multidisciplinary meetings/discussions.

Resectability Status	Arterial	Venous
Resectable	• No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	• No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[b]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180°. • Solid tumor contact with variant arterial anatomy (eg, accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180°.	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Locally Advanced[b,c]	Head/uncinate process: • Solid tumor contact >180° with the SMA or CA. Pancreatic body/tail: • Solid tumor contact of >180° with the SMA or CA. • Solid tumor contact with the CA and aortic involvement.	• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus).

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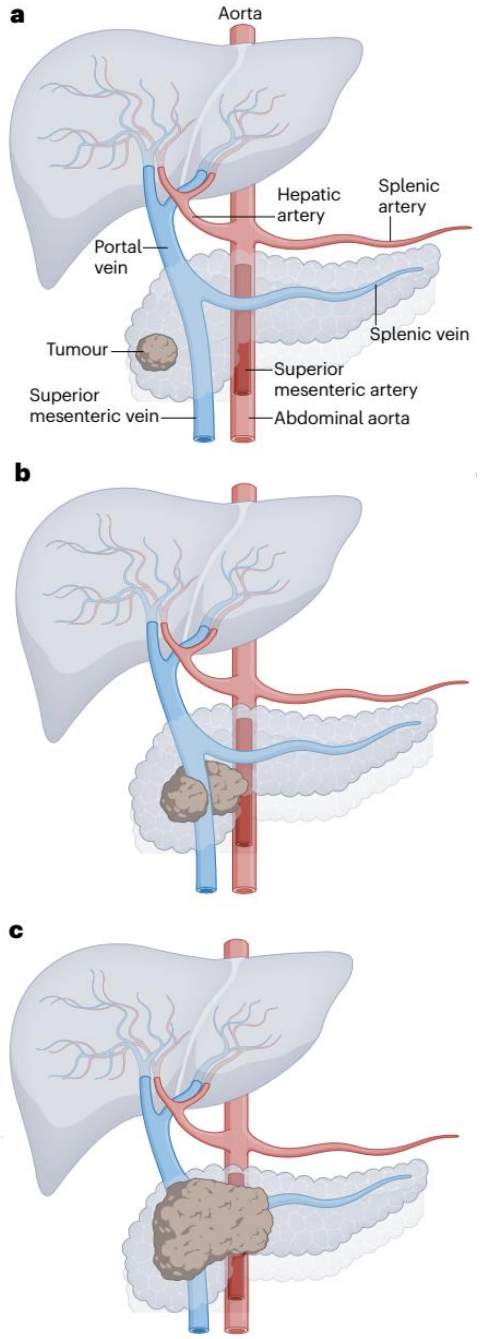
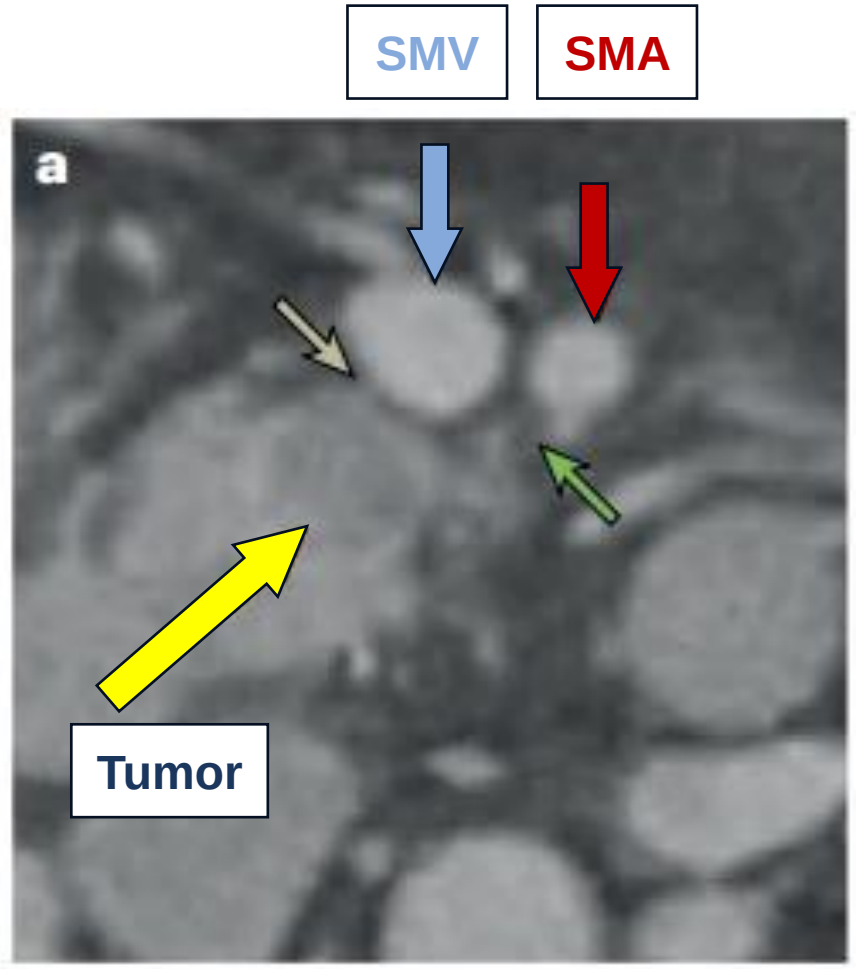


Springfield C *Nat Rev Clin Oncol* 2023

Resectable Pancreatic Cancer

- No arterial tumor contact
- No tumor contact with the SMV or PV or ≤180-degree contact without vein contour irregularity
- **Surgery first is still the gold standard**
- 6 months of adjuvant chemotherapy
  - FOLFIRINOX is the standard of care
  - Gemcitabine + capecitabine
  - Gemcitabine



Springfield C *Nat Rev Clin Oncol* 2023

Adjuvant Therapy – Randomized Trials

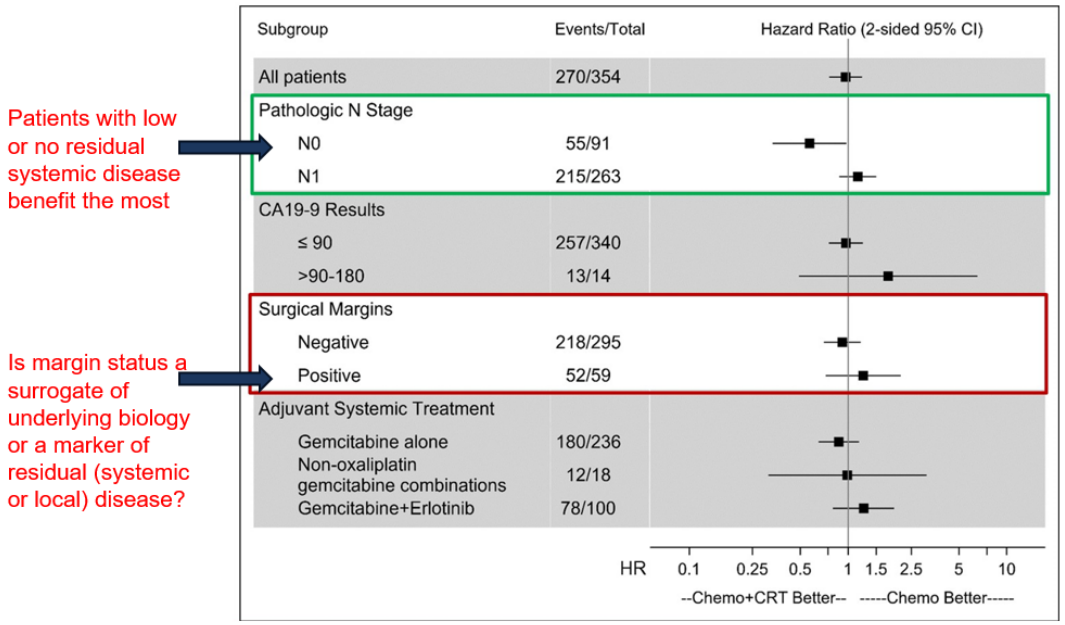
Study	Number of Patients	R1 Resection (%)	Treatment Assignment Median Survival Months	Treatment Assignment Median Survival Months	P Value
GITSG	49	0	5FU Chemoradiation 21.0	Observation 10.9	0.035
ESPAC-1	289	18	5FU/leucovorin 20.1	5FU-based Chemoradiation 15.5	0.009
CONKO-001	388	19	Gemcitabine 22.8	Observation 20.2	0.005
ESPAC-3	1088	18	Gemcitabine 23.6	5FU/leucovorin 23	0.39
ESPAC-4	730	60	Gemcitabine 25	Gemcitabine/capecitabine 28	0.032
PRODIGE 24/CCTG PA.6	493	40	Gemcitabine 35	FOLFIRINOX 54	0.003
APACT	866	24	Gemcitabine 37.7	Gemcitabine/nab-paclitaxel 41.8	0.0091

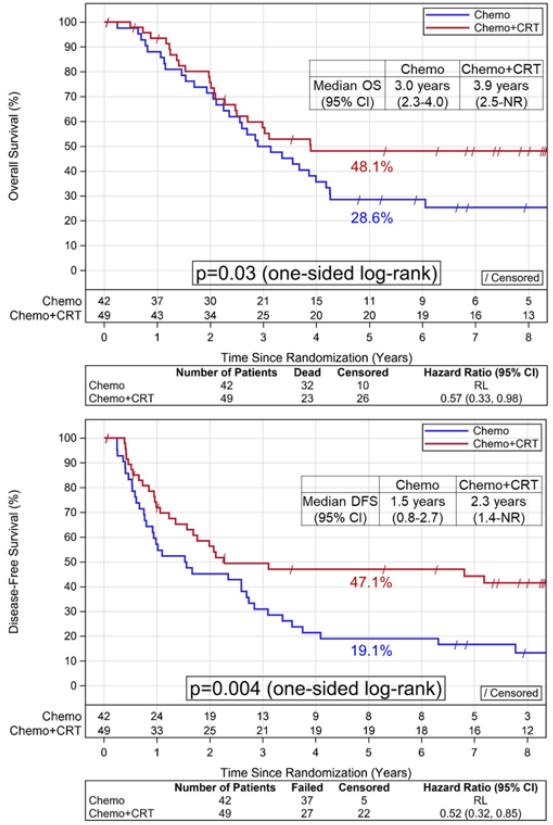
Oettle H *JAMA* 2007; Kaiser H *J Clin Oncol* 1985; Neoptolemos JP *N Engl J Med* 2004; Neoptolemos JP *JAMA* 2010; Conroy T *N Engl J Med* 2018; Tempero M *Ann Oncol* 2021; Neoptolemos JP *Lancet* 2017

No Defined Role for Adjuvant Radiation Therapy

- 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 3.2024)
- 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.

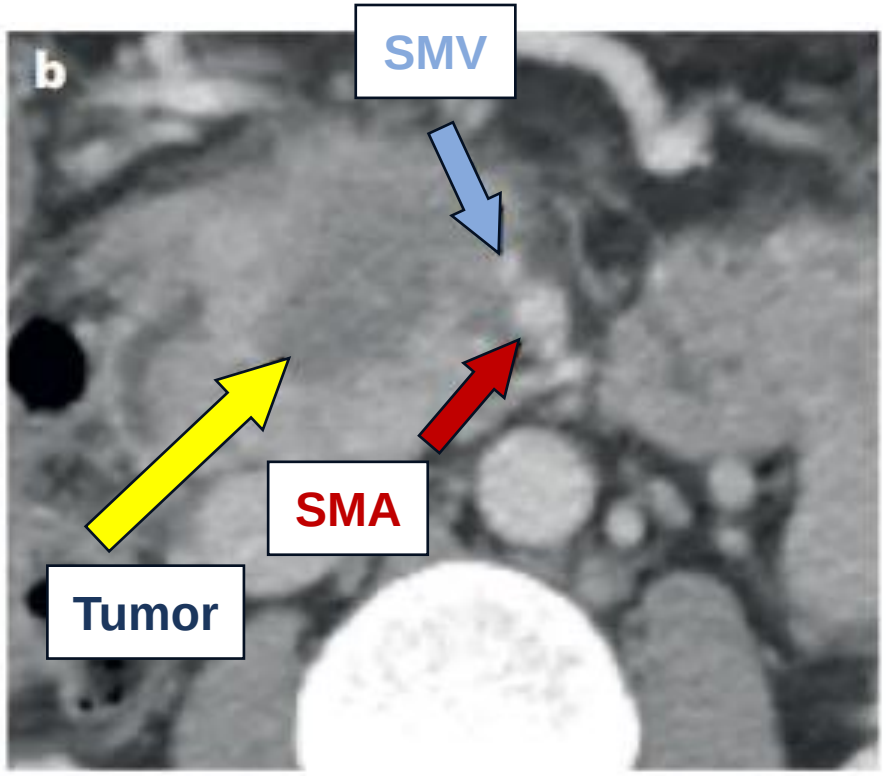




Presented by Goodman KA ASCO 2024

Borderline Resectable Pancreatic Cancer

- **Any tumor not “cleanly resectable” without vascular resection**
  - Venous involvement of any degree
  - Focal and non-circumferential involvement of the HA or SMA



Springfield C *Nat Rev Clin Oncol* 2023

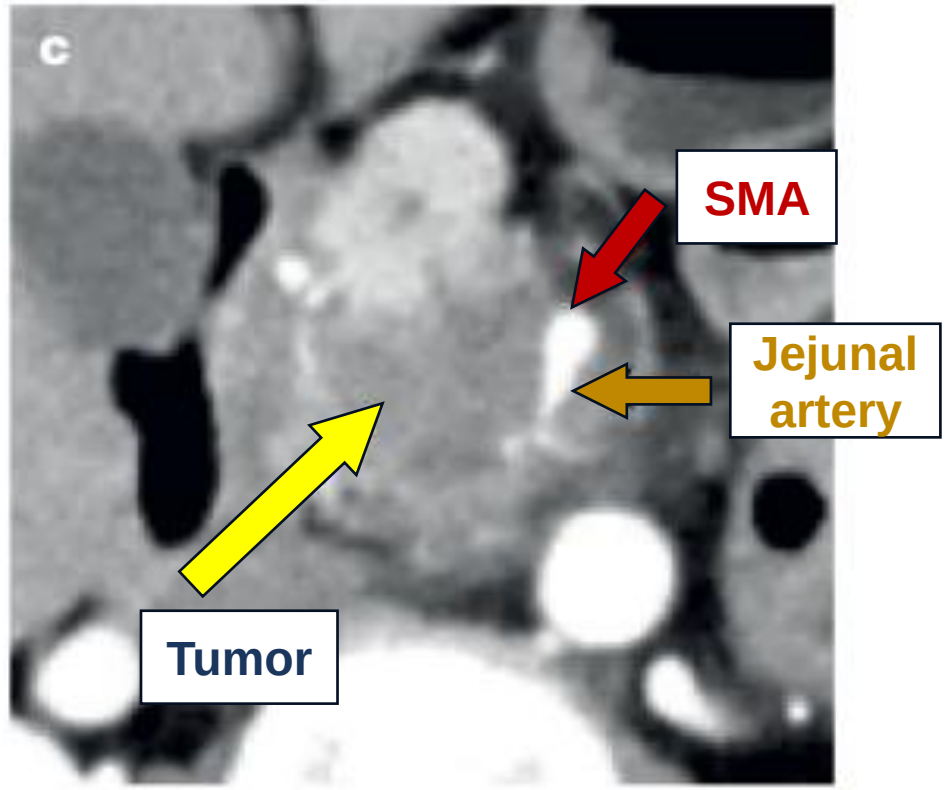
Several Trials Shed Light on Neoadjuvant Therapy

- Neoadjuvant **chemotherapy**:
  - ❖Tumor downstaging (e.g., fewer R1 resections)
  - ❖Less chemotherapy dose adjustments
  - ❖Patient selection (favorable tumor biology vs disease progression)
- Neoadjuvant **radiation** may increase margin-negative resection and local control, but its role remains uncertain

Trial	Population	Treatment arms	Survival outcomes
SWOG S1505	Resectable	mFOLFIRINOX>surgery >mFOLFIRINOX (n=55) vs GEM-NabP>surgery>GEM-NabP (n=47)	mOS: 23.2 vs 23.6 months 2-yr OS: 47% vs 48%
PREOPANC1	Resectable, borderline resectable	CRT+ GEM>surgery>GEM (n=54) vs surgery>GEM (n=59)	mOS: 15.7 vs 14.3 (p=0.025), NS in pts with resectable disease
ESPAC-5	Borderline resectable	Surgery>adjuvant CTX (n=32) vs neoadjuvant GEMCAP (n=20), FOLFIRINOX (n=20), or CAP-CRT (n=16)>surgery>adjuvant CTX	1-year OS: 39% vs 76% for the combined neoadjuvant groups (p=0.0052) 1-yr OS 78%, 80%, and 60% for neoadjuvant GEMCAP, FOLFIRINOX, and CAP-CRT subgroups, respectively
Alliance A021501	Borderline resectable	mFOLFIRINOX>surgery (n=54) vs mFOLFIRINOX>SBRT> surgery (n=56)	18-month OS: 66.7% vs 47.3% mOS: 29.8 vs 17.1 mo

Locally Advanced Pancreatic Cancer

- Radiographic evidence of **vascular encasement (T4)**
- **Unreconstructable**
- No evidence of distant metastatic disease
- Systemic therapy with a combination regimen (gemcitabine/nab-paclitaxel, FOLFIRINOX) x 6 mo
- After definitive therapy, re-evaluate with the multidisciplinary team to determine if now resectable
- In the absence of disease progression, consider chemoradiation with concurrent capecitabine (may improve PFS, not OS)



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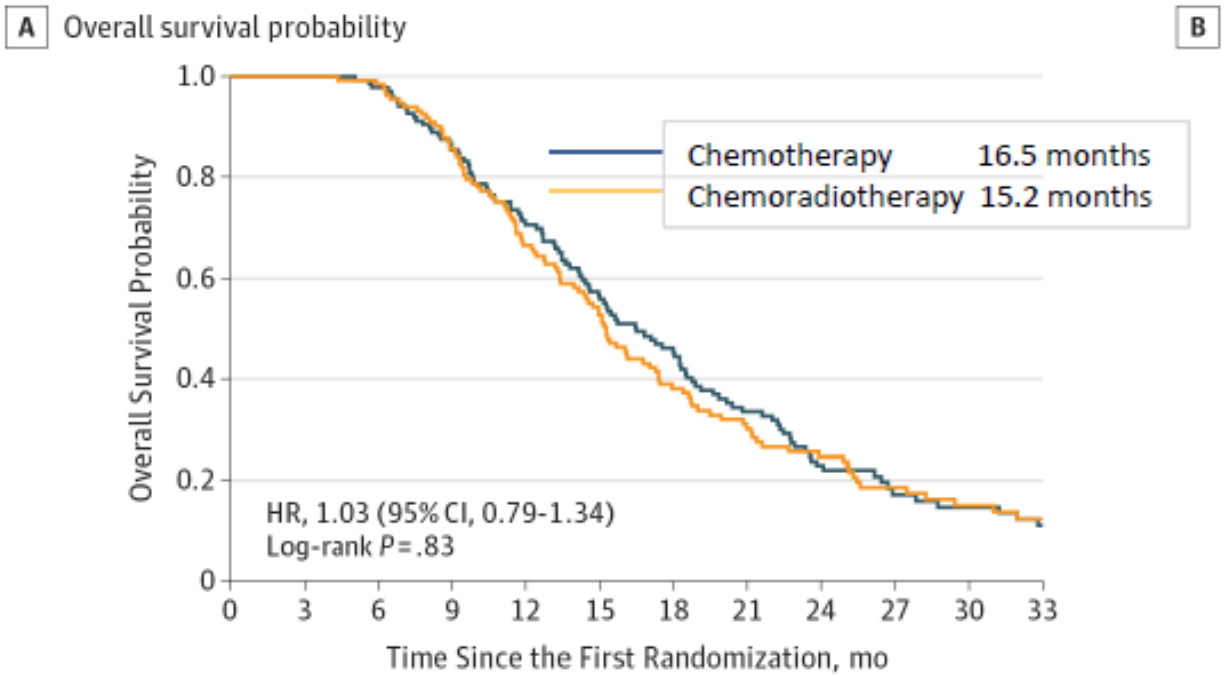
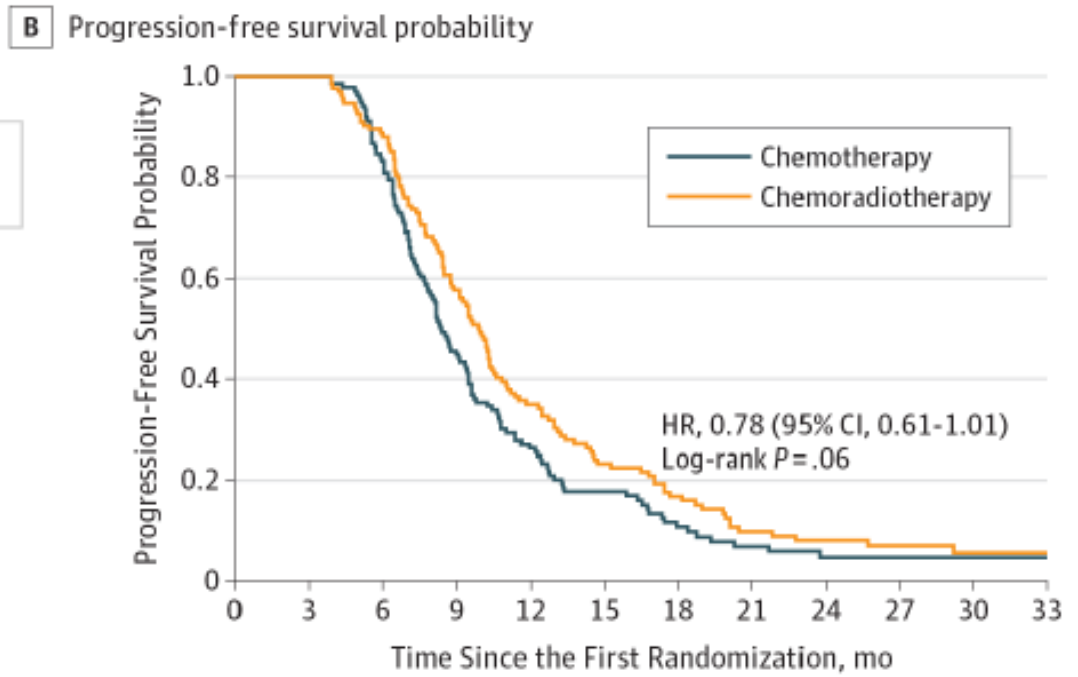
Locally Advanced Pancreatic Cancer: LAP 07 Trial



Chemotherapy												
No. at risk	136	136	133	117	94	70	55	39	24	14	12	8
No. of events	0	0	4	20	40	60	73	87	99	104	106	109
Chemoradiotherapy												
No. at risk	133	133	131	113	87	66	45	34	26	18	12	9
No. of events	0	0	3	20	45	63	80	89	96	101	105	106



Chemotherapy												
No. at risk	136	136	113	61	35	21	12	7	3	1	1	1
No. of events	0	0	24	76	101	112	119	124	125	125	125	125
Chemoradiotherapy												
No. at risk	133	133	117	76	45	30	21	11	8	7	4	4
No. of events	0	0	18	57	87	102	110	118	120	120	121	121

Hammel P et al *JAMA* 2016

Metastatic Pancreatic Cancer

- ALL patients should have early referral to palliative care
- Median survival in untreated patients is ~4 months

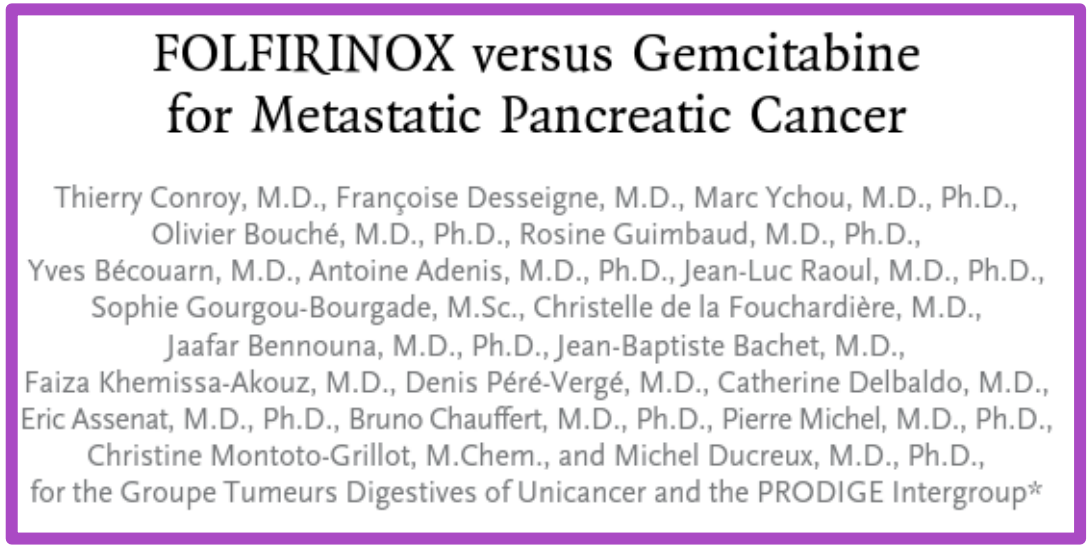
- mFOLFIRINOX (or NALIRIFOX) and gemcitabine plus nab-paclitaxel are frontline therapies
- If g*BRCA1/2* or *PALB2*, gemcitabine + cisplatin is an alternative regimen

- Performance status is linked to survival
  - Combination therapy in poor PS patients is detrimental
  - Patients with poor PS, advanced age, and significant comorbidities could still be considered candidates for single-agent gemcitabine therapy

Metastatic Pancreatic Cancer: Landmark Clinical Trials

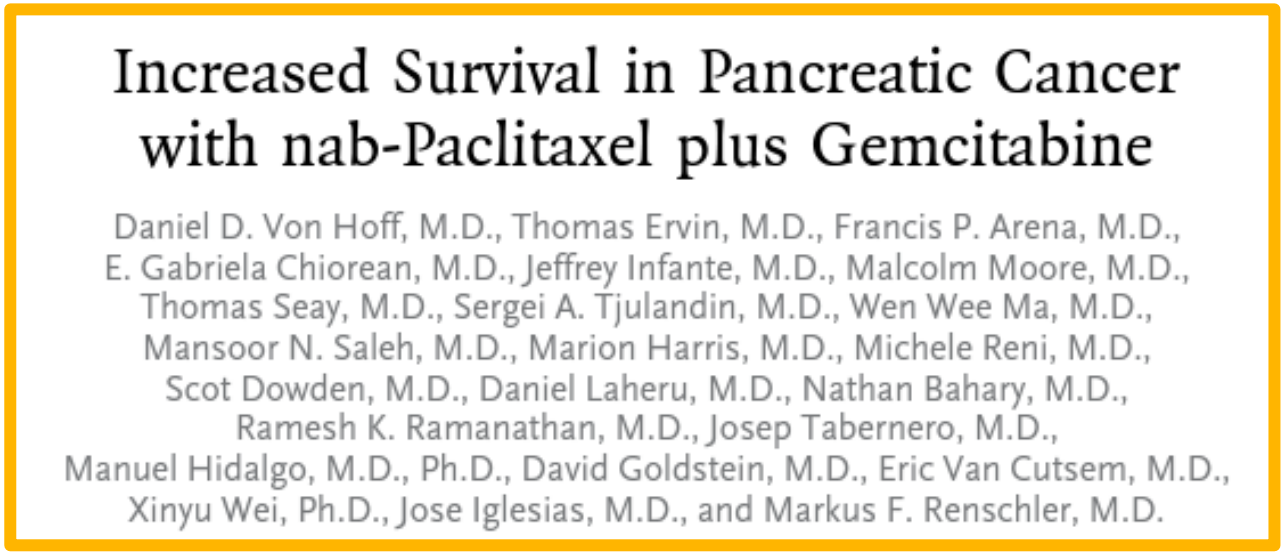
	Year	Investigational Therapy	Comparator Therapy	Overall Survival (Months)
Burris et al	1997	Gemcitabine	Fluorouracil	5.65 vs 4.41
Moore et al – NCIC CTG PA.3	2007	Gemcitabine + Erlotinib	Gemcitabine + placebo	6.24 vs 5.91
Conroy et al – PRODIGE4/ACCORD 11	2011	FOLFIRINOX	Gemcitabine	11.8 vs 6.8
Von Hoff et al – MPACT	2013	Gemcitabine + Nab-Paclitaxel	Gemcitabine	8.5 vs 6.7
Wang-Gillam et al – NAPOLI-1	2016	Nanoliposomal irinotecan + fluorouracil	Fluorouracil	6.1 vs 4.2
Kindler et al - POLO trial	2022	Olaparib	Placebo	NS (19.0 vs 19.2)
Wainberg et al – NAPOLI-3	2023	NALIRIFOX	Gemcitabine + nab-paclitaxel	11.1 vs 9.2

Metastatic Pancreatic Cancer: Frontline Therapy


FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

Thierry Conroy, M.D., Françoise Desseigne, M.D., Marc Ychou, M.D., Ph.D., Olivier Bouché, M.D., Ph.D., Rosine Guimbaud, M.D., Ph.D., Yves Bécouarn, M.D., Antoine Adenis, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Sophie Gourgou-Bourgade, M.Sc., Christelle de la Fouchardière, M.D., Jaafar Bennouna, M.D., Ph.D., Jean-Baptiste Bachet, M.D., Faiza Khemissa-Akouz, M.D., Denis Péré-Vergé, M.D., Catherine Delbaldo, M.D., Eric Assenat, M.D., Ph.D., Bruno Chauffert, M.D., Ph.D., Pierre Michel, M.D., Ph.D., Christine Montoto-Grillot, M.Chem., and Michel Ducreux, M.D., Ph.D., for the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup*

N Engl J Med 2011


Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

Daniel D. Von Hoff, M.D., Thomas Ervin, M.D., Francis P. Arena, M.D., E. Gabriela Chiorean, M.D., Jeffrey Infante, M.D., Malcolm Moore, M.D., Thomas Seay, M.D., Sergei A. Tjulandin, M.D., Wen Wee Ma, M.D., Mansoor N. Saleh, M.D., Marion Harris, M.D., Michele Reni, M.D., Scot Dowden, M.D., Daniel Laheru, M.D., Nathan Bahary, M.D., Ramesh K. Ramanathan, M.D., Josep Tabernero, M.D., Manuel Hidalgo, M.D., Ph.D., David Goldstein, M.D., Eric Van Cutsem, M.D., Xinyu Wei, Ph.D., Jose Iglesias, M.D., and Markus F. Renschler, M.D.

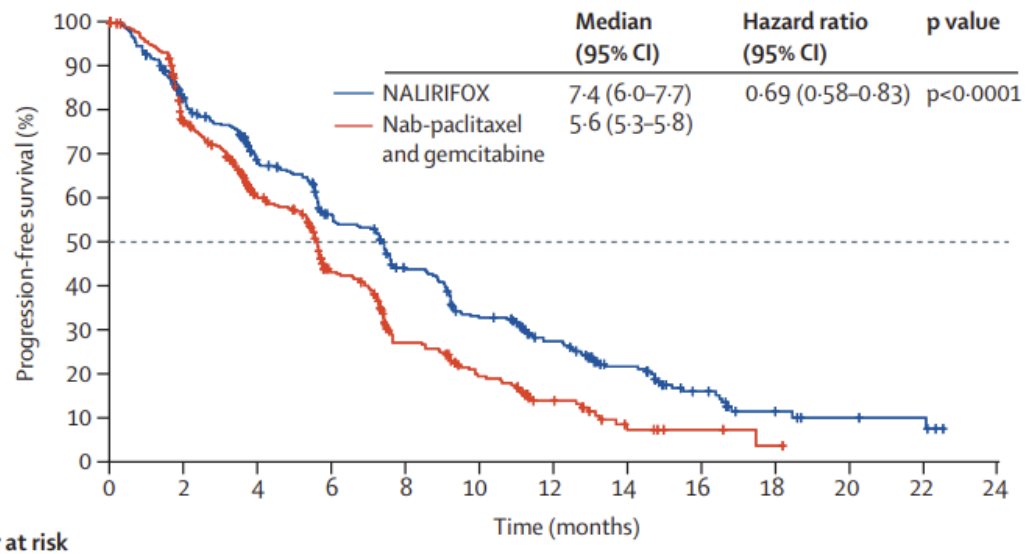
N Engl J Med 2013

- N=342, treatment-naïve, PS 0-1
- Gemcitabine vs FOLFIRINOX
- FOLFIRINOX improved:
  - ❖ ORR, 32% vs 9%
  - ❖ Median PFS, 6.4 vs 3.3 months
  - ❖ Median OS, 11.1 vs 6.8 months

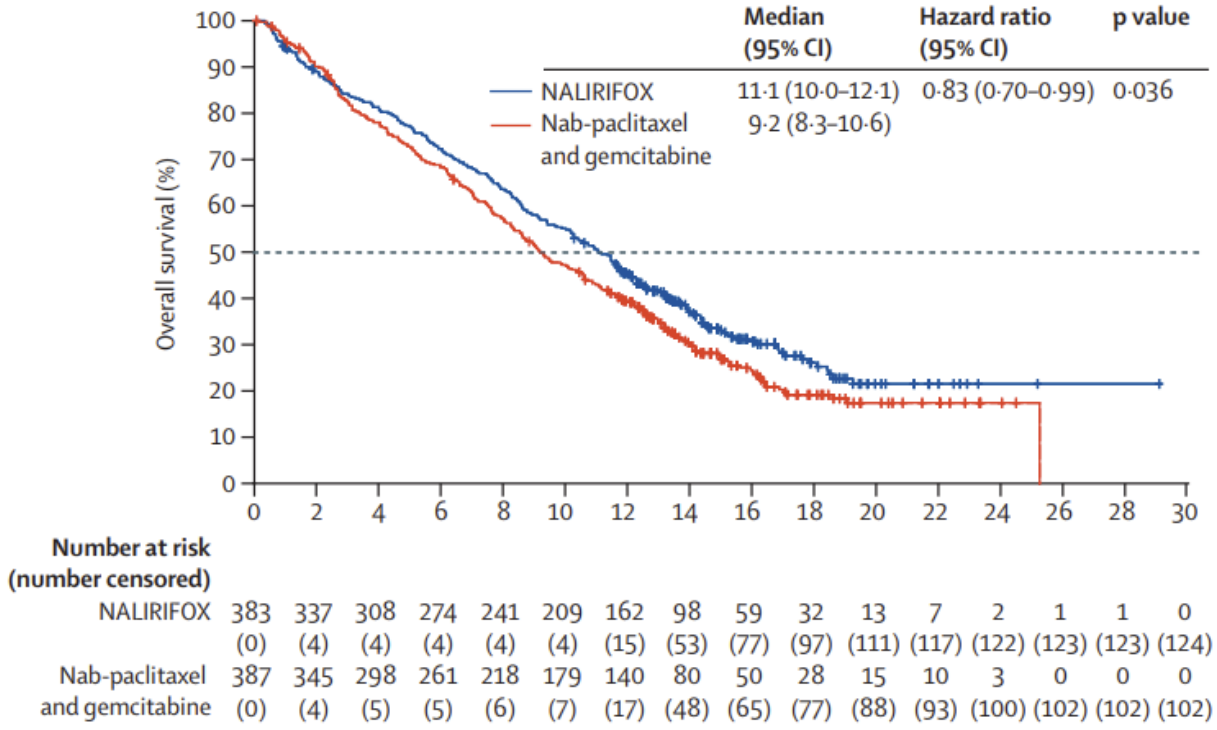
- N=861, previously untreated, KPS ≥70
- Gemcitabine vs gemcitabine plus nab-paclitaxel
- Gemcitabine/nab-paclitaxel improved:
  - ❖ ORR (23% vs 7%)
  - ❖ Median OS (8.5 vs 6.7 months)

Improved OS With 1st-Line Triplet vs Doublet Chemotherapy (NAPOLI 3)

Progression-free survival (PFS)



Overall survival (OS)



Wainberg ZA *Lancet* 2023

Metastatic Pancreatic Cancer: Germline BRCA Pathogenic Mutation

Randomized, Multicenter, Phase II Trial of Gemcitabine and Cisplatin With or Without Veliparib in Patients With Pancreas Adenocarcinoma and a Germline *BRCA/PALB2* Mutation

J Clin Oncol 2019

- N=50, gBRCA or PALB2, stage III/IV, PS 0-1
- Adding veliparib to gemcitabine plus cisplatin did not significantly improve ORR (74 vs 65%), DCR (100 vs 78%), median PFS (10.1 vs 9.7 mo), or OS (15.5 vs 16.4 mo).
- 2- and 3-year survival rates for the entire cohort were 31 and 18%, respectively

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Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D., Eric Van Cutsem, M.D., Ph.D., Teresa Macarulla, M.D., Ph.D., Michael J. Hall, M.D., Joon-Oh Park, M.D., Ph.D., Daniel Hochhauser, M.D., Ph.D., Dirk Arnold, M.D., Ph.D., Do-Youn Oh, M.D., Ph.D., Anke Reinacher-Schick, M.D., Ph.D., Giampaolo Tortora, M.D., Ph.D., Hana Algül, M.D., Ph.D., M.P.H., Eileen M. O'Reilly, M.D., David McGuinness, M.Sc., Karen Y. Cui, M.D., Ph.D., Katia Schlienger, M.D., Ph.D., Gershon Y. Locker, M.D., and Hedy L. Kindler, M.D.

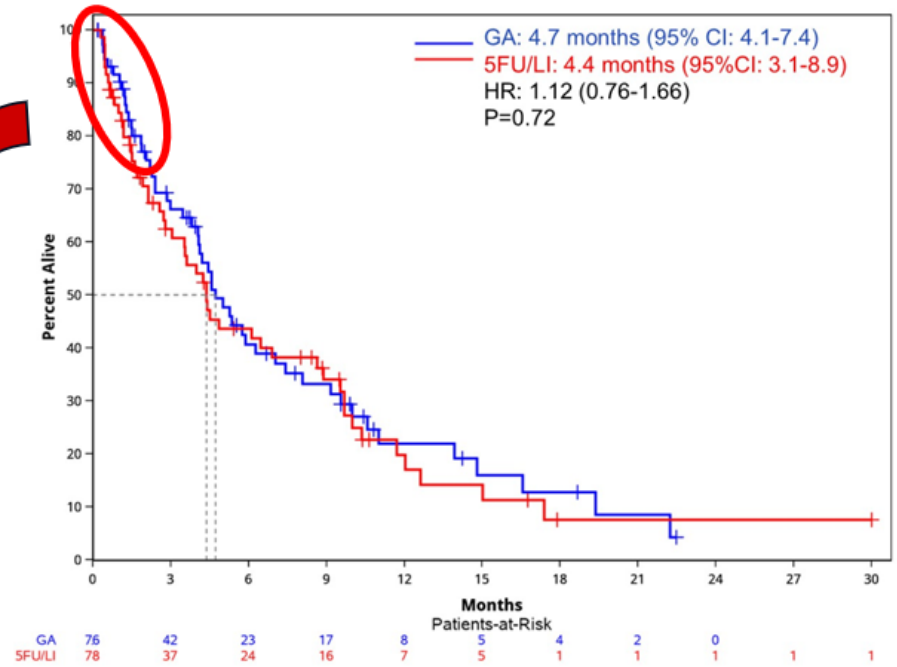
N Engl J Med 2019

- N=154, gBRCA-mutated, stage IV, no progression on ≥16 weeks of 1st-line platinum-based chemotherapy
- Placebo vs maintenance Olaparib
- Olaparib improved:
  - ❖ ORR, 23 vs 10%
  - ❖ Median DOR, 4.9 vs 3.7 mo
  - ❖ Median PFS, 7.4 vs 3.8 mo
  - ❖ No difference in median OS (19.0 vs 19.2 mo)

Kindler HL et al *J Clin Oncol* 2022

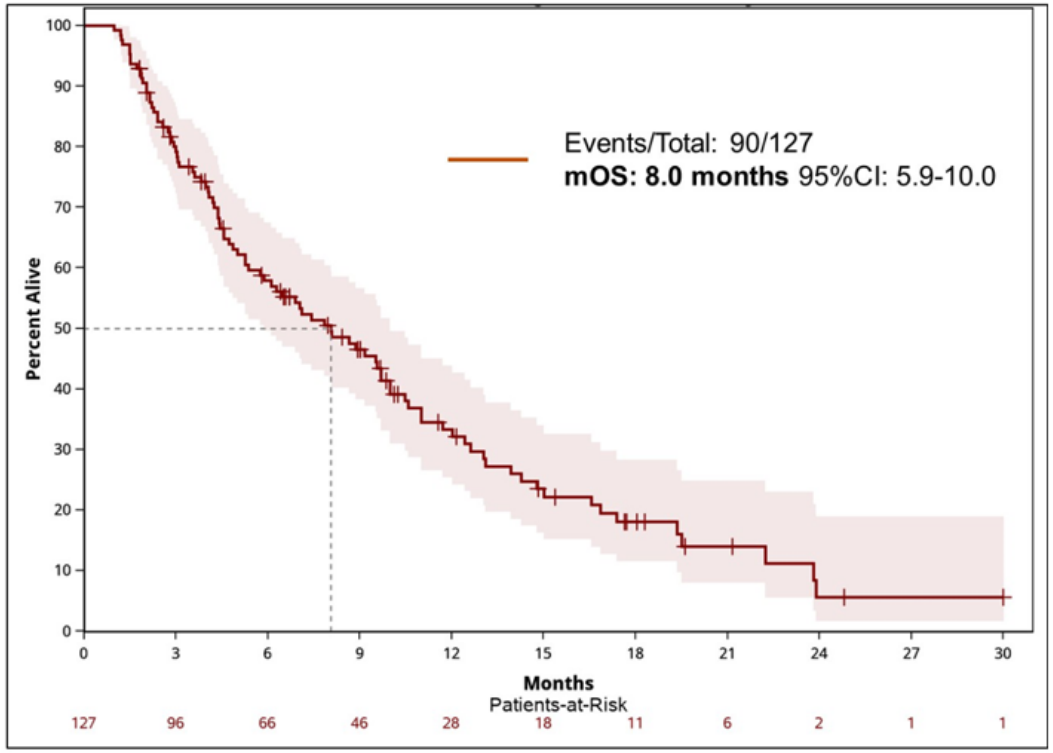
EA2186 (GIANT) Study: Poor Outcomes Among Elderly Patients

OS (ITT)



There is a subgroup of patients who perhaps need aggressive supportive care more than chemotherapy.

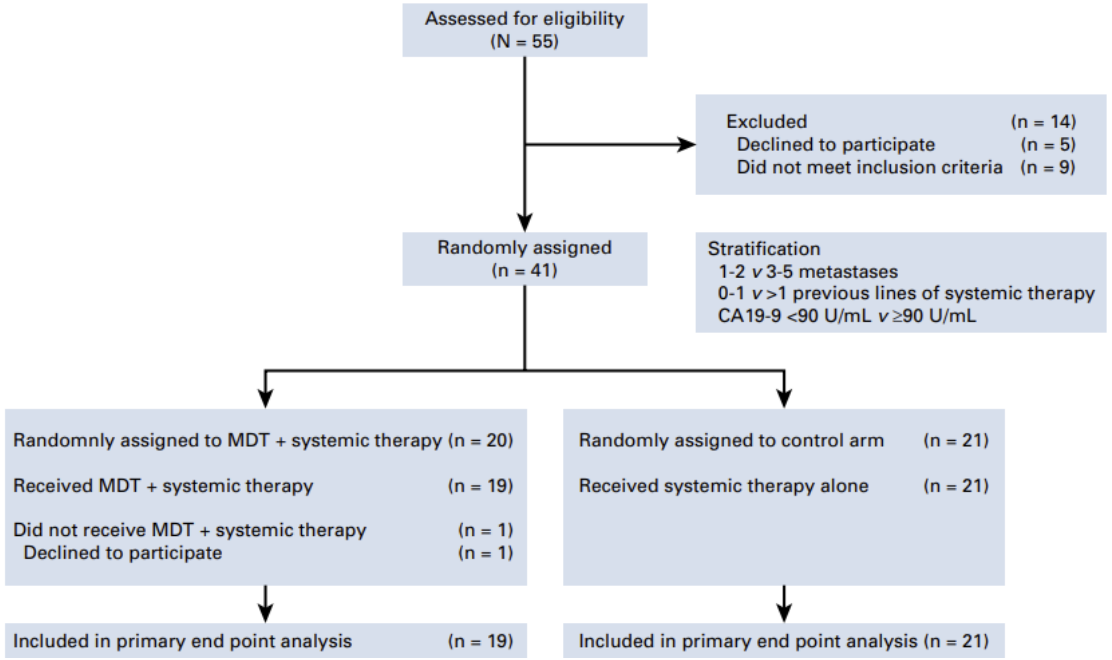
OS (≥4 weeks of treatment)

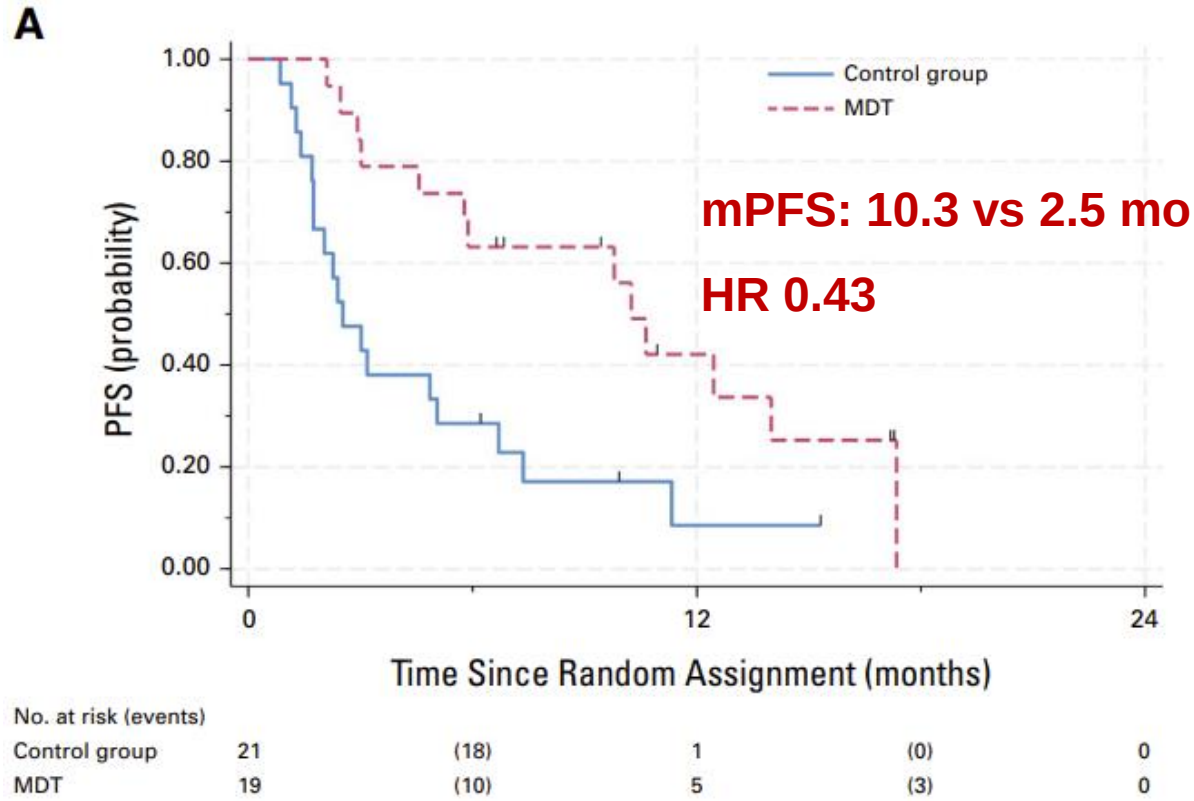


Only 72% of patients received ≥ 2 chemotherapy doses.

Presented by Dotan E ASCO 2024

EXTEND Phase II trial: Metastasis-Directed Therapy (MDT) for Select Patients with Oligometastatic PDA



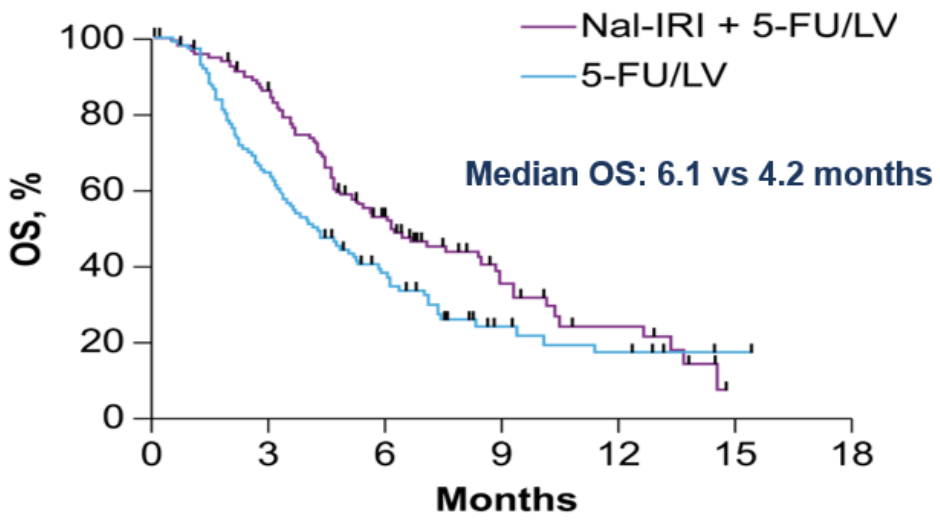


Ludmir EB *J Clin Oncol* 2024

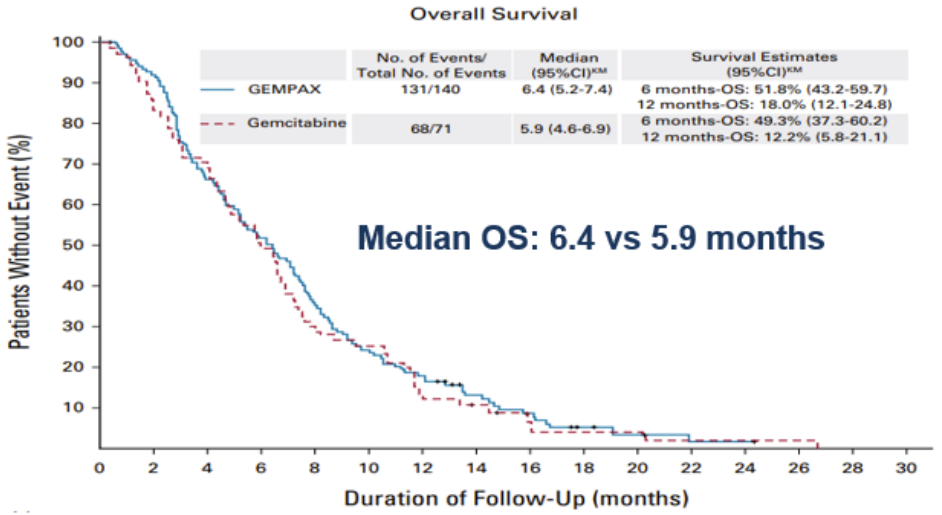
Metastatic Pancreatic Cancer: Second-Line Treatment and Beyond

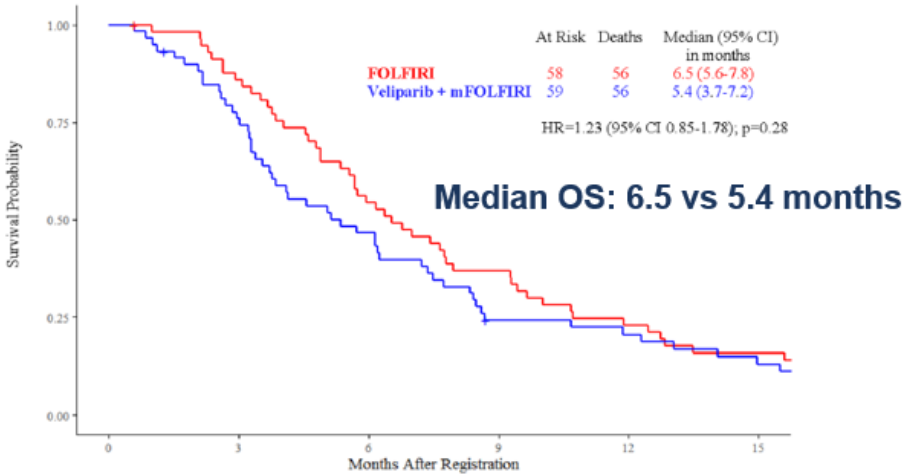
- Consider enrollment on a clinical trial
- Treatment choice is often based on first-line regimen, PS, and organ function
- **NAPOLI-1**: liposomal irinotecan plus 5FU and LV significantly improved OS compared with patients in the 5FU and LV (6.1 months vs 4.2 months, HR 0.67)
- Useful in certain circumstances:
  - Pembrolizumab if MSI-H/dMMR, or TMB-H defined as ≥10 mut/Mb
    - Dostarlimab (MSI-H/dMMR) and nivolumab + ipilimumab/nivolumab (TMB-H) are alternative regimens
  - Larotrectinib, entrectinib, or repotrectinib if *NTRK* gene fusion positive
  - Dabrafenib + trametinib if *BRAF V600E* mutation positive
  - Selpercatinib if *RET* gene fusion positive
  - Adagrasib or sotorasib if *KRAS G12C* mutation positive
  - Trastuzumab deruxtecan if HER2 positive (IHC 3+)

Median OS ~6 Months With 2nd-line Chemotherapy

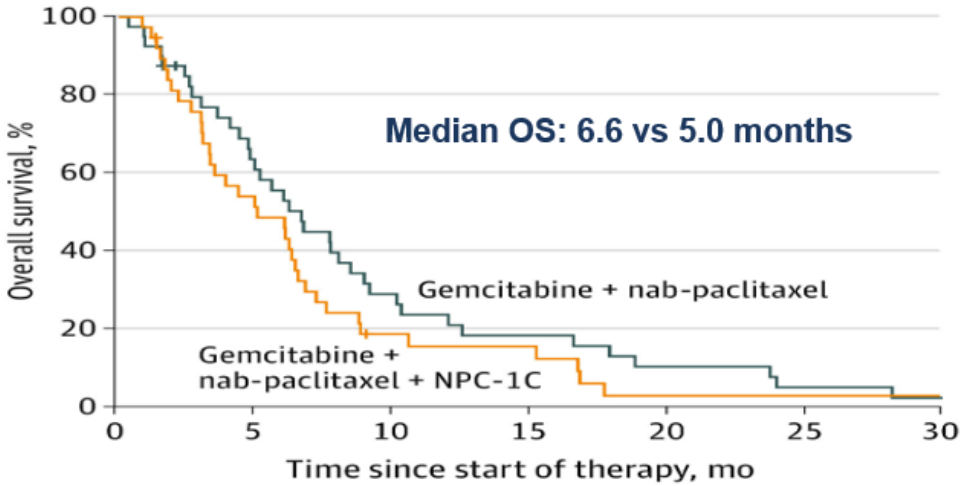


Wang Gillam A, et al. *Lancet* 2016





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

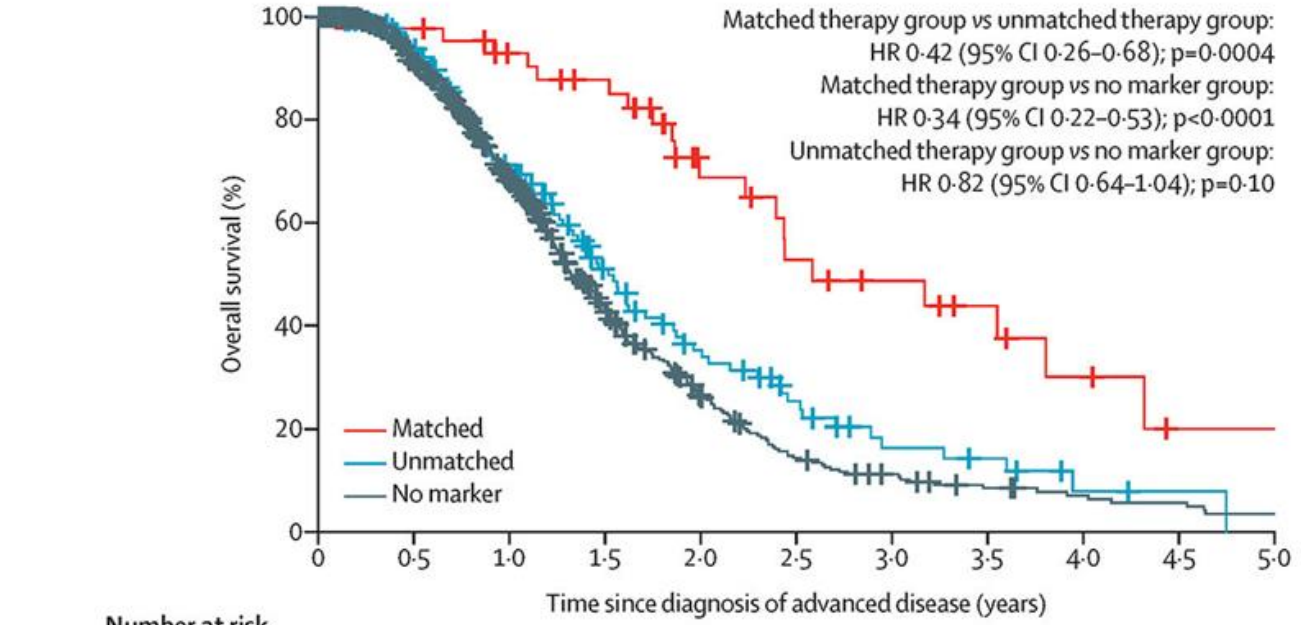
Molecular Profiling of Pancreatic Cancer

- **All patients with locally advanced or metastatic PDA**
- Testing on tumor tissue preferred
- Consider re-biopsy at progression if adequate tissue not available
- Consider ctDNA if tumor tissue is not feasible

NCCN Guidelines Version 3.2024

Know Your Tumor Registry Trial

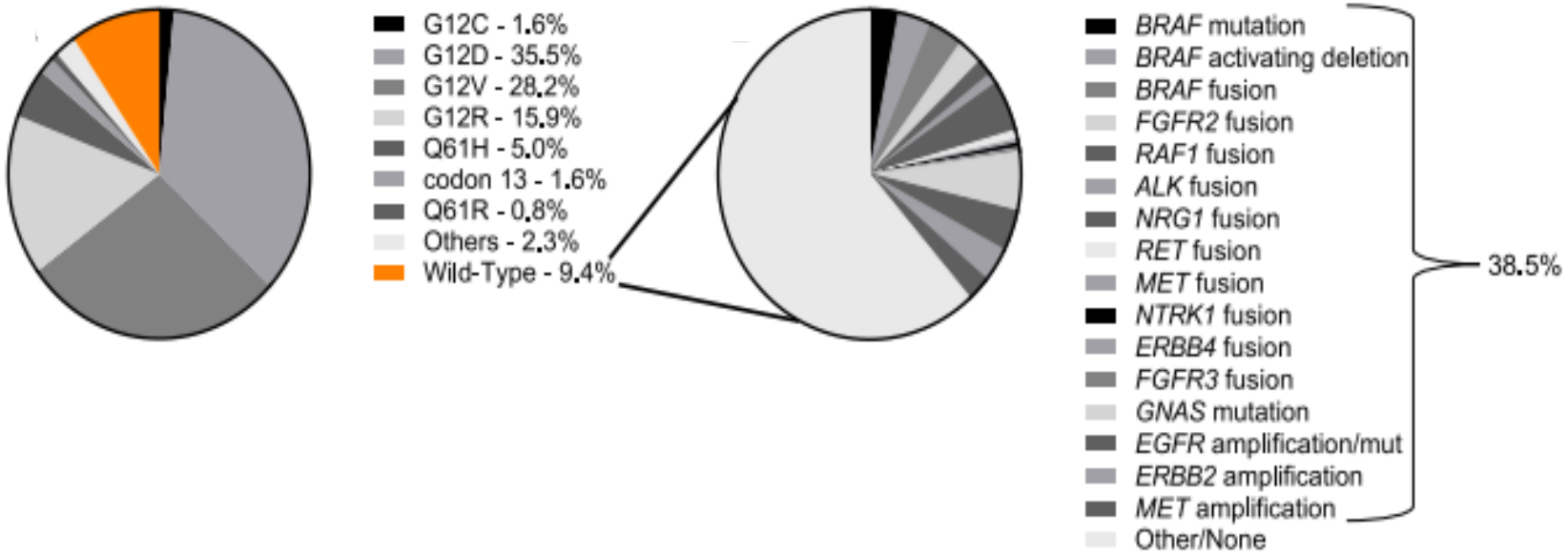
Patients with actionable alterations derive considerable benefit from receiving a matched therapy.



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

Molecular Alterations in Pancreatic Cancer



BRAF V600E: Dabrafenib/trametinib

NTRK fusion: Entrectinib, larotrectinib, repotrectinib

RET fusion: Selpercatinib

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

KRAS G12C: Adagrasib, Sotorasib

HER2 IHC 3+: T-DXd

- Germline testing and tumor sequencing identifies predictive biomarkers for investigational or newly approved drugs in ~20% of pancreas cancer
- Enrichment of actionable gene alterations among KRAS WT (8-10%)
- Tumors deficient in homologous recombination repair are clinically relevant
- dMMR/MSI-high ~1%
- Targeting *RAS* mutations (e.g., KRAS G12C inhibitors)

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

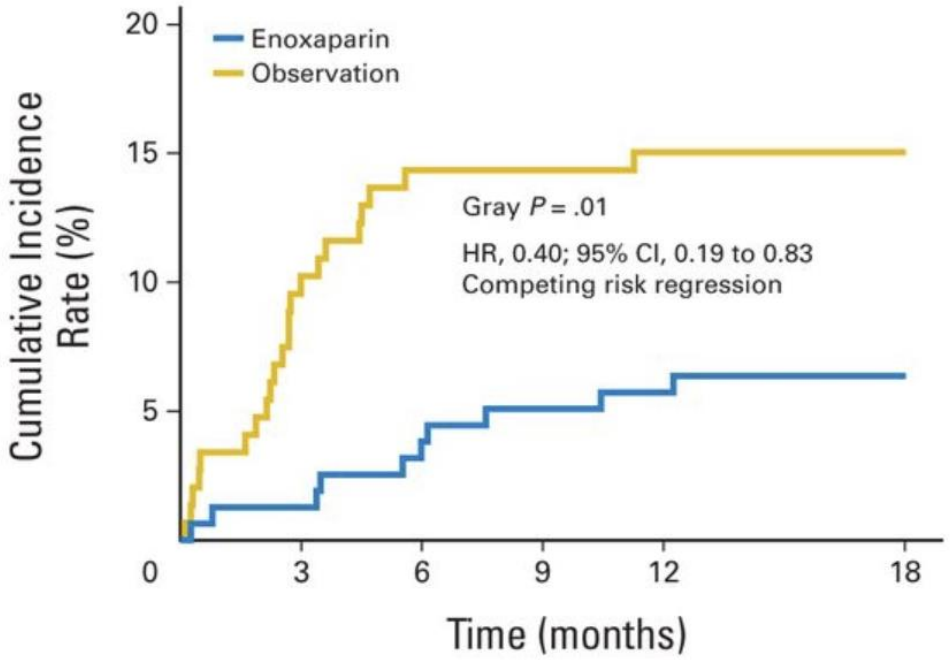
Principles of Palliation and Supportive Care

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
Pain	• Opioids +/- EUS-guided celiac plexus neurolysis • SBRT
Anorexia	• Daily low-dose olanzapine
Depression and fatigue	• Formal palliative care or mental health provider evaluation • Exercise program +/- PT
Exocrine pancreatic insufficiency and nutrition	• Pancreatic enzyme replacement if EPI • Nutritional evaluation with a registered dietician

NCCN Guidelines Version 3.2024

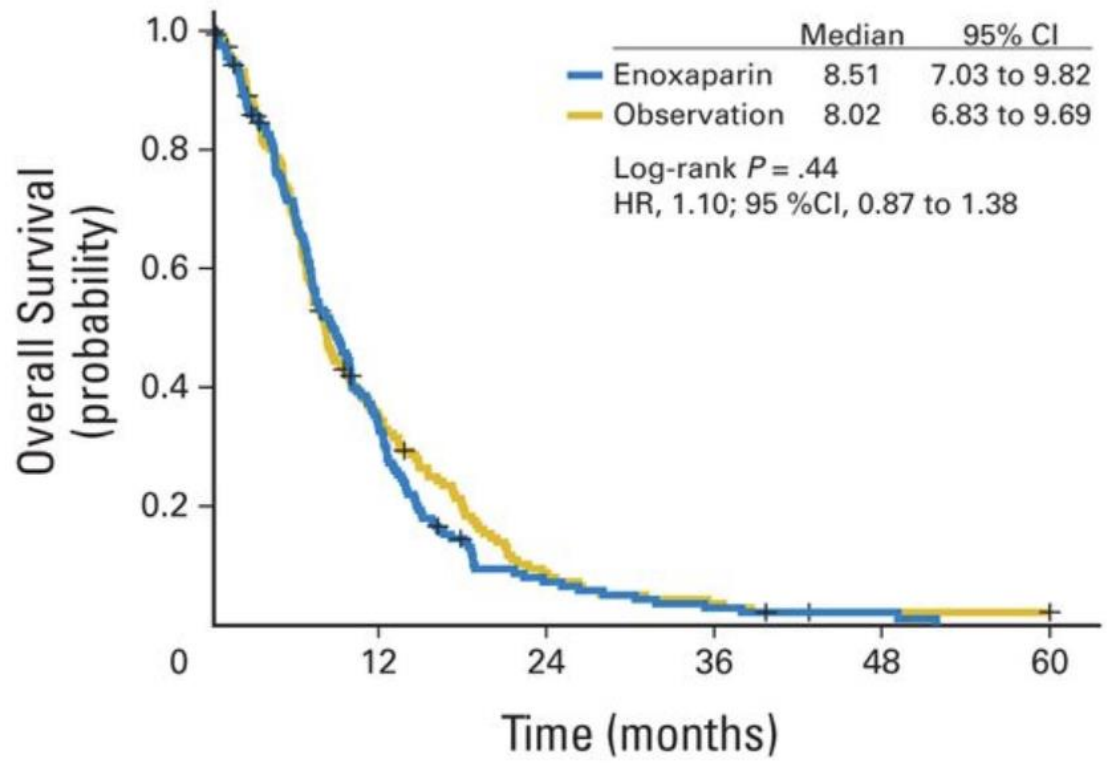
Prophylactic LMWH Decreases VTE but No OS Benefit

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

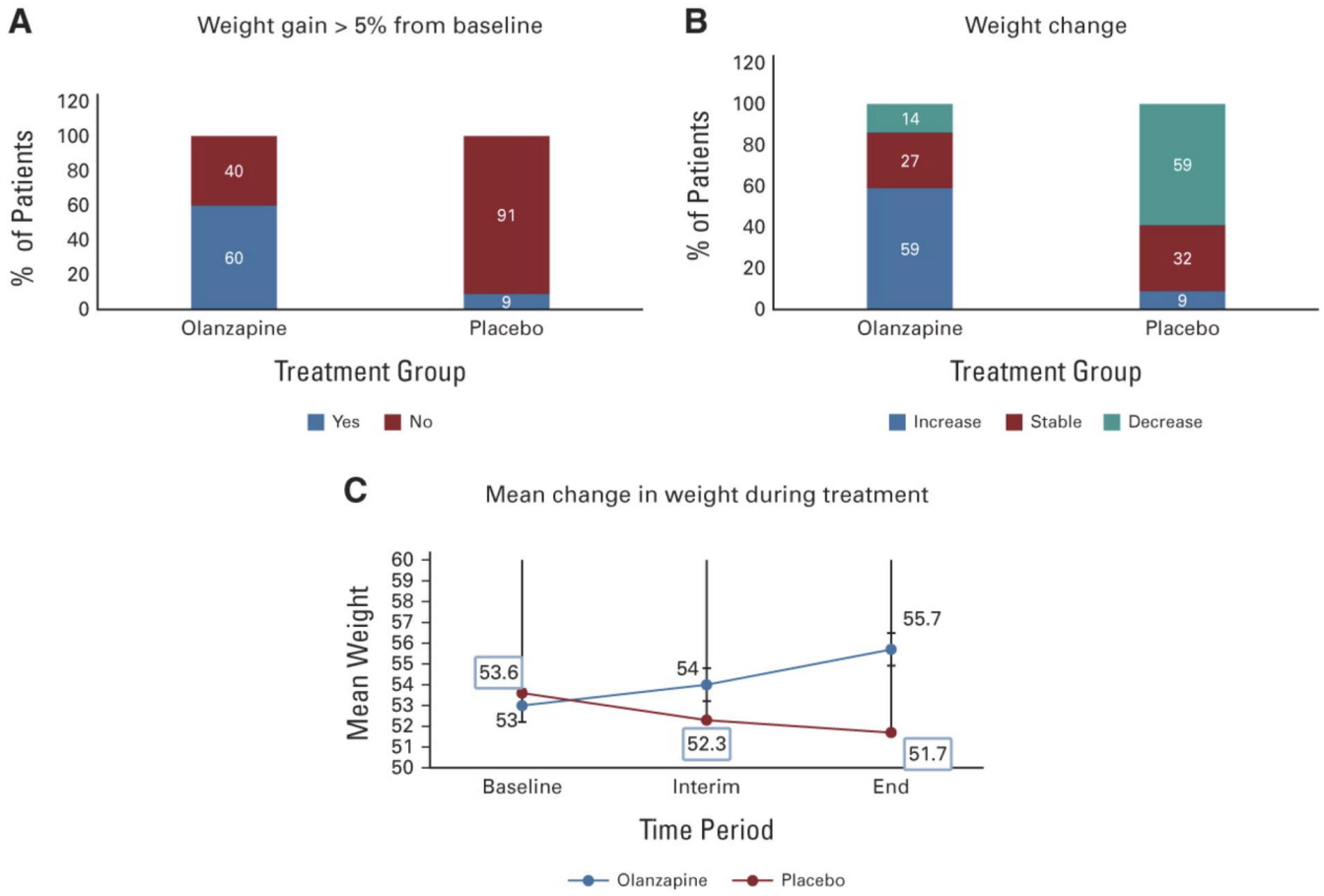


No. at risk						
Enoxaparin	160	49	10	4	2	0
Observation	152	48	11	5	2	2

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

- All patients require germline testing and those with locally advanced, unresectable or metastatic disease need somatic mutation testing (tissue)
- Multiphase CT chest, abdomen, and pelvis should be performed to assess extent of disease
- Determination of resectability must be made with a multi-disciplinary team
- Upfront surgical resection followed by 6 months of adjuvant chemotherapy (mFOLFIRINOX preferred) is standard of care for resectable PDA
- mFOLFIRINOX (or NALIRIFOX) and gemcitabine + nab-paclitaxel are appropriate 1st-line regimens for patients with metastatic PDA

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