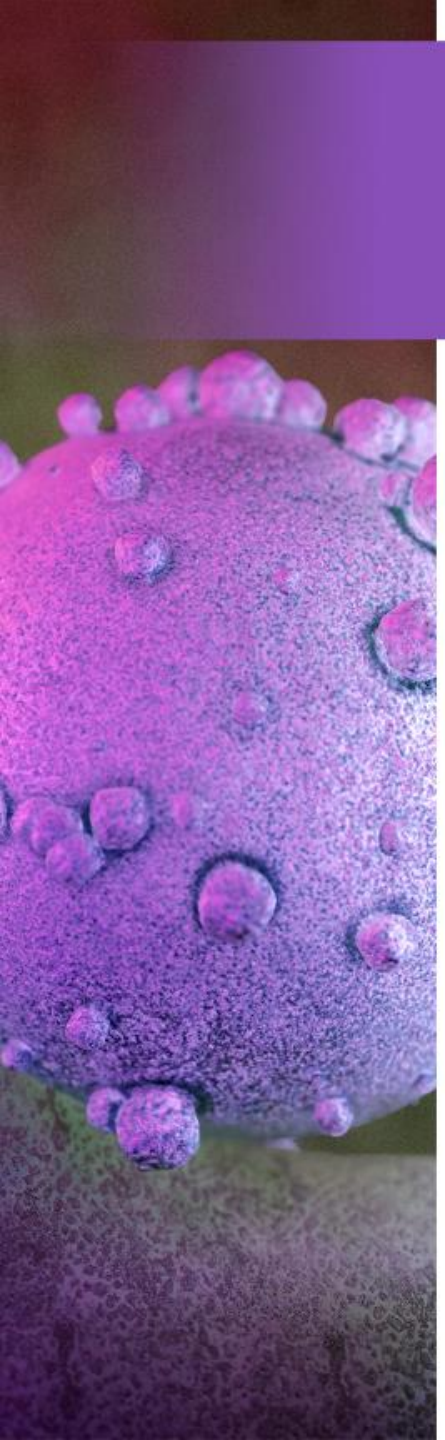
Improving Outcomes in Pancreatic Cancer

Pharmacist Updates on the Expanding Treatment Landscape



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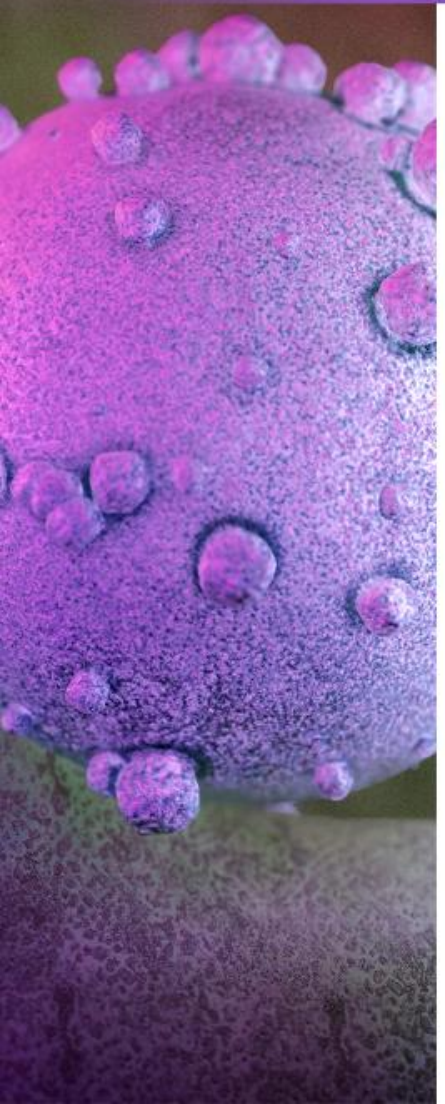
Faculty



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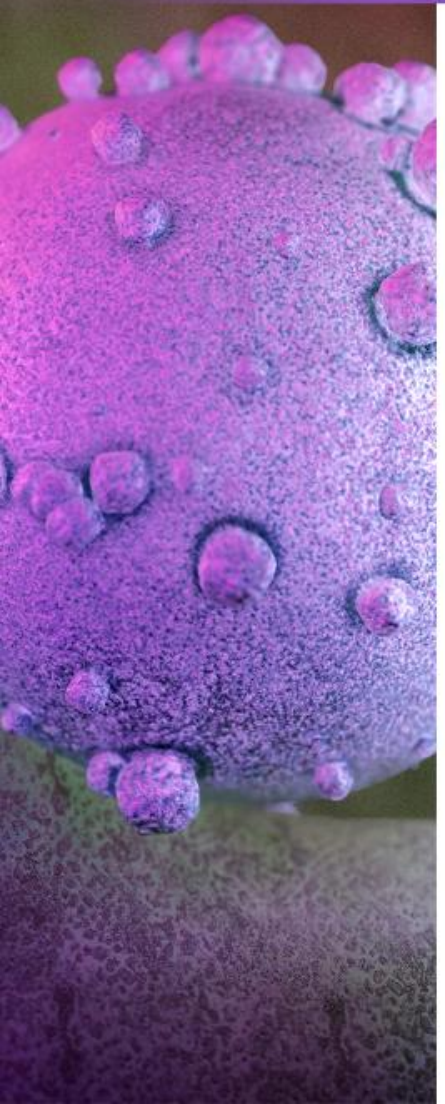
Dr. Soefje earned his Bachelor's Degree in Pharmacy from The University of Texas at Austin and then, after almost 5 years of hospital practice, he returned to earn a PharmD from the joint program at The University of Texas at Austin and The University of Texas Health Sciences Center at San Antonio. He completed an ASHP-accredited specialty residency in oncology from the Audie L. Murphy Veterans Hospital and then a Clinical Pharmacology Fellowship from The University of Texas M.D. Anderson Cancer Center in Houston. He has also obtained an MBA focusing on healthcare from The George Washington University. He has been recognized as a Fellow by the American College of Clinical Pharmacy and the Hematology Oncology Pharmacy Association. Dr. Soefje has been board certified in oncology pharmacy since 2000.

Disclosures



Dr. Soefje has disclosed that he has served on the Pfizer Speaker's Bureau.

The clinical reviewer, **Megan May**, **PharmD, BCOP**, has no actual or potential conflict of interest in relation to this program.

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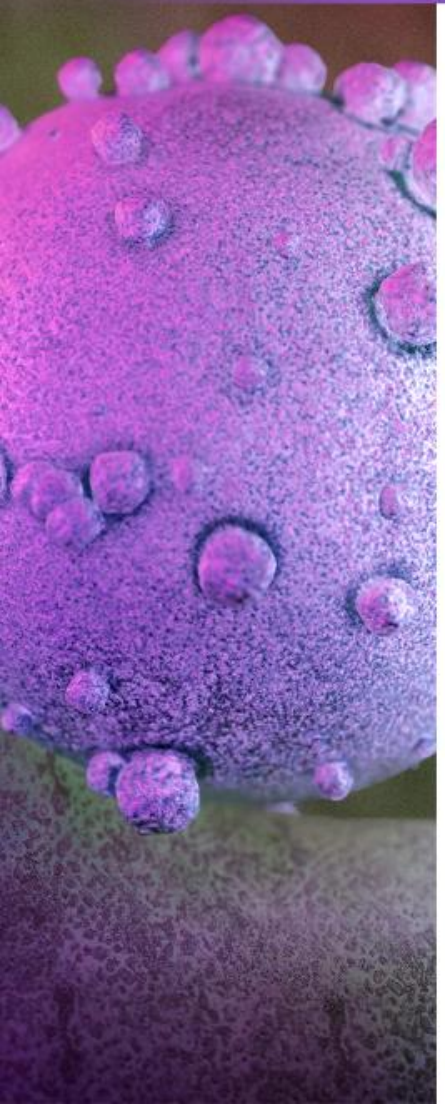

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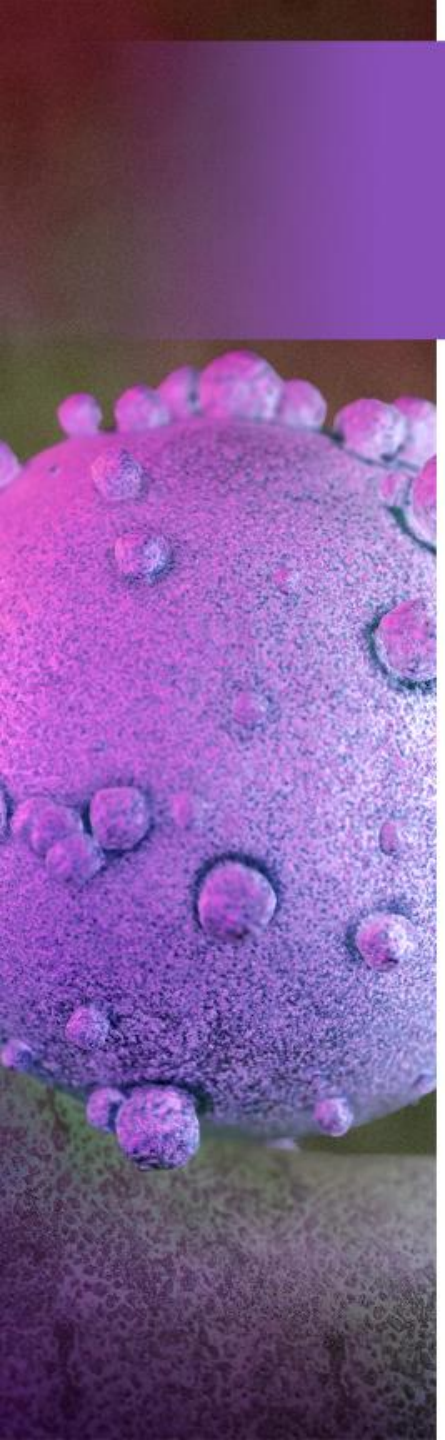
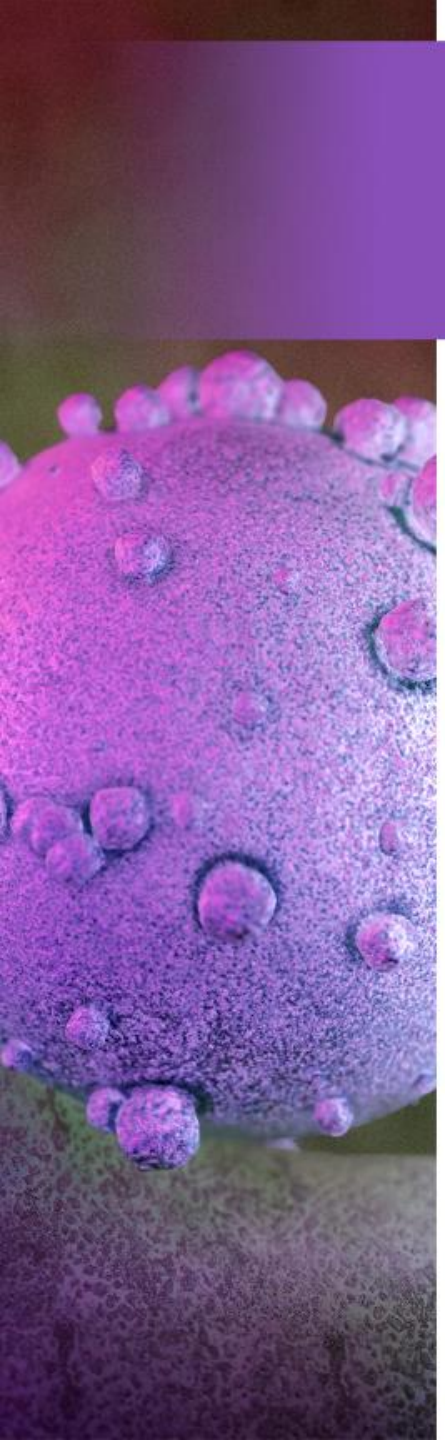


Learning Objectives

- **Discuss** the standard-of-care options for pancreatic cancer patients
- **Describe** the mechanisms by which pancreatic cancer interacts with the immune system
- **Examine** emerging data for the treatment of pancreatic cancer
- **Demonstrate** pharmacist-driven strategies to effectively manage patients with pancreatic cancer



Presentation Outline: Pancreatic Cancer

1. Introduction

- Epidemiology
- Etiology
- Diagnosis
- Staging
- Prognosis

2. Current treatment

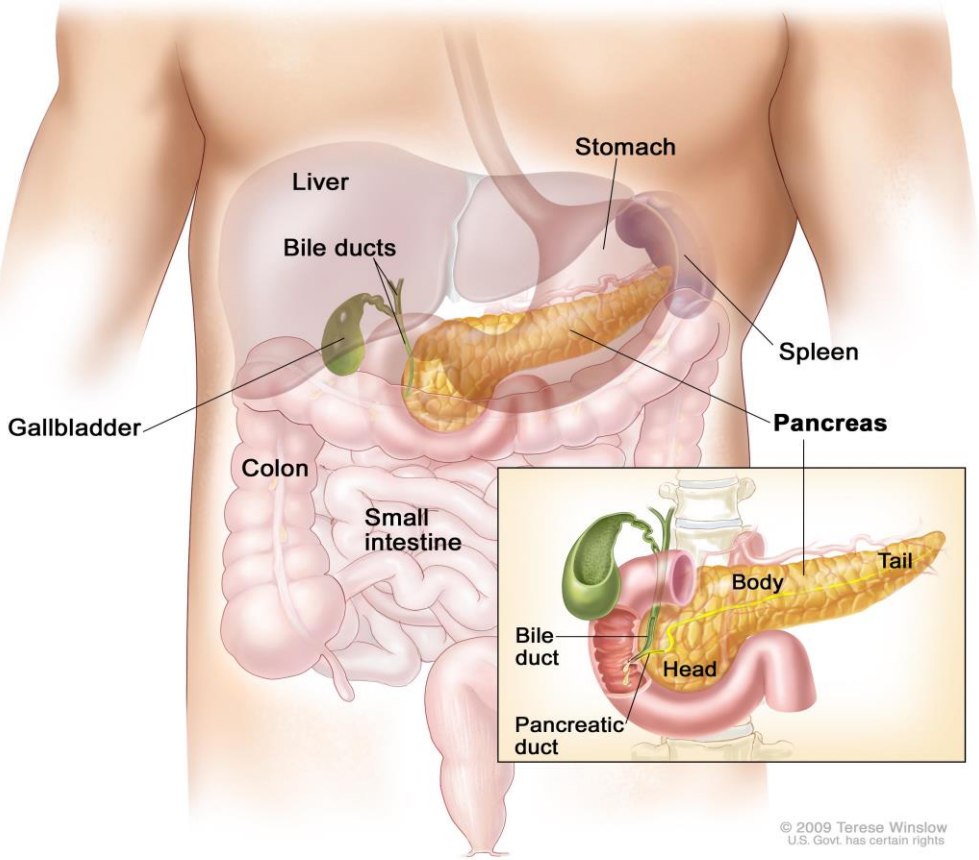
- Surgery
- Radiation
- Chemotherapy
  - Neoadjuvant therapy
  - Adjuvant therapy
  - Advanced disease
    - Chemotherapy
    - Immunotherapy
    - Targeted therapy
    - Vaccines
    - Adoptive cellular therapy

3. Pharmacist considerations

- Recognition, prevention, and management of toxicities
  - Pain management
  - Anorexia and weight loss
  - Neutropenia and neutropenic fever
  - Diarrhea
  - Peripheral neuropathy

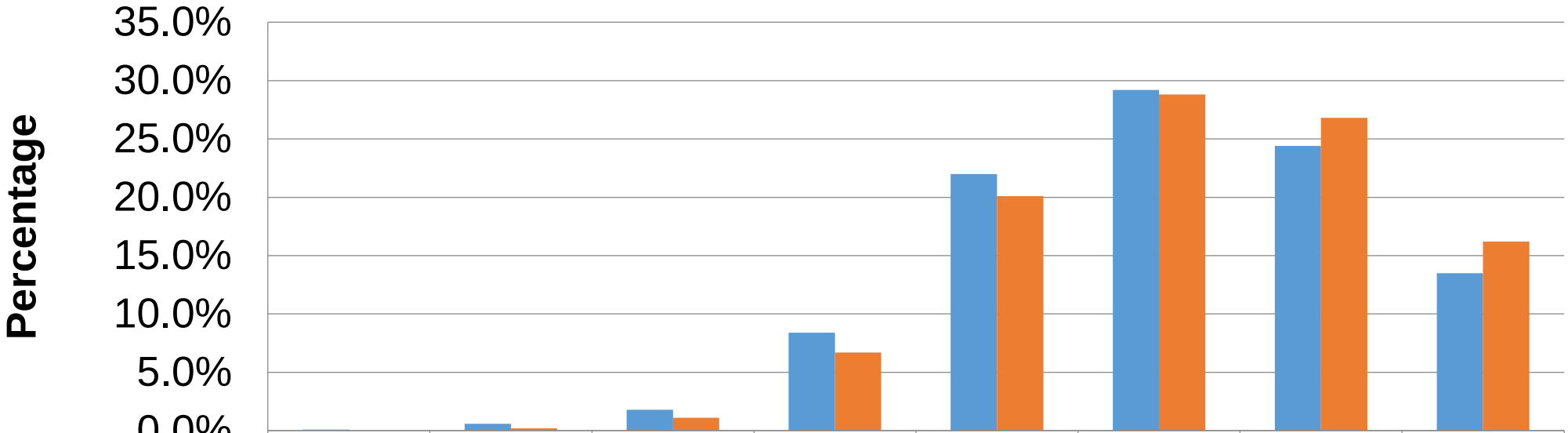
Pancreatic Cancer

- Total new cancers (2019)
  - 1,762,450
  - New pancreatic cancers: 56,770
- Total cancer deaths (2019)
  - 606,880
  - Pancreatic cancer deaths: 45,750
- *Pancreatic cancer is projected to be the 2nd leading cause of death by 2030*



National Cancer Institute. https://seer.cancer.gov/statfacts/html/pancreas.html. 2019.

Pancreatic Cancer: A Disease of Old Age



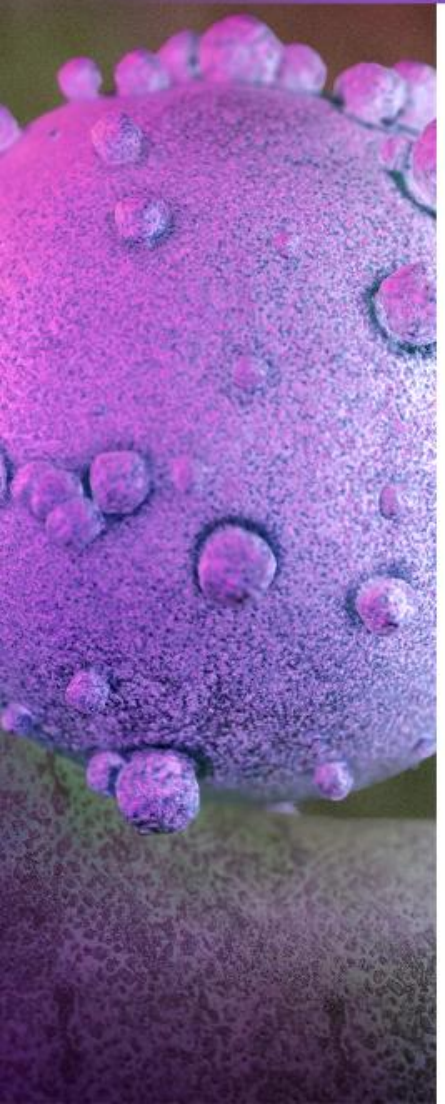
	<20	20-34	35-44	45-54	55-64	65-74	75-84	>84
New Cases	0.1%	0.6%	1.8%	8.4%	22.0%	29.2%	24.4%	13.5%
Deaths	0.0%	0.2%	1.1%	6.7%	20.1%	28.8%	26.8%	16.2%

Age (years)

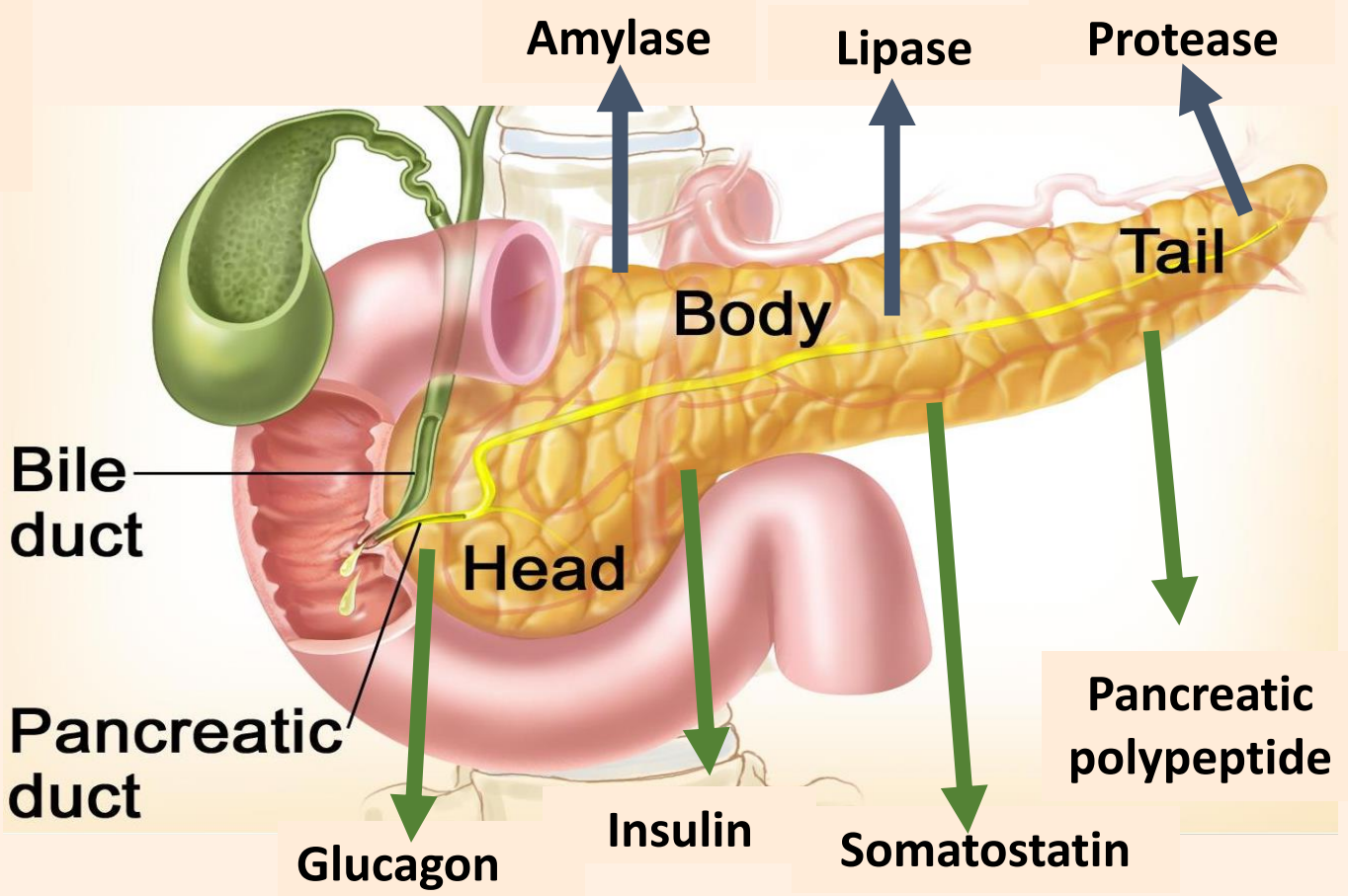
Median age at diagnosis: 70 years old
Median age at death: 72 years old

National Cancer Institute. https://seer.cancer.gov/statfacts/html/pancreas.html. 2019.

Function of the Pancreas

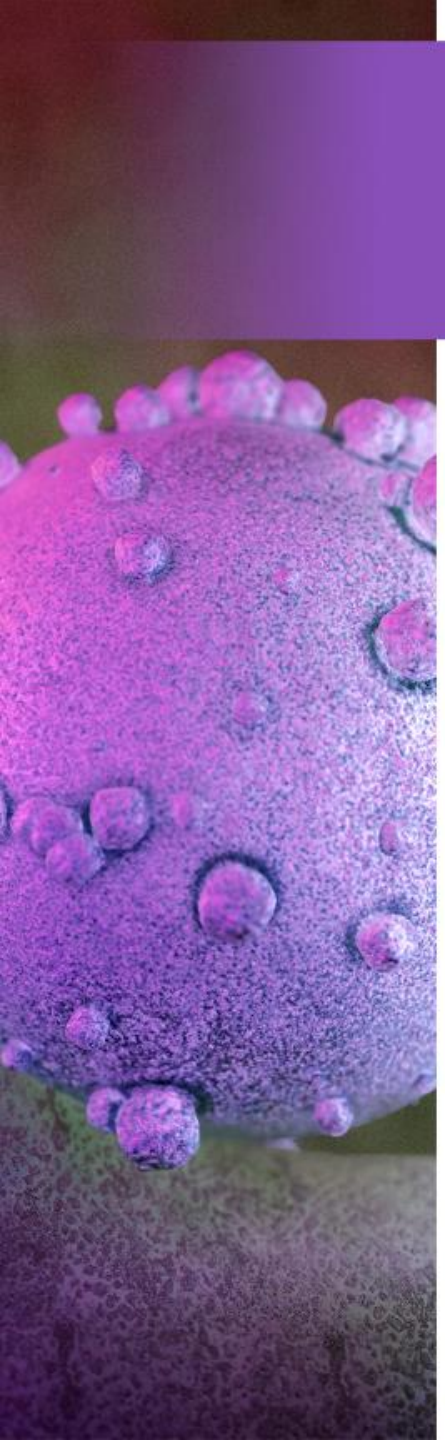


Exocrine function:
produces enzymes that help to digest food



Endocrine function:
produces hormones that regulate glucose

National Cancer Institute. https://www.cancer.gov/types/pancreatic/patient/pancreatic-treatment-pdq#section/all. 2018.

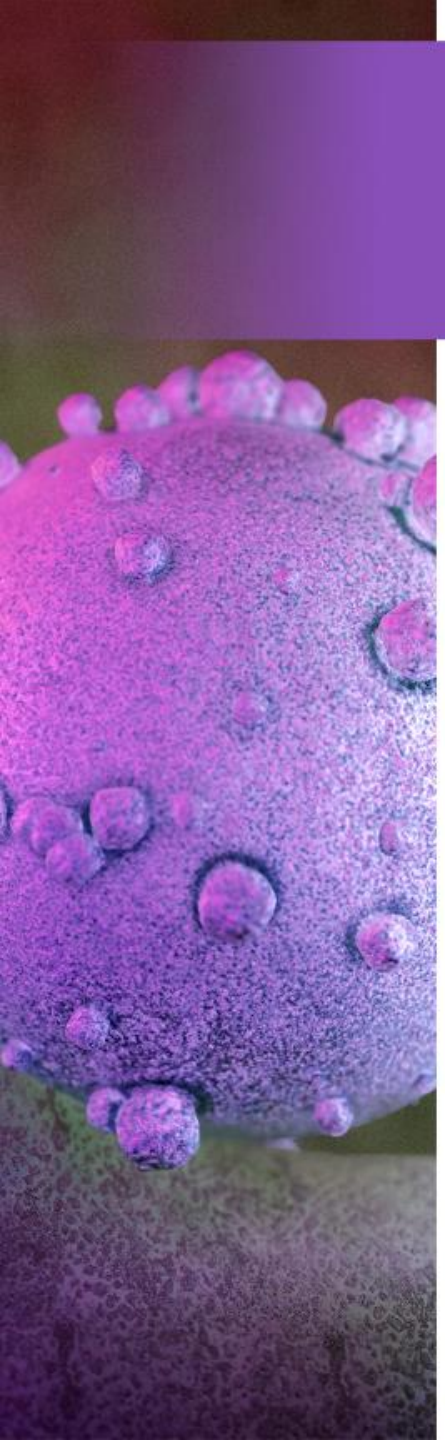


Pancreatic Cancer: Risk Factors

Exact etiology is unknown

- Family history
- Smoking
- Alcohol
- Obesity
- Chronic pancreatitis
- Diabetes
- Rare genetic syndromes

McGuigan A, et al. *World J Gastroenterol*. 2018;24(43):4846-61.

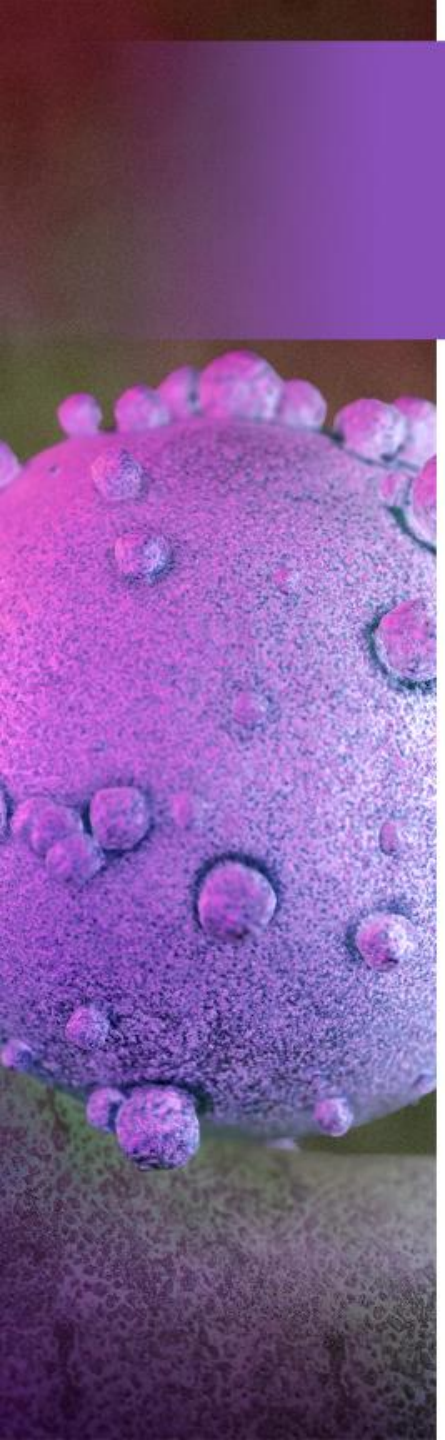


Risk of Pancreatic Cancer Associated with Specific Syndromes

Gene	Syndrome	Relative risk increase
BRCA2	Hereditary breast & ovarian cancer	2.2 – 5.9
BRCA1		1.6 – 4.7
STK11	Peutz-Jegher syndrome	76.2 – 139
PRSS1	Hereditary pancreatitis	53 – 87
CDKN2A	Familial atypical multiple mole melanoma	14.8 – 80
MMR	Hereditary nonpolyposis colorectal cancer	0 – 10.7

BRCA, breast cancer gene; CDKN2A, cyclin-dependent kinase inhibitor 2A; MMR, mismatch repair; PRSS1, protease serine 1; STK11, serine/threonine kinase 11.

McGuigan A, et al. *World J Gastroenterol*. 2018;24(43):4846-61.

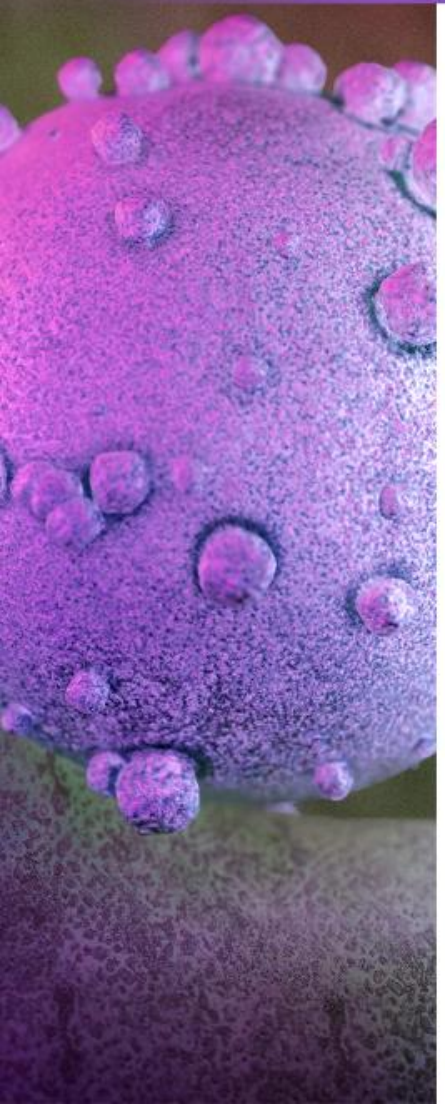


Common Symptoms of Pancreatic Cancer

- *Often no symptoms until obstruction occurs*
- Jaundice
- Pain in upper or middle abdomen
- Pain in back
- Unexplained weight loss
- Fatigue
- Loss of appetite
- Dark urine
- Light-colored stools

Adel N. *Am J Manag Care*. 2019;25 (1 Suppl):S3-10.;
McGuigan A, et al. *World J Gastroenterol*. 2018;24(43):4846-61.

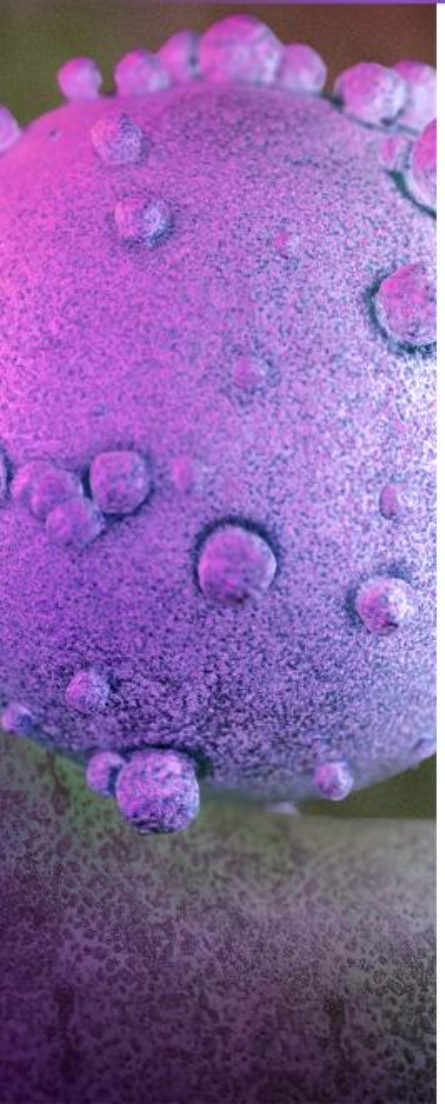
Diagnosis



- Computed tomography (CT)
- Endoscopic ultrasonography (EUS)
- Magnetic resonance imaging (MRI) scans or transabdominal ultrasonography
  - To evaluate liver lesions or determine if there is arterial involvement
- Positron emission tomography (PET) – *controversial*
  - Does not distinguish between pancreatic cancer and pancreatitis
  - Offers no added value over CT scan
  - Currently not recommended, except to find metastatic disease
- Endoscopic retrograde cholangiopancreatography (ERCP)
  - Allows for cytopathology and tissue biopsy if needed
  - Stent placement when required

McGuigan A, et al. *World J Gastroenterol*. 2018;24(43):4846-61.

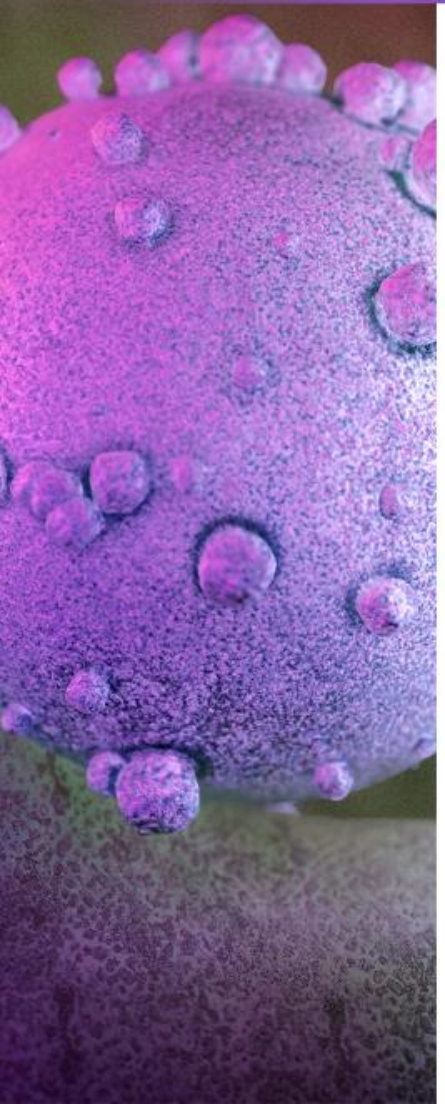
Diagnosis



- Histology
  - Pancreatic ductal adenocarcinoma: > 90%
  - Pancreatic neuroendocrine tumors: 3%-5%
- Location
  - Head of the pancreas accounts for 60%-70% of tumors
  - The rest of the tumors are found equally in the body and the tail
  - At the time of surgery, most tumors have spread beyond the pancreas and nodal metastases are common
- No tumor biomarkers exist that are specific for pancreatic cancer
  - CA19-9 can be followed as a marker of response
    - Has a low specificity for diagnosis

McGuigan A, et al. *World J Gastroenterol*. 2018;24(43):4846-61.

Staging



- Staging is done to determine surgical resectability
- The Tumor, Node, Metastasis (TNM) system is used
  - American Joint Committee on Cancer (AJCC) 8th edition is the most recent version
- Surgically, tumors are described as
  - Resectable
  - Borderline
  - Unresectable
- Most tumors are advanced or metastatic at diagnosis
  - Approximately 10% are fully resectable

Adel N. *Am J Manag Care*. 2019;25 (1 Suppl):S3-10.;
McGuigan A, et al. *World J Gastroenterol*. 2018;24(43):4846-61.

TNM Staging System – AJCC 8th Edition

Primary tumor size (T)

TX – Primary tumor cannot be assessed

T0 – No evidence of primary tumor

Tis – Carcinoma in situ

T1 – Tumor ≤ 2 cm in greatest dimension

(T1a: < 0.5 cm; T1b: 0.5-1 cm; T1c: 1-2 cm)

T2 – Tumor 2-4 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

Number of regional lymph nodes affected (N)

NX – Regional lymph nodes cannot be assessed

N0 – No regional lymph node metastasis

N1 – Metastasis in 1 to 3 regional lymph nodes

N2 – Metastasis in 4 or more regional lymph nodes

Presence of distant metastasis (M)

M0 – No distant metastasis

M1 – Distant metastasis

Resection (R)

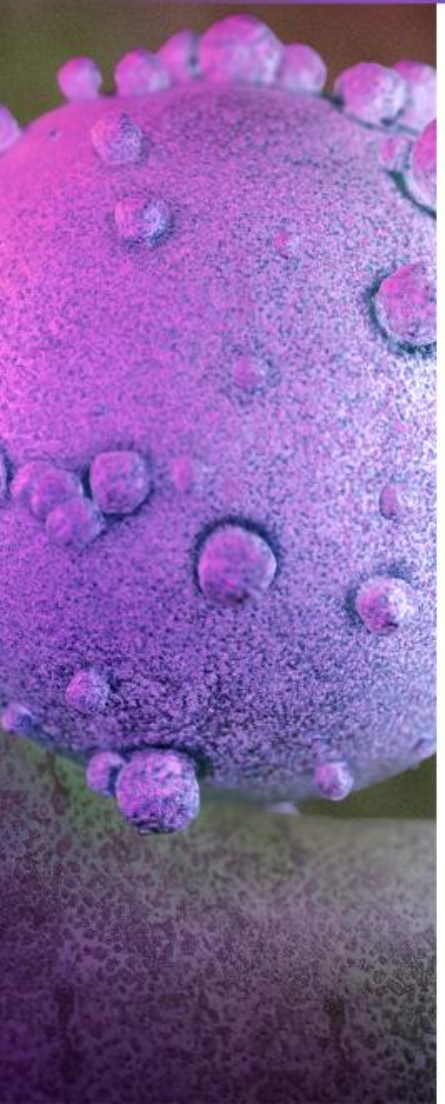
R0 – No residual tumor

R1 – Microscopic residual

R2 – Macroscopic residual

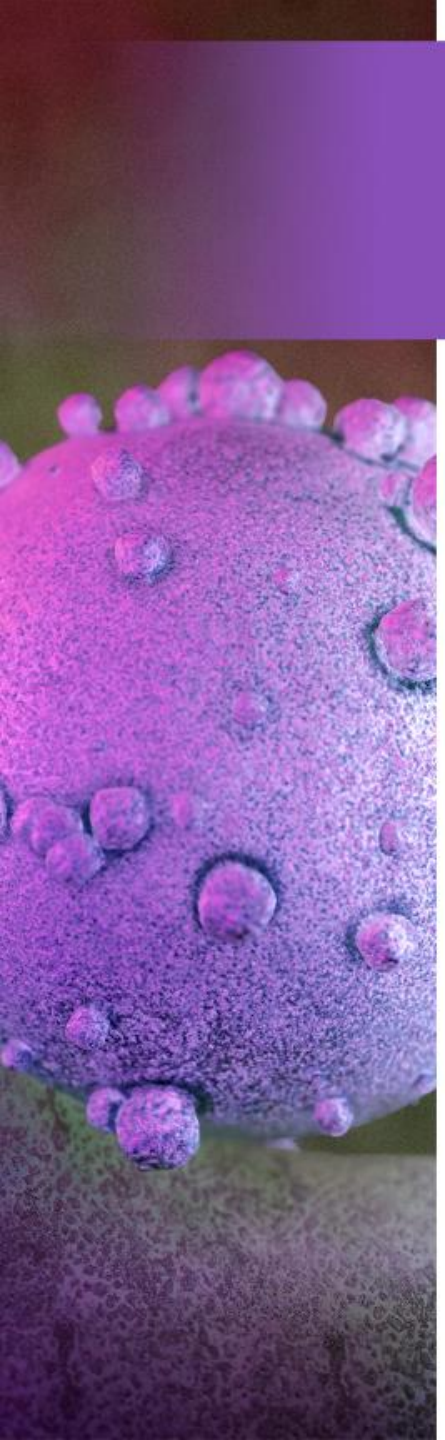
Kakar S, et al. Exocrine pancreas. In: Amin MB, et al, eds. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer;2016:337-50.

TNM Staging System



Stage	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

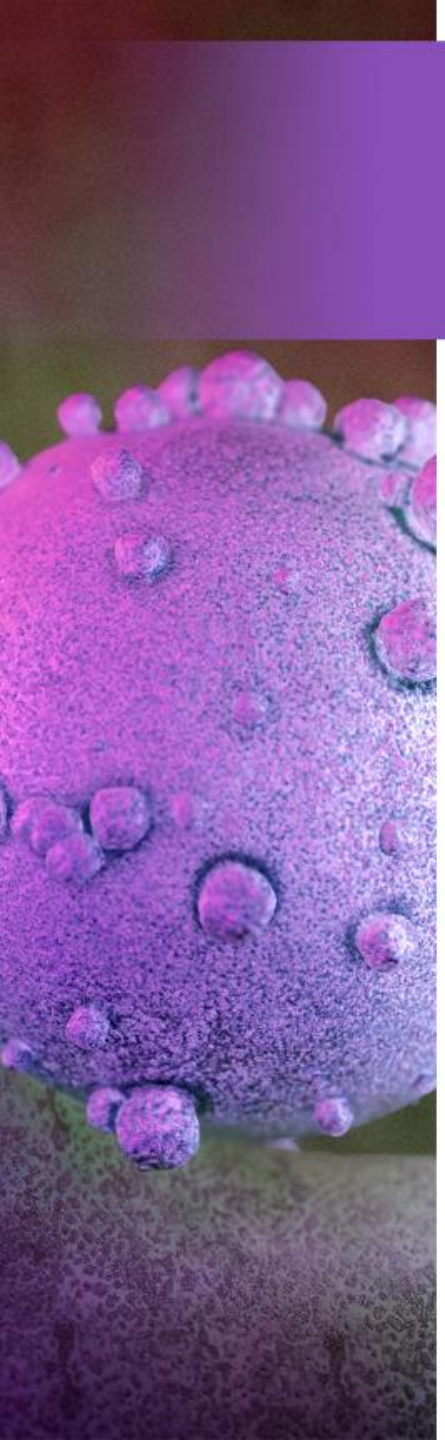
Kakar S, et al. Exocrine pancreas. In: Amin MB, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer;2016:337-50.



Incidence and 5-Year Survival Rate

Stage	Incidence	5-year survival
Localized (confined to primary site)	10%	37.4%
Regional (spread to regional lymph nodes)	29%	12.4%
Distant (metastasized)	53%	2.9%
Unknown (unstaged)	8%	5.6%
All stages		9%

National Cancer Institute. https://seer.cancer.gov/statfacts/html/pancreas.html. 2019.

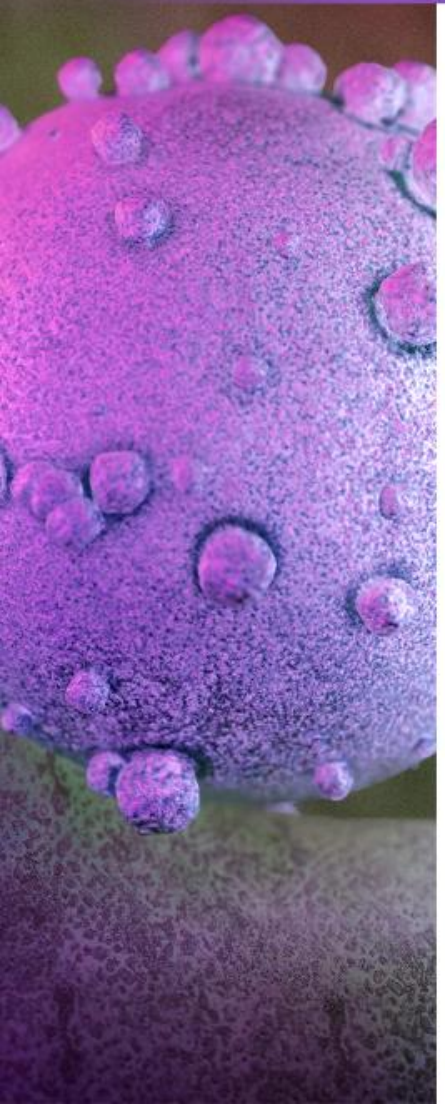


Sites of Metastasis

- Liver
- Peritoneum
- Lung
- Adrenal
- Bone
- Rarely central nervous system

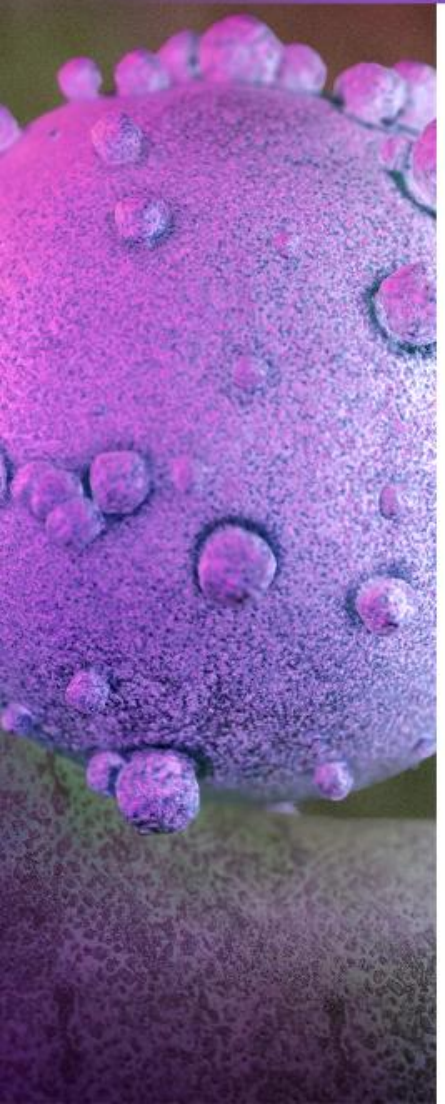
National Cancer Institute. https://seer.cancer.gov/statfacts/html/pancreas.html. 2019.

Essentials of Treatment



- Surgical resection is the only cure
- Performance status drives selection of therapy in most cases
- Neoadjuvant therapy (prior to surgery) is unproven but part of standard practice
- Adjuvant therapy (after surgery) is the standard of care
- Unresectable disease is treated with chemotherapy
- Best supportive care (BSC) is the standard for advanced disease in patients with poor performance status

ECOG Performance Scale

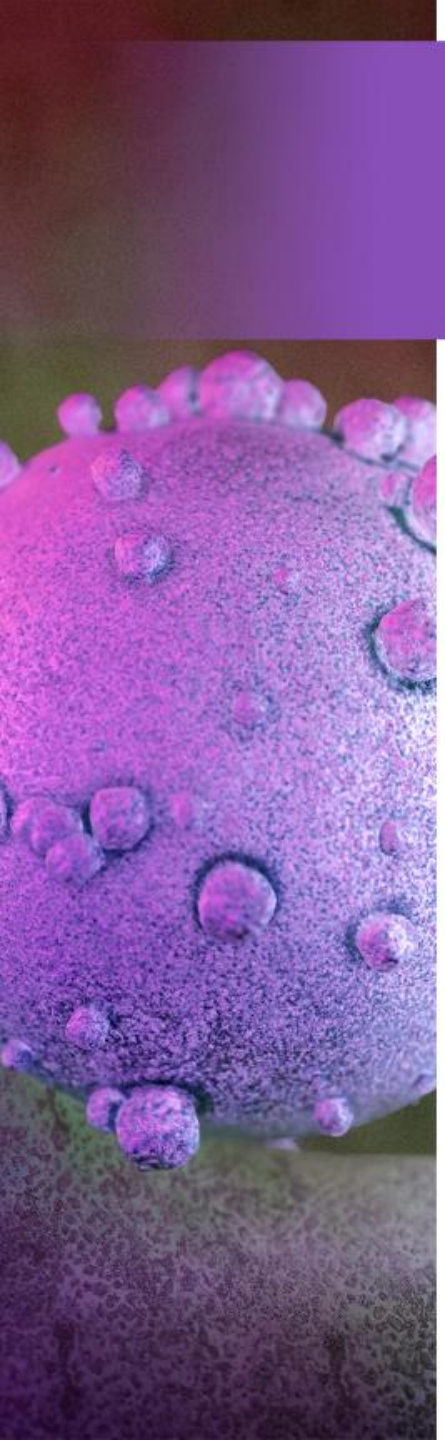


Grade	Performance status
0	Fully active, able to carry on all pre-disease activities w/o restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

ECOG, Eastern Cooperative Oncology Group.

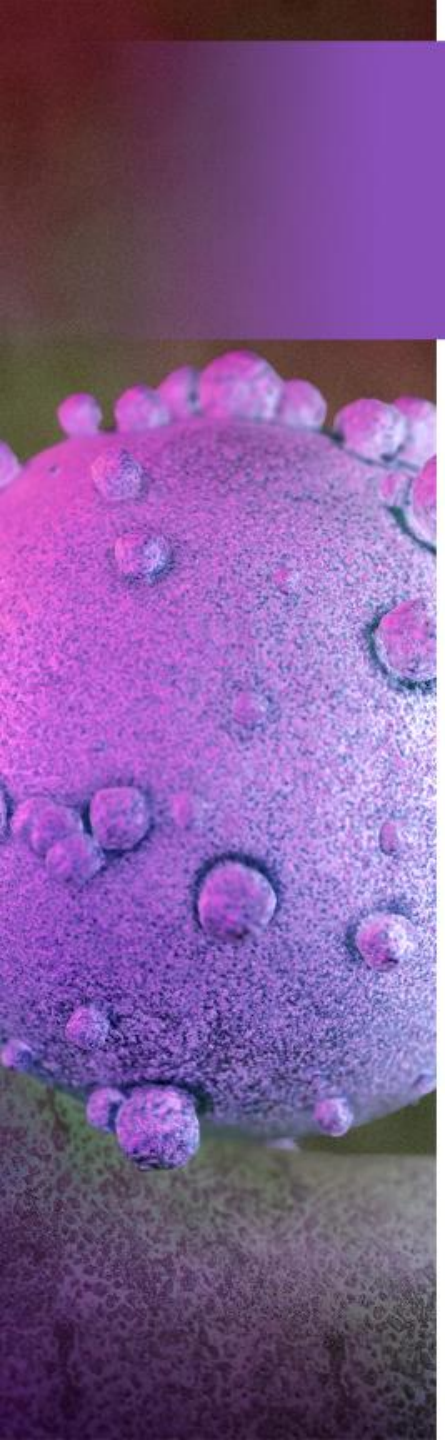
Oken MM, et al. *Am J Clin Oncol*. 1982;5(6):649-55.

Chemotherapy – Most Commonly Used



- DNA crosslinking agents:
  - Oxaliplatin
  - Cisplatin
- Fluorinated pyrimidine antimetabolites:
  - Fluorouracil (5-FU)
  - Capecitabine
  - Tegafur, gimeracil, oteracil (S-1)
    - *Common outside of the United States*
- Nucleoside analog:
  - Gemcitabine (GEM)
- Topoisomerase I inhibitors:
  - Irinotecan
  - Nanoliposomal irinotecan (nal-IRI)
- Tubulin inhibitors:
  - Paclitaxel
  - Nanoparticle albumin-bound (nab) paclitaxel

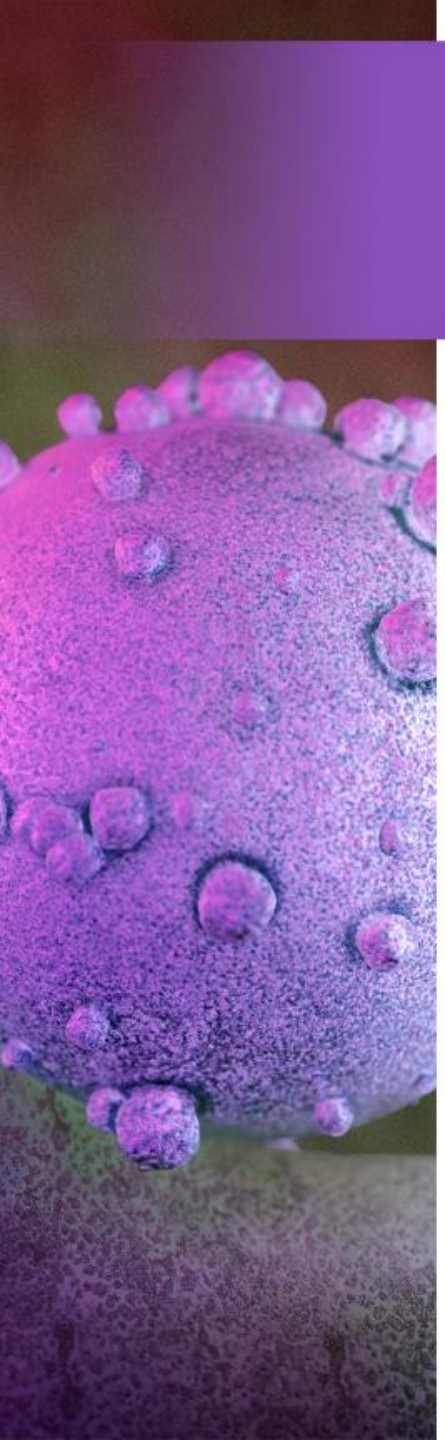
Adel N. *Am J Manag Care*. 2019;25 (1 Suppl):S3-10.



Common Chemotherapy Regimens

- FOLFIRINOX – repeat every 14 days
  - Oxaliplatin 85 mg/m^2
  - Irinotecan 180 mg/m^2
  - Leucovorin (LV) 400 mg/m^2
  - 5-FU bolus 400 mg/m^2 followed by 2400 mg/m^2 over 46 hours
- mFOLFIRINOX
  - *Deletes 5-FU bolus*
  - *Dose reduces irinotecan to 150 mg/m^2*
- Nab-paclitaxel plus GEM – repeat every 28 days
  - Nab-paclitaxel 125 mg/m^2 on days 1, 8, and 15
  - GEM 1000 mg/m^2 on days 1, 8, and 15

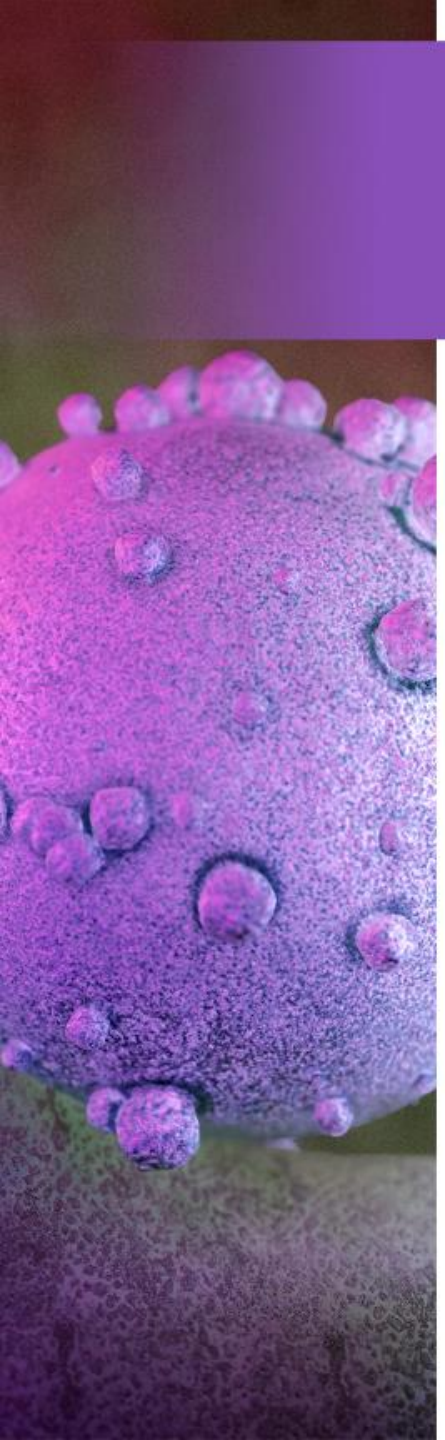
Kang H, et al. *World J Gastrointest Oncol*. 2018;10(11):421-30.;
Von Hoff DD. *N Engl J Med.* 2013;369(18):1691-703.



Main Guidelines for Treatment of Pancreatic Cancer

- American Society of Clinical Oncology (ASCO)
  - Broken down to:
    - Curable – originally published 2016, updated 2019
    - Locally advanced, unresectable – originally published 2016
    - Metastatic – originally published 2016, updated 2018
- European Society of Medical Oncology (ESMO)
  - Originally published 2015
  - Updated electronically March 2019
- National Comprehensive Cancer Network (NCCN)
  - Current version 1.2020
  - Published November 2019

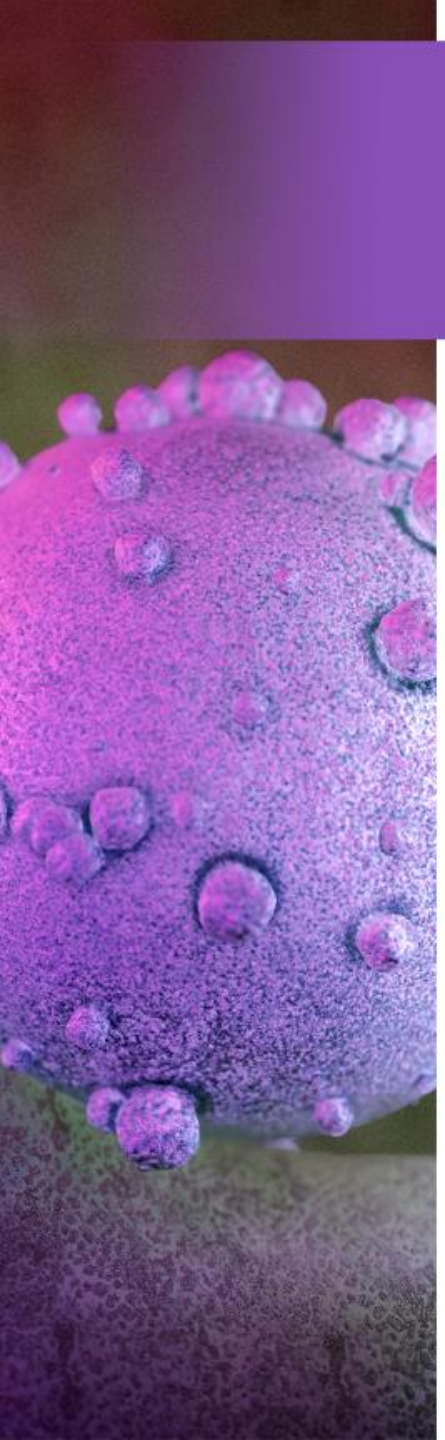
Adel N. *Am J Manag Care*. 2019;25 (1 Suppl):S3-10.



Surgery

- Only curable therapy: 10% of patients are eligible at diagnosis
- The goal is to have complete resection with a clear margin of healthy tissue of greater than 1 mm (R0)
- Regional lymph nodes are also removed
- Tumor in the head of the pancreas: pancreaticoduodenectomy – *Whipple procedure*
- Tumors in the body or tail (left side of the pancreas): pancreatectomy
- Splenectomy is generally recommended

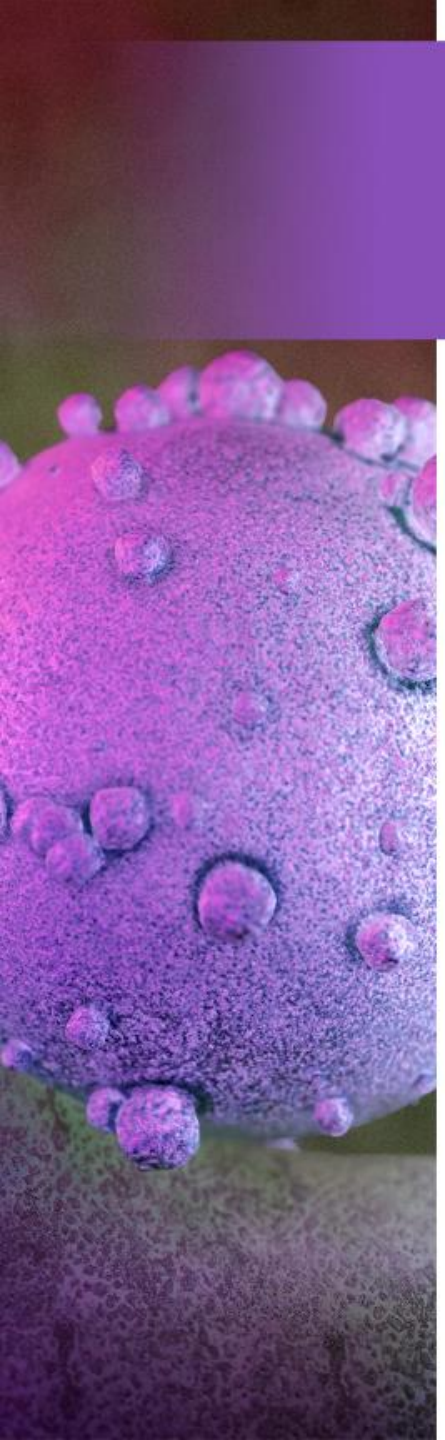
Kamisawa T, et al. *Lancet.* 2016;388(10039):73-85.



Advances in Surgical Techniques

- Laparoscopic approaches
- The use of risk scales
- Better nutritional assessment
- Enhanced recovery after surgery (ERAS) programs
- Improved biliary stents
- Centralization of surgeries to create high volume centers of excellence

Kamisawa T, et al. *Lancet.* 2016;388(10039):73-85.;
Lambert A. *Ther Adv Med Oncol*. 2019;11:1-43.;
McGuigan A, et al. *World J Gastroenterol*. 2018;24(43):4846-61.

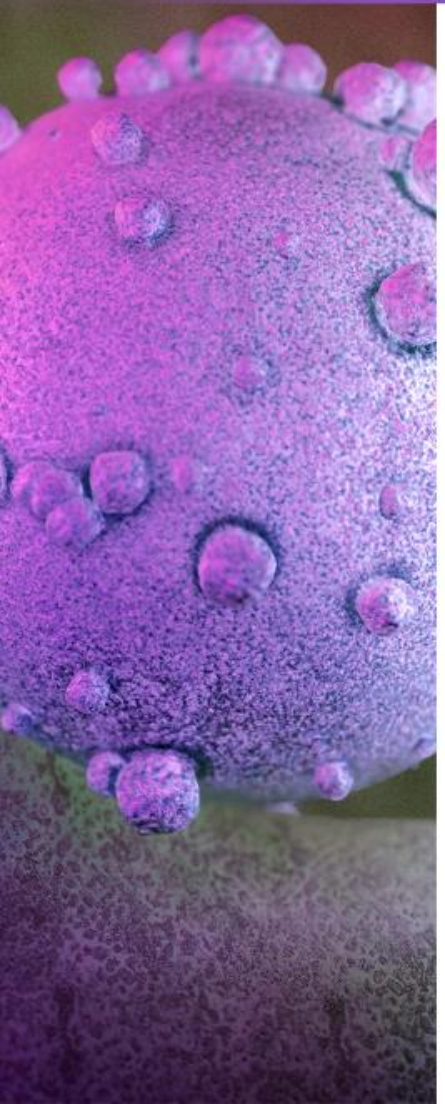


Radiation/Chemoradiation

- Radiation therapy most often given with chemotherapy radio-sensitizers
  - 5-FU
  - GEM
- ASCO and NCCN guidelines
  - Moderate recommendations to use chemoradiotherapy (CRT) in the adjuvant setting in patients with node-positive or R1 disease
- ESMO guidelines
  - Does not recommend the addition of CRT to adjuvant therapy
  - No overall survival (OS) benefit over GEM monotherapy

Conroy T, et al. *Curr Opin Oncol.* 2019;31(4):346-53.

Trials of Adjuvant CRT for Pancreatic Cancer

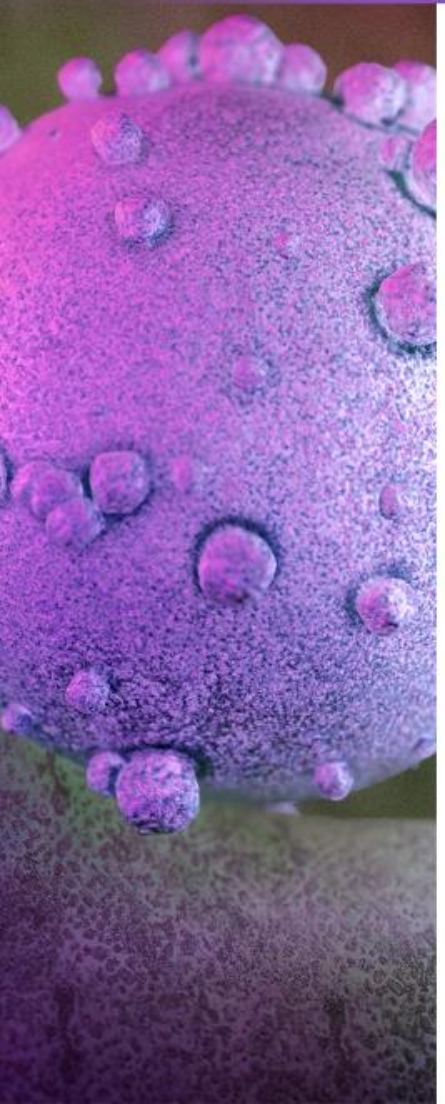


Study	n	Treatment arms	Median DFS (months)	p-value	Median OS (months)	p-value
GITSG	43	Observation	NR	NR	20	0.035
		CRT + adjuvant 5-FU	NR		10.9	
EORTC 40891	114	Observation	NR	NR	12.6	0.10
		CRT	NR		17.1	
ESPAC-1	353	No CRT	15.2	0.04	17.9	0.05
		CRT	10.7		15.9	
RTOG 9704	451	CRT + 5-FU	17.2	0.12	NR	NR
		CRT + GEM	20.5		NR	
EORTC 40013	90	GEM + CRT	11.8	ns	24.3	ns
		GEM alone	10.9		24.4	

DFS, disease-free survival; NR, not reported; ns, not statistically significant.

Kalser MH, et al. *Arch Surg*. 1985;120(8):899-903.; Klinkenbijl JH, et al. *Ann Surg*. 1999;230(6):776-84.; Neoptolemos JP, et al. *N Eng J Med*. 2004;350(12):1200-10.; Regine WF, et al. *Ann Surg Oncol*. 2011;18(5):1319-26.; Van Laethem JL, et al. *J Clin Oncol*. 2010;28(29):4450-6.

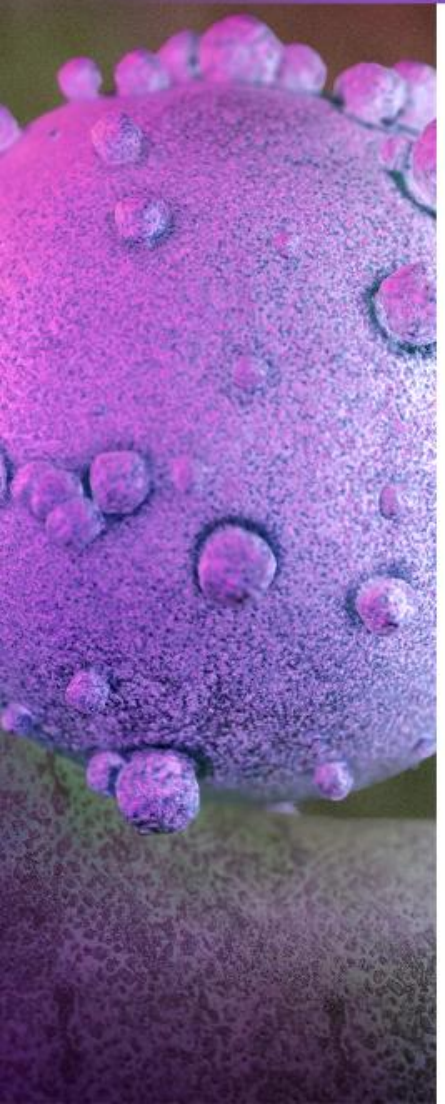
Neoadjuvant Therapy



- The goal is to shrink the tumor to allow for a better surgical outcome
- No phase III trial has shown a benefit
- Neoadjuvant therapy can be considered for patients with high-risk resectable disease or with borderline resectable disease
- High-risk features:
  - Extremely high CA19-9
  - Exceptionally large tumor
  - Large regional lymph nodes
  - Excessive weight loss
  - Extreme pain
- When considering neoadjuvant therapy, a high-volume center should be consulted, and the patient should be enrolled in a clinical trial when possible

Balaban EP, et al. J C*lin Oncol. 2*016;34(22):2654-68.;
Khorana AA, et al. *J Clin Oncol.* 2019;37(23):2082-8.

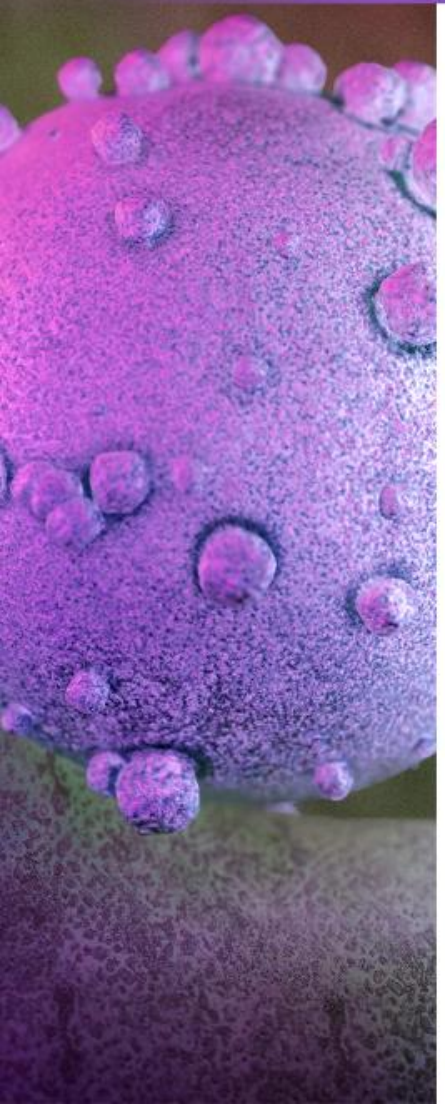
Neoadjuvant Therapy



Guidelines	Recommendations
ASCO	Recommended only for high-risk patients GEM or FOLFIRINOX ± CRT
ESMO	Not recommended GEM or FOLFIRINOX ± CRT
NCCN	Recommended only for high-risk patients FOLFIRINOX ± CRT Nab-paclitaxel plus GEM ± CRT BRCA 1/2 or PALB2 mutations FOLFIRINOX ± CRT GEM with cisplatin ± CRT

ESMO. https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Cancer-of-the-Pancreas/eUpdate-Cancer-of-the-Pancreas-Treatment-Recommendations. March 15, 2019.; Khorana AA, et al. *J Clin Oncol.* 2019;37(23):2082-8.; NCCN. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic_blocks.pdf. November 26, 2019.

Adjuvant Therapy



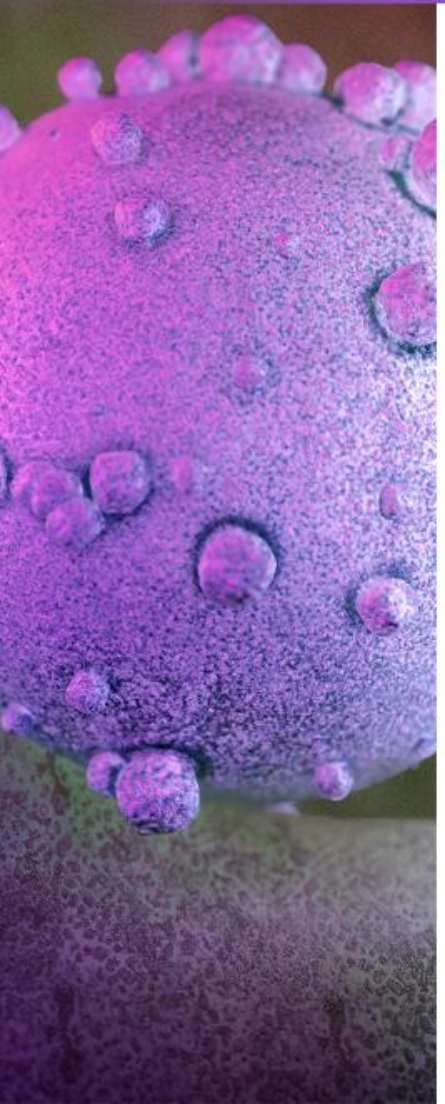
- Considered standard of care
- CRT has not shown benefit
- Chemotherapy has shown clear benefit
- Performance status drives decision of therapy
- No trial comparing the top 2 regimens

Guidelines	ECOG PS 0-1	ECOG PS 2	ECOG PS 3-4
ASCO	mFOLFIRINOX	GEM + capecitabine	BSC
ESMO			
NCCN			

PS, performance status.

ESMO. https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Cancer-of-the-Pancreas/eUpdate-Cancer-of-the-Pancreas-Treatment-Recommendations. March 15, 2019.; Khorana AA, et al. *J Clin Oncol.* 2019;37(23):2082-8.; NCCN. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic_blocks.pdf. November 26, 2019.

Adjuvant Therapy Trials for Resectable Disease

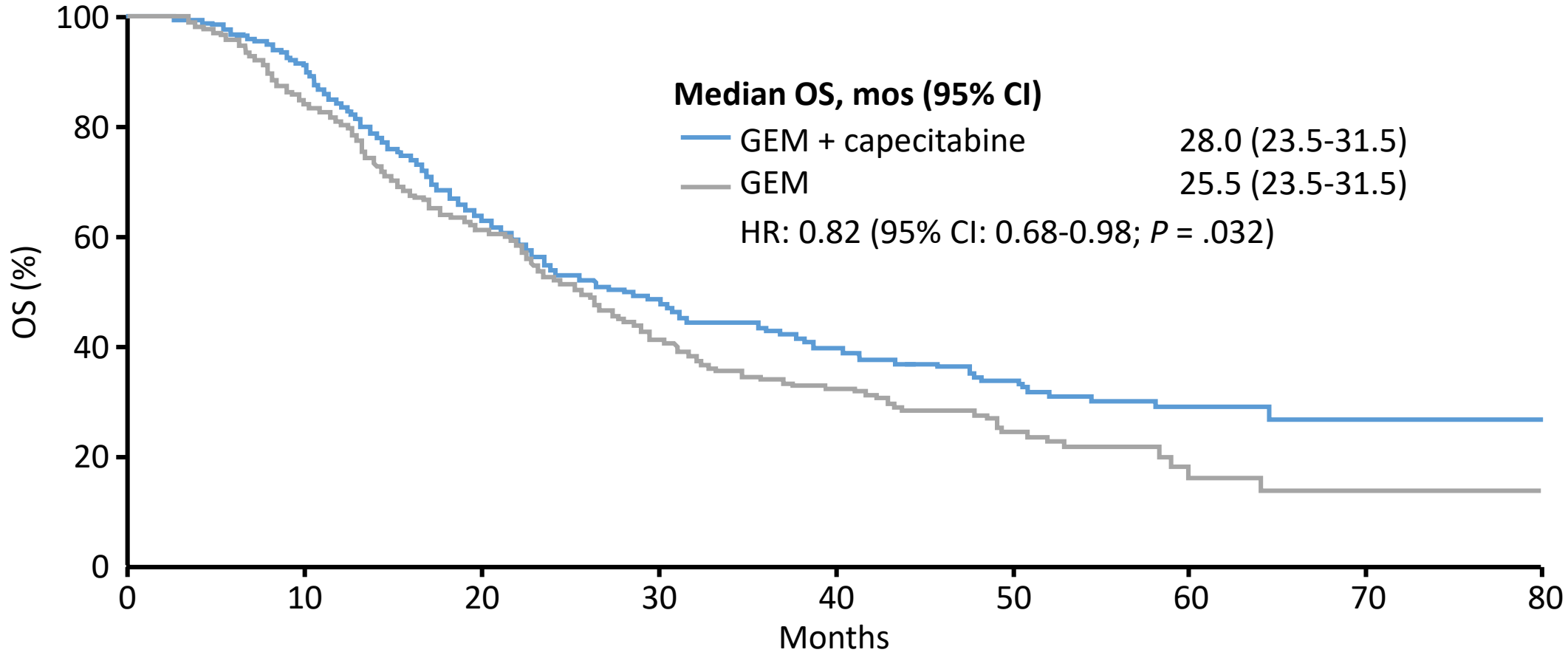


Trial	n	Group	Median OS (months)	p-value	Median DFS (months)	p-value
ESPAC-1	289	No chemotherapy	15.5	0.009	9.4	0.02
		5-FU	20.1		15.4	
CONKO-001	368	Observation	20.2	0.01	20.2	0.01
		GEM	22.8		22.8	
ESPAC 3	1088	5-FU/LV	23.0	0.39	14.1	0.53
		GEM	23.6		14.3	
JASPAC-01	378	GEM	26	< 0.001	11.3	0.0001
		S-1	46		22.9	
ESPAC 4	732	GEM	25.5	0.032	13.1	0.082
		GEM + capecitabine	28		13.9	
APACT	866	GEM	36.2	0.045	18.8	0.1824
		Nab-paclitaxel + GEM	40.5		19.4	
PRODIGE 24	493	GEM	35	0.003	12.8	< 0.001
		mFOLFIRINOX	54.4		21.6	

Conroy T, et al. *N Engl J Med* 2018;379(25):2395-406.; Maeda A, et al. *Jpn J Clin Oncol.* 2008;38(3):227-9.; Neoptolemos JP, et al. *JAMA.* 2010;304(10):1073-81.; Neoptolemos JP, et al. *Lancet.* 2017;389(10073):1011-24.; Oettle H, et al. *JAMA.* 2013;310(14):1473-81.; Tempero MA, et al. *J Clin Oncol.* 2019;37:4000.

ESPAC-4: Adjuvant GEM ± Capecitabine

- Multicenter, randomized, open-label phase III trial (N = 732)

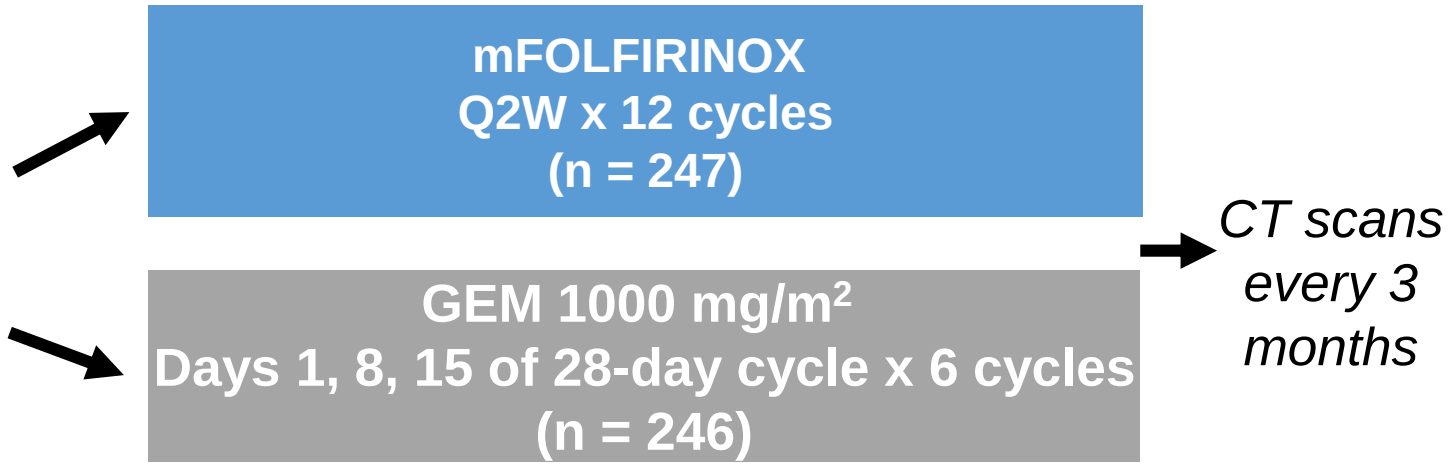


Neoptolemos JP, et al. *Lancet.* 2017;389(10073):1011-24.

PRODIGE 24/CCTG PA.6: Adjuvant mFOLFIRINOX vs. GEM

- Multicenter, randomized phase III trial

Patients 18-79 years old with histologically confirmed R0 or R1 resected pancreatic ductal adenocarcinoma;
CA19-9 level < 180 U/mL ≤ 12 wks post surgery;
ECOG PS 0/1;
no prior chemotherapy or RT (N = 493)

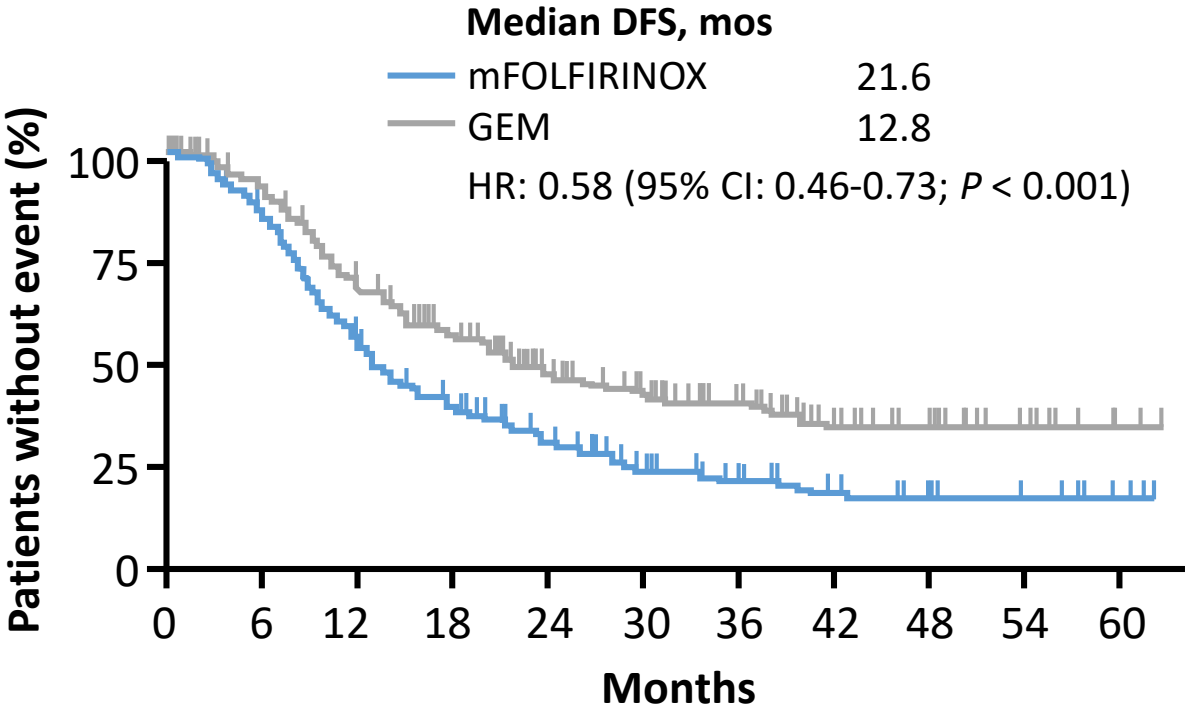


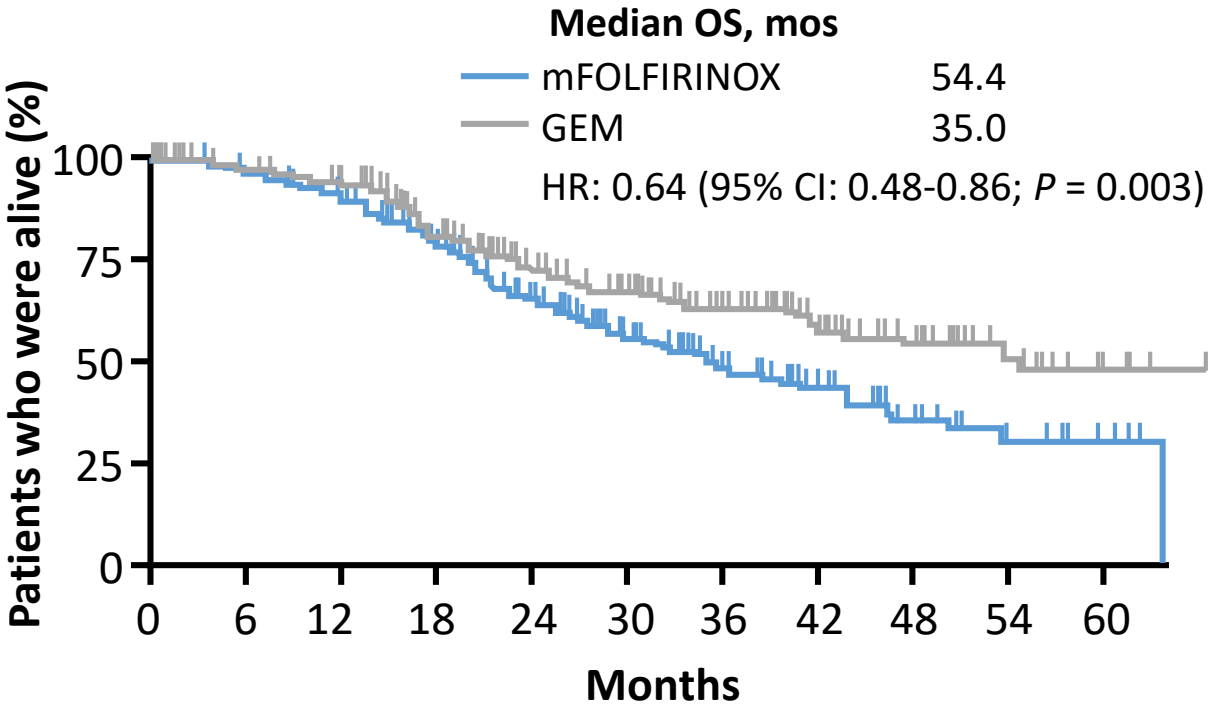
- Primary endpoint: DFS
- Secondary endpoints: toxicity, OS, cancer-specific survival, metastasis-free survival

Q2W, every 2 weeks.

Conroy T, et al. *N Engl J Med* 2018;379(25):2395-406.

PRODIGE 24/CCTG PA.6: Survival Outcomes





Survival outcome	mFOLFIRINOX (n = 247)	GEM (n = 246)
3-yr DFS, % (95% CI)	39.7 (32.8-46.6)	21.4 (15.8-27.5)

Survival outcome	mFOLFIRINOX (n = 247)	GEM (n = 246)
3-yr OS, % (95% CI)	63.4 (55.7-70.1)	48.6 (40.9-55.8)

Conroy T, et al. *N Engl J Med* 2018;379(25):2395-406.

PRODIGE 24/CCTG PA.6: Safety

AE, %	mFOLFIRINOX (n = 238)		GEM (n = 243)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Diarrhea	84.4	18.6*	49	3.7
Fatigue	84	11	77.6	4.6
PN	61.2	9.3	8.7	--
Vomiting	46	5	29	1.2
Mucositis	33.8	2.5	14.9	0
Alopecia	27	--	19.5	--
Hand-foot syndrome	5	0.4	0.8	--

AE, %	mFOLFIRINOX (n = 238)		GEM (n = 243)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Headache	8.4	--	19.4	--
Fever	16.5	0.4	32.4	0.4
Flu-like symptoms	1.3	--	5.0	0.4
ALT increase	64	4.2	73.5	5.0
AST increase	67	3.8	69	3.3

Grade 3/4 hematologic AEs > 5%, mFOLFIRINOX/GEM:
G-CSF use, 59.9%/3.7%; neutropenia, 28.4%/26.0%

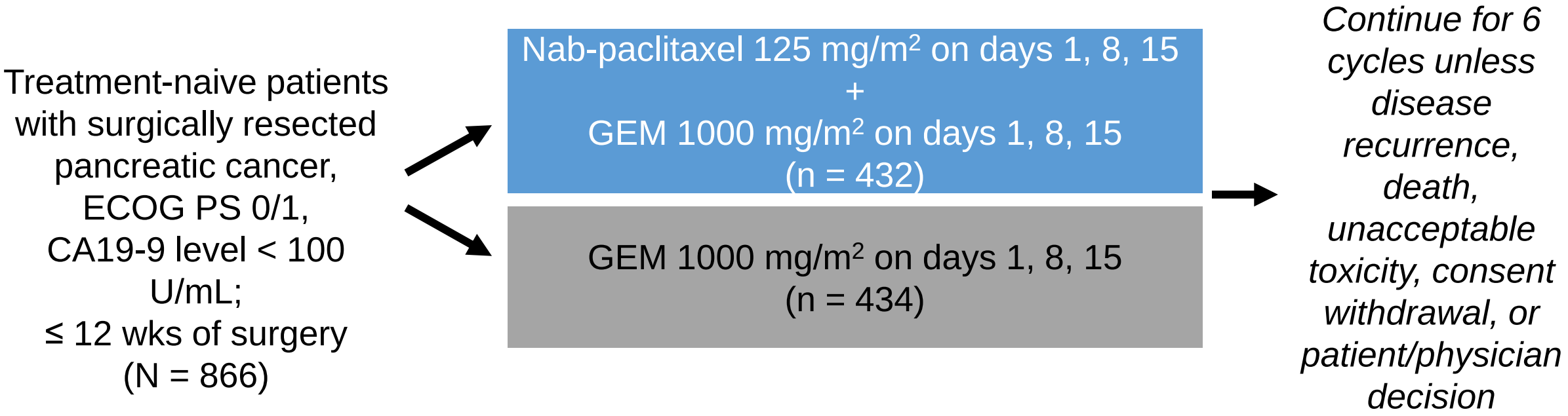
*Cycle 1: 8.6%; cycle 2: 6.3%; cycles 3-5: 3%; cycles 6-12: 1%.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PN, peripheral neuropathy.

Conroy T, et al. *N Engl J Med* 2018;379(25):2395-406.

APACT: Adjuvant Nab-Paclitaxel Plus GEM vs. GEM

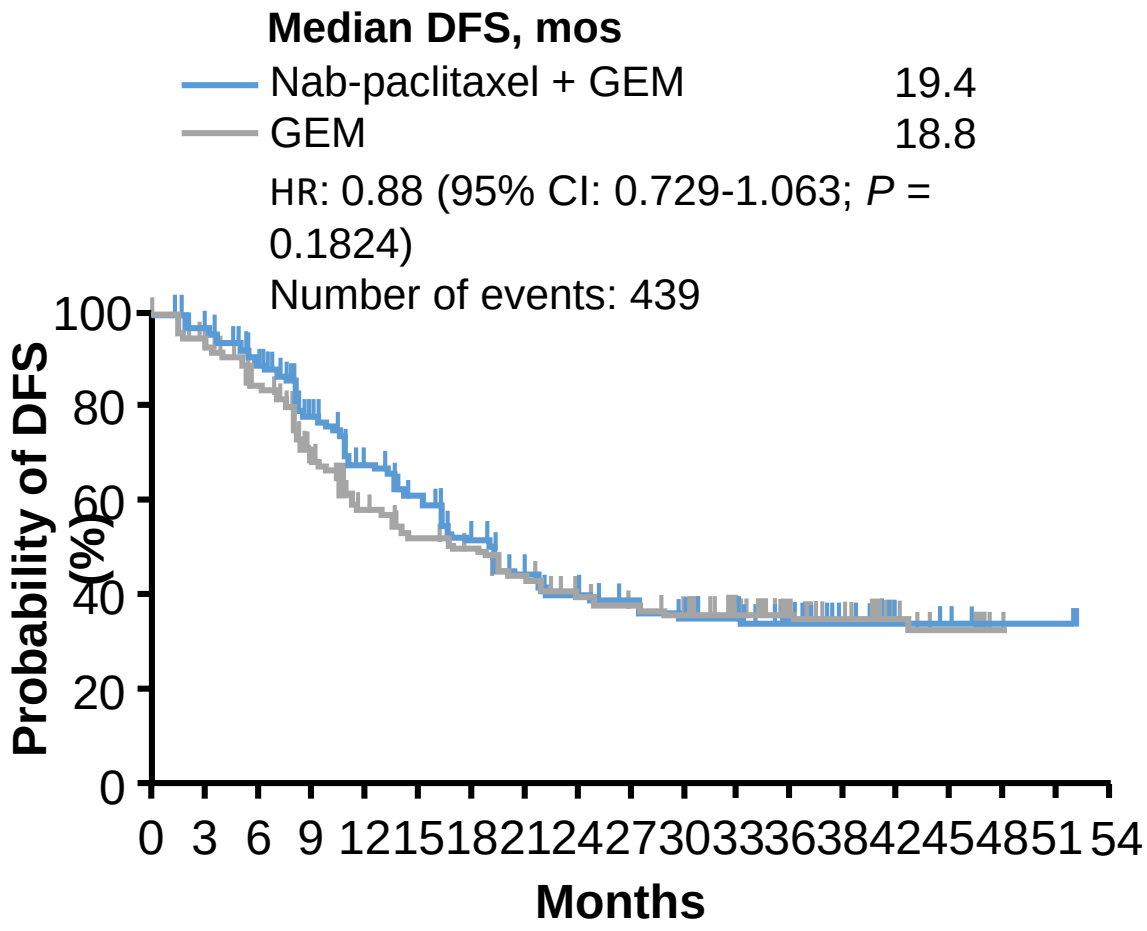
- Multicenter, randomized, open-label phase III trial

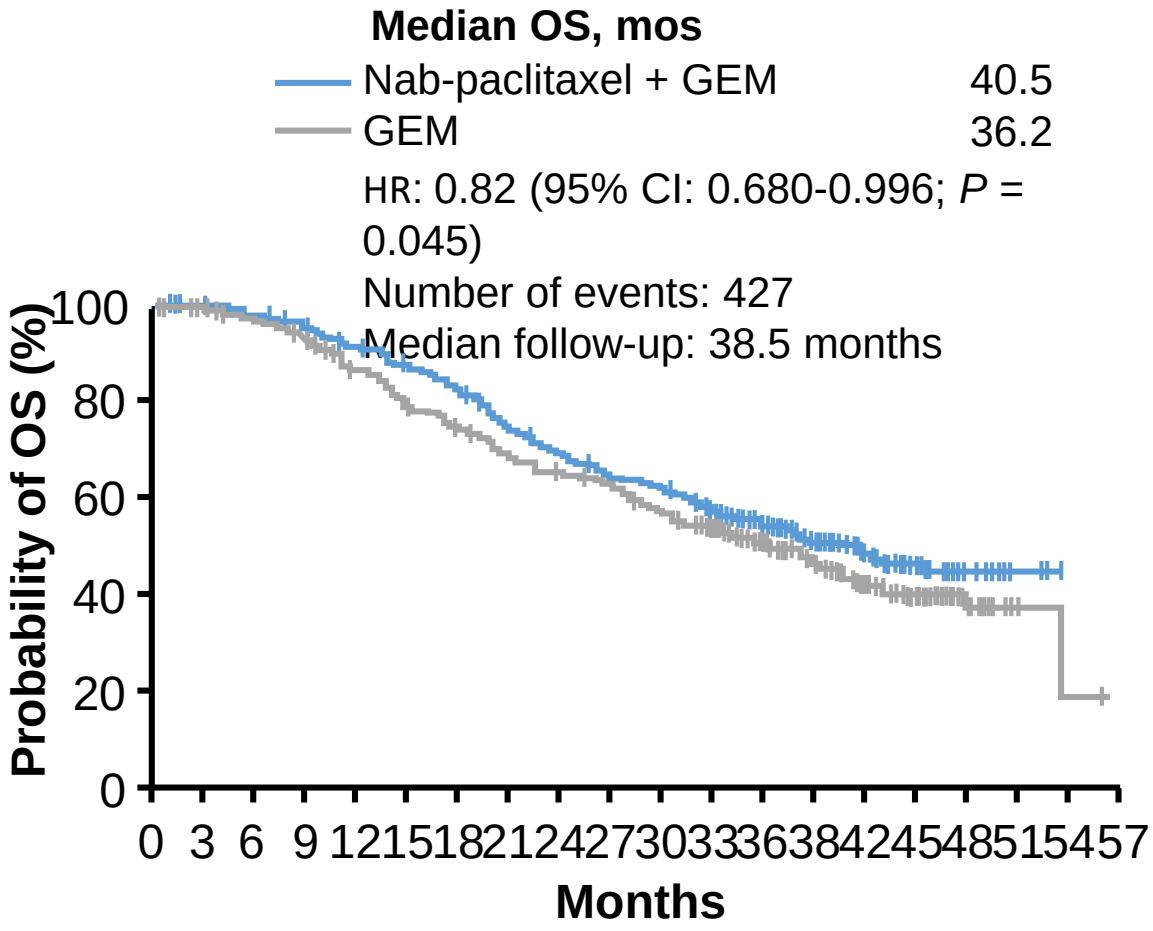


- Primary endpoint: DFS by independent review (first adjuvant trial in pancreatic cancer using independently assessed DFS as the primary endpoint)
- Secondary endpoints: OS, safety

Tempero MA, et al. *J Clin Oncol.* 2019;37:4000.

APACT: Survival Outcomes





Tempero MA, et al. *J Clin Oncol.* 2019;37:4000.

APACT: Safety

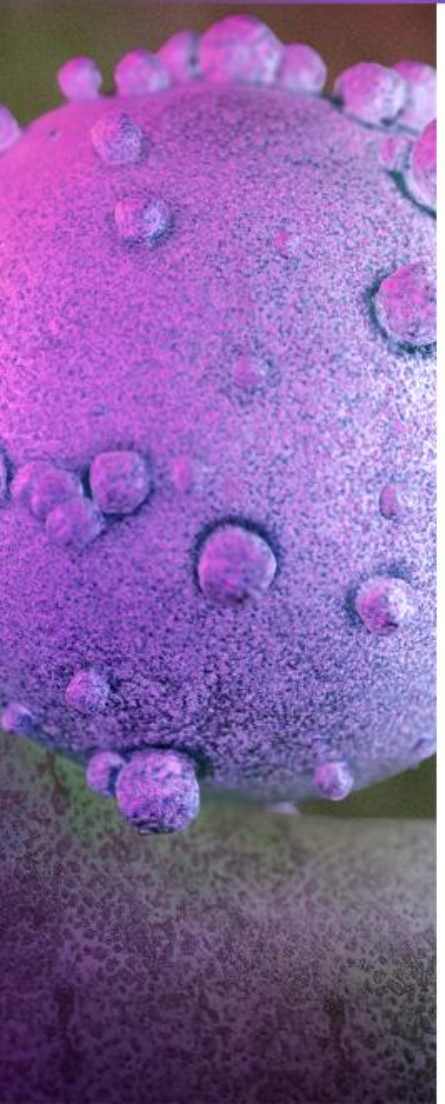
AE, n (%)	Nab-paclitaxel + GEM (n = 429)	GEM (n = 423)
TEAE leading to death	2 (< 1)	2 (< 1)
Patients with ≥ 1 grade ≥ 3 TEAE	371 (86)	286 (68)
Patients with ≥ 1 serious TEAE	176 (41)	96 (23)
Grade ≥ 3 hematologic TEAEs occurring in ≥ 5% of patients in either treatment arm		
▪ Any	250 (58)	204 (48)
▪ Neutropenia	212 (49)	184 (43)
▪ Anemia	63 (15)	33 (8)
▪ Leukopenia	36 (8)	20 (5)
▪ Febrile neutropenia	21 (5)	4 (1)
Grade ≥ 3 nonhematologic TEAEs occurring in ≥ 5% of patients in either treatment arm		
▪ Peripheral neuropathy*	64 (15)	0
▪ Fatigue	43 (10)	13 (3)
▪ Diarrhea	22 (5)	4 (1)
▪ Asthenia	21 (5)	8 (2)
▪ Hypertension	17 (4)	27 (6)

TEAE, treatment-emergent adverse events.

*10 patients improved to grade ≤ 1.

Tempero MA, et al. *J Clin Oncol.* 2019;37:4000.

Advanced/Metastatic Disease



- Chemotherapy is the standard
- 5-FU with LV bolus was the standard until late 1990s
- GEM showed improved “clinical benefit” and improved OS and PFS compared to 5-FU/LV
  - Clinical benefit defined as:
    - Controlling pain
    - Improvement in functional status
    - Improvement in weight
- Over the next few years, more than 20 trials with GEM vs. GEM combinations were evaluated
  - No added benefit observed

Adel N. *Am J Manag Care*. 2019;25(1 Suppl):S3-10.;
Lambert A, et al. *Ther Adv Med Oncol*. 2019;11:1-43.;
McGuigan A, et al. *World J Gastroenterol*. 2018;24(43):4846-61.

PRODIGE 4/ACCORD 11: FOLFIRINOX vs. GEM
Patients with Metastatic Pancreatic Cancer

- Multicenter, randomized, phase II/III trial

Patients with untreated metastatic pancreatic cancer;
< 76 years old; ECOG PS 0/1; adequate bone marrow, platelet count, liver and renal function
(N = 342)

FOLFIRINOX
Oxaliplatin 85 mg/m² + LV 400 mg/m² + irinotecan 180 mg/m² + 5-FU bolus 400 mg/m², then 2400 mg/m² IV over 46 hrs
(n = 171)

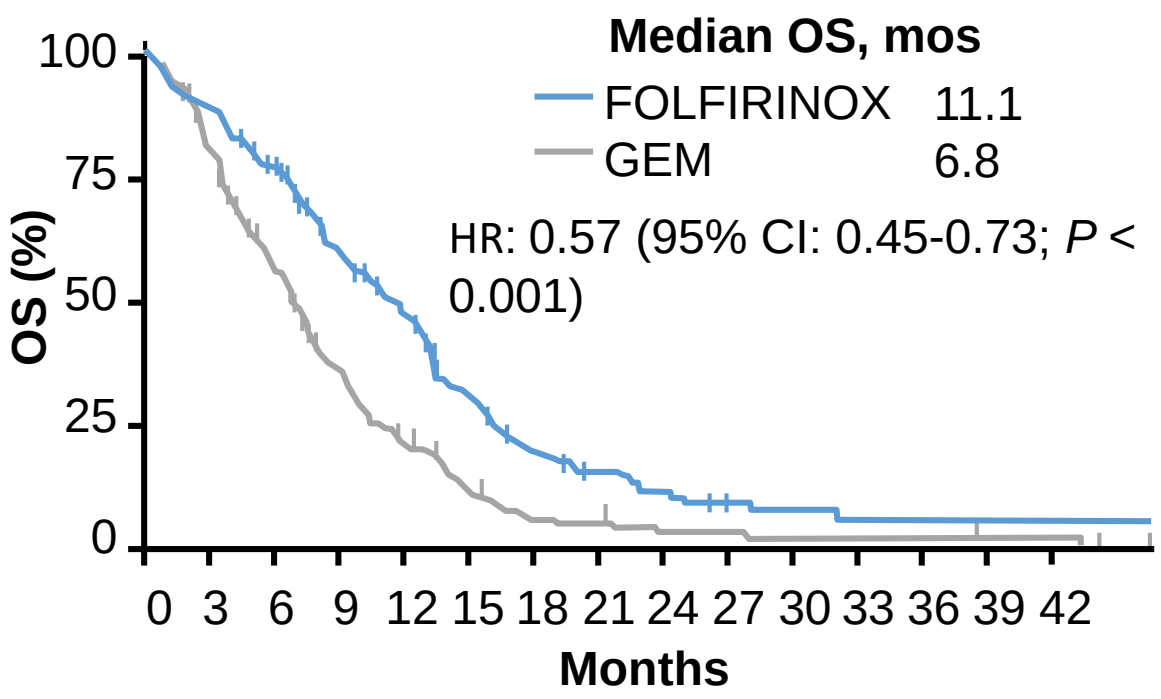
GEM
1000 mg/m² weekly x 7 of 8, then weekly x 3 of 4
(n = 171)

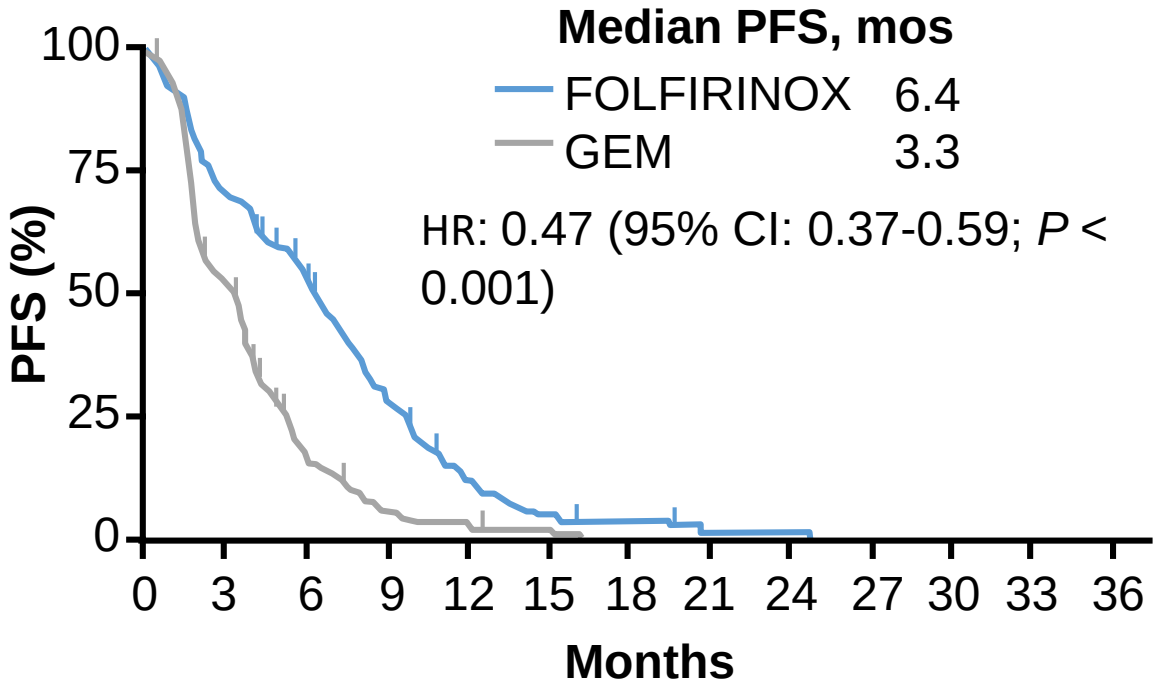
- Primary endpoints: Overall response rate (ORR) (phase II), OS (phase III)

IV, intravenously.

Conroy T, et al. *New Engl J Med*. 2011;364(19):1817-25.

PRODIGE 4/ACCORD 11: FOLFIRINOX vs. GEM

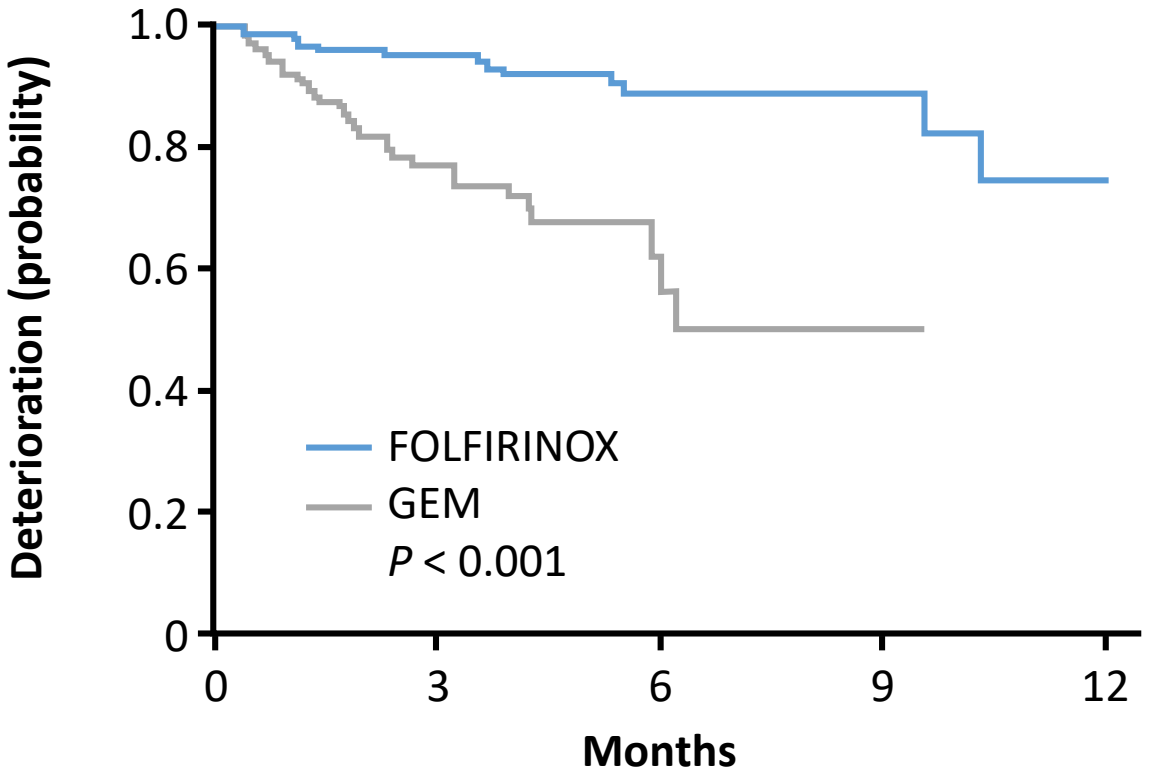




Conroy T, et al. *New Engl J Med*. 2011;364(19):1817-25.

PRODIGE 4/ACCORD 11: FOLFIRINOX vs. GEM
Quality of Life

Time Until Definitive Deterioration > 20 Points, EORTC-C30 Global Health Status/QoL Questionnaire



- Prolongation of QoL in patients treated with FOLFIRINOX compared with GEM, despite greater toxicity
- Specifically, longer time to deterioration in:
  - Global health status
  - Physical, cognitive, and social functioning
  - Symptoms such as fatigue, nausea/vomiting, pain, and anorexia

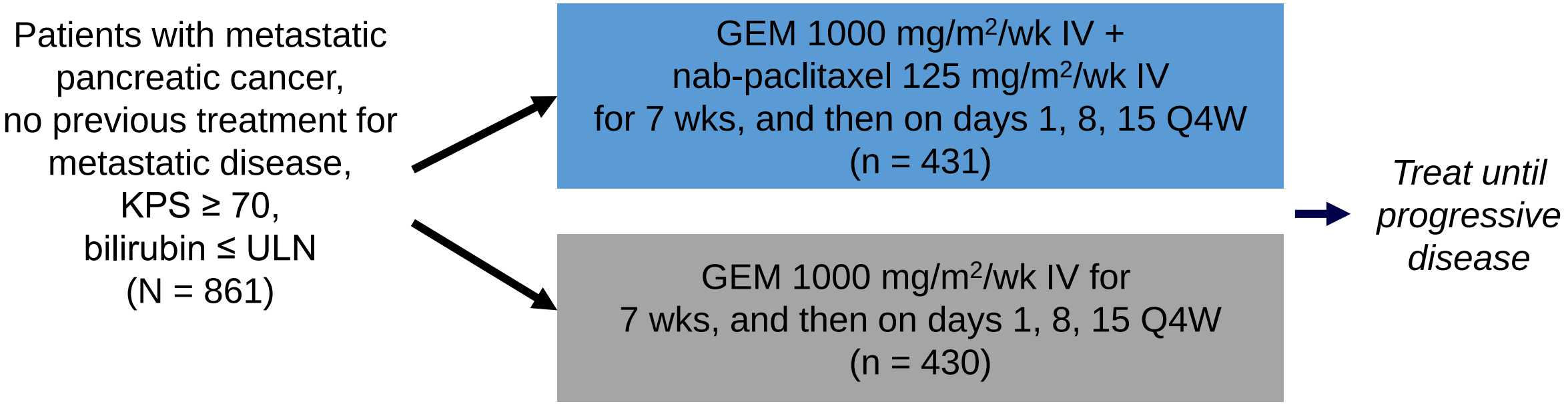
QoL, quality of life.

Gourgou-Bourgade S, et al. *J Clin Oncol*. 2013;31(1):23-9.

MPACT: GEM ± Nab-Paclitaxel

Patients With Metastatic Pancreatic Cancer

- Multicenter, open-label, randomized, phase III trial

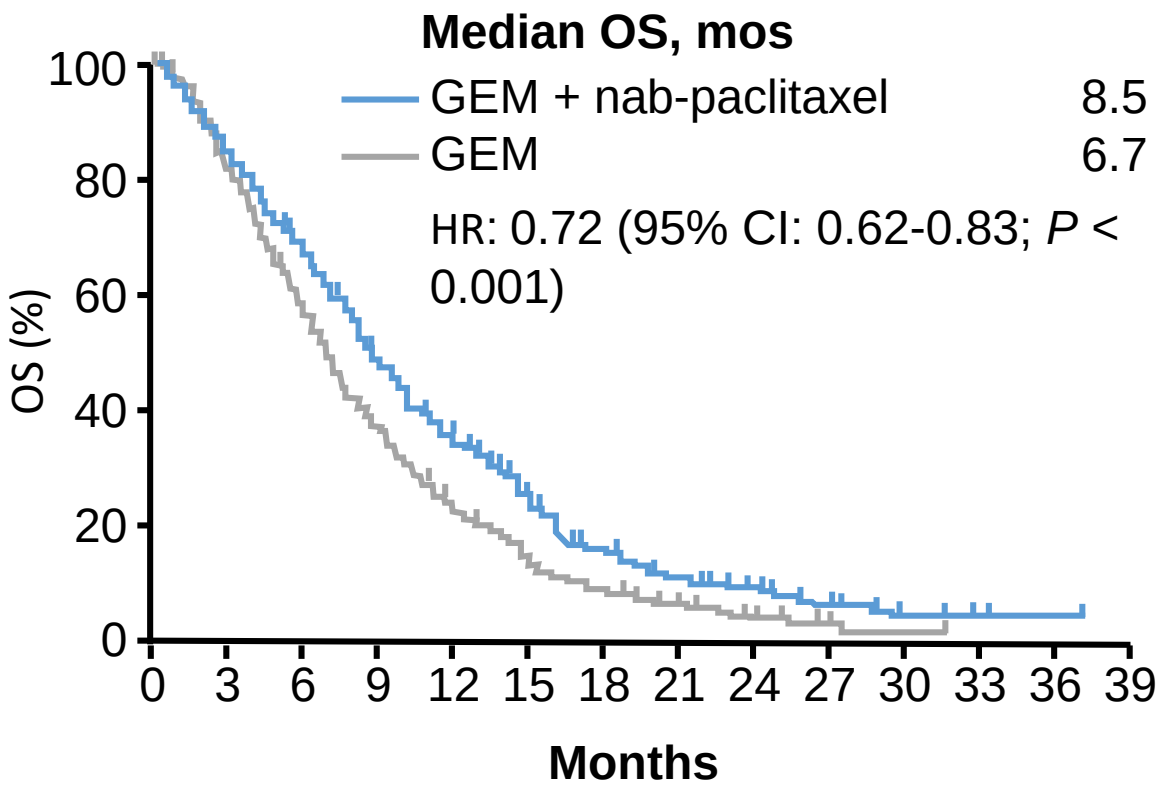


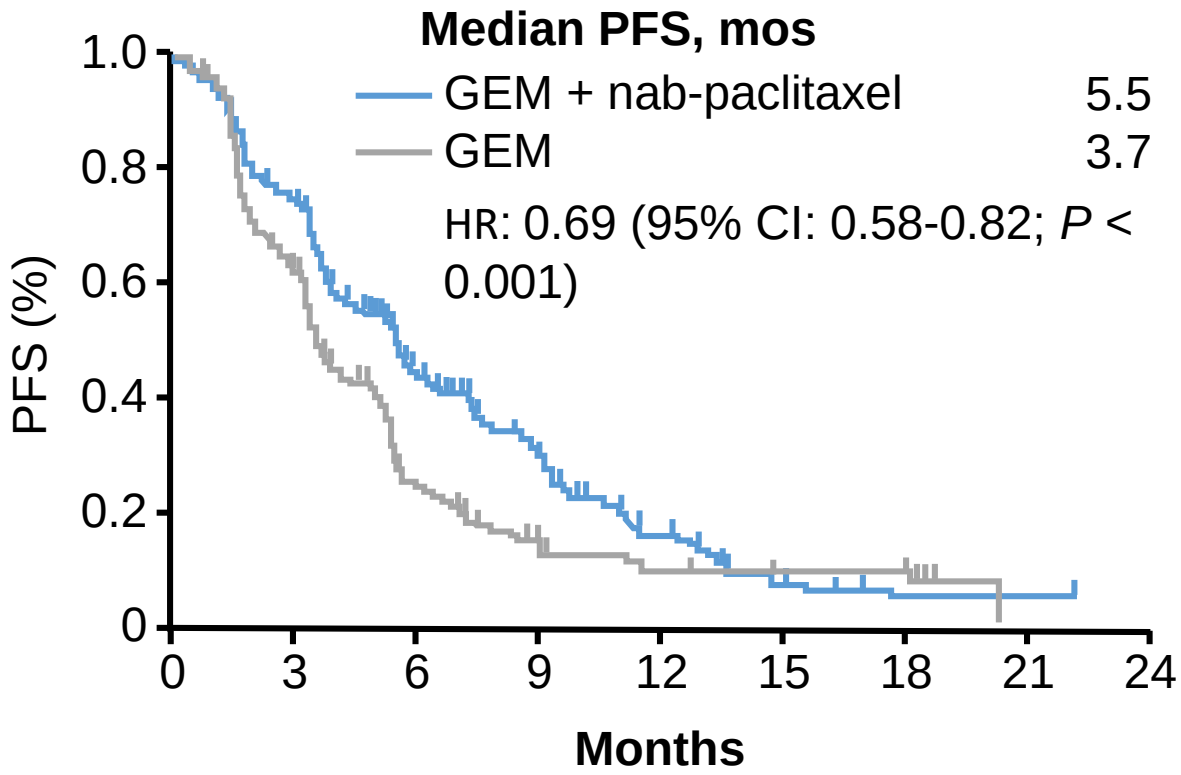
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, safety

KPS, Karnofsky performance scale; Q4W, every 4 weeks; ULN, upper limit of normal.

Von Hoff DD, et al. *New Engl J Med*. 2013;369(18):1691-703.

MPACT: GEM ± Nab-Paclitaxel





Von Hoff DD, et al. *New Engl J Med*. 2013;369(18):1691-703.

Pivotal Front-Line Metastatic Pancreatic Cancer Trials

Trial characteristics and outcomes	PRODIGE 4/ACCORD 11 FOLFIRINOX vs. GEM (N = 342)		MPACT Nab-pac + GEM vs. GEM (N = 861)	
Median age, years (range)	61 (25-76)		62 (27-86)	
Male, %	62		57	
ECOG PS/KPS (0/100, 1/80-90, 2/60-70), %	37/62/1		16/76/8	
Tumor location (H/B/T), %	39/31/26		43/31/25	
Median involved metastatic sites, n	2		2.5	
Outcomes	**FOLFIRINOX**	**GEM**	**Nab-pac + GEM**	**GEM**
ORR	32%	9%	23%	7%
Disease control rate	70%	51%	48%	33%
Median PFS, months	6.4	3.3	5.5	3.7
Median OS, months	11.1	6.8	8.5	6.7

Gourgou-Bourgade S, et al. *J Clin Oncol*. 2013;31(1):23-9.; Von Hoff DD, et al. *New Engl J Med*. 2013;369(18):1691-703.

Pivotal Front-Line Metastatic Pancreatic Cancer Trials

AEs	FOLFIRINOX	GEM	Nab-pac + GEM	GEM
Neutropenia	45.7%	21%	38%	27%
Febrile neutropenia	5.4%	1.2%	3%	1%
Leukopenia	-	-	31%	16%
Thrombocytopenia	9.1%	3.6%	13%	9%
Anemia	7.8%	6%	13%	12%
Fatigue	23.6%	17.8%	17%	7%
Vomiting	14.5%	8.3%	-	-
Diarrhea	12.7%	1.8%	6%	1%
Neuropathy	9%	-	17%	1%
Elevated ALT	7.3%	20.8%	-	-
Thromboembolism	6.6%	4.1%	-	-

Gourgou-Bourgade S, et al. *J Clin Oncol*. 2013;31(1):23-9.; Von Hoff DD, et al. *New Engl J Med*. 2013;369(18):1691-703.

Guideline Recommendations for Advanced or Metastatic Disease

Guideline	ECOG PS 0-1	ECOG PS 2	ECOG PS 3-4
ASCO	FOLFIRINOX Nab-paclitaxel + GEM	GEM GEM + erlotinib Capecitabine	BSC Cancer-directed therapy on a case-by-case basis
ESMO	FOLFINOX Nab-paclitaxel + GEM	PS 2 or bilirubin > 1.5 ULN: GEM PS 2 due to high tumor burden: nab-paclitaxel + GEM	BSC
NCCN	FOLFINOX Nab-paclitaxel + GEM	GEM Nab-paclitaxel + GEM (if patient is still caring for self)	BSC GEM

ESMO. https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Cancer-of-the-Pancreas/eUpdate-Cancer-of-the-Pancreas-Treatment-Recommendations. March 15, 2019.; Khorana AA, et al. *J Clin Oncol.* 2019;37(23):2082-8.; NCCN. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic_blocks.pdf. November 26, 2019.

Relapsed/Recurrence of Disease

	CONKO-003		PANCREOX		NAPOLI-1		
Population	PD on GEM therapy		Prior GEM therapy		Prior GEM therapy		
N	160		108		417		
Treatment	OFF (n = 76)	5-FU/LV (n = 84)	mFOLFOX6 (n = 54)	5-FU/LV (n = 54)	Nal-IRI + 5-FU/LV (n = 117)	5-FU/LV (n = 149)	Nal-IRI (N=151)
Median OS, months	5.9	3.3	6.1	9.9	6.1	4.2	4.9
	HR: 0.66 (95% CI: 0.48-0.91) p = 0.01		HR: 1.78 (95% CI: 1.08-2.93) p = 0.02		HR: 0.67 (95% CI: 0.41-0.92) p = 0.012	HR: 0.99 (95% CI: 0.77-1.28) P = 0.94	
Median PFS, months	2.9	2.0	3.1	2.9	3.1	1.5	2.7
	HR: 0.68 (95% CI: 0.50-0.94) p = 0.02		HR: 1.00 (95% CI: 0.66-1.53) p = 0.99		HR: 0.56 (95% CI: 0.41-0.75) p = 0·0001	HR: 0.81 (95% CI: 0.63-1.04) p = 0.1	
Median ORR, %	NR		13.2	8.5	16	1	6
			p = 0.36		p < 0.001	p = 0.02	

OFF, oxaliplatin, 5-FU, + LV; PD, progressive disease.

Gill S, et al. *J Clin Oncol*. 2016;34(32):3914-20.; Oettle H, et al. *J Clin Oncol*. 2014;32(23):2423-9.; Wang-Gillam A, et al. *Lancet*. 2016;387(10018):545-57.

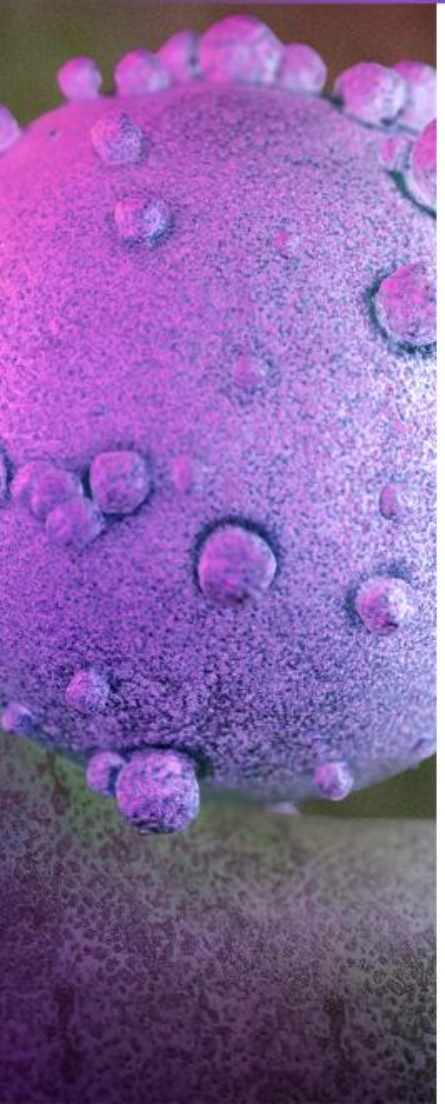
Current Treatment Sequencing for Metastatic Pancreatic Cancer

First-line therapy*		FOLFIRINOX	Nab-paclitaxel + GEM	GEM
Second-line*	ECOG PS 0-1	GEM-based therapy Nab-paclitaxel + GEM GEM	Nal-IRI + 5-FU Fluoropyrimidine-based therapy	5-FU-based therapy
	ECOG PS 2	GEM BSC	Fluoropyrimidine alone BSC	BSC
	ECOG PS 3-4	BSC	BSC	BSC

*Clinical trial should always be offered if available

Lambert A, et al. *Ther Adv Med Oncol*. 2019;11:1-43.

Immunotherapy

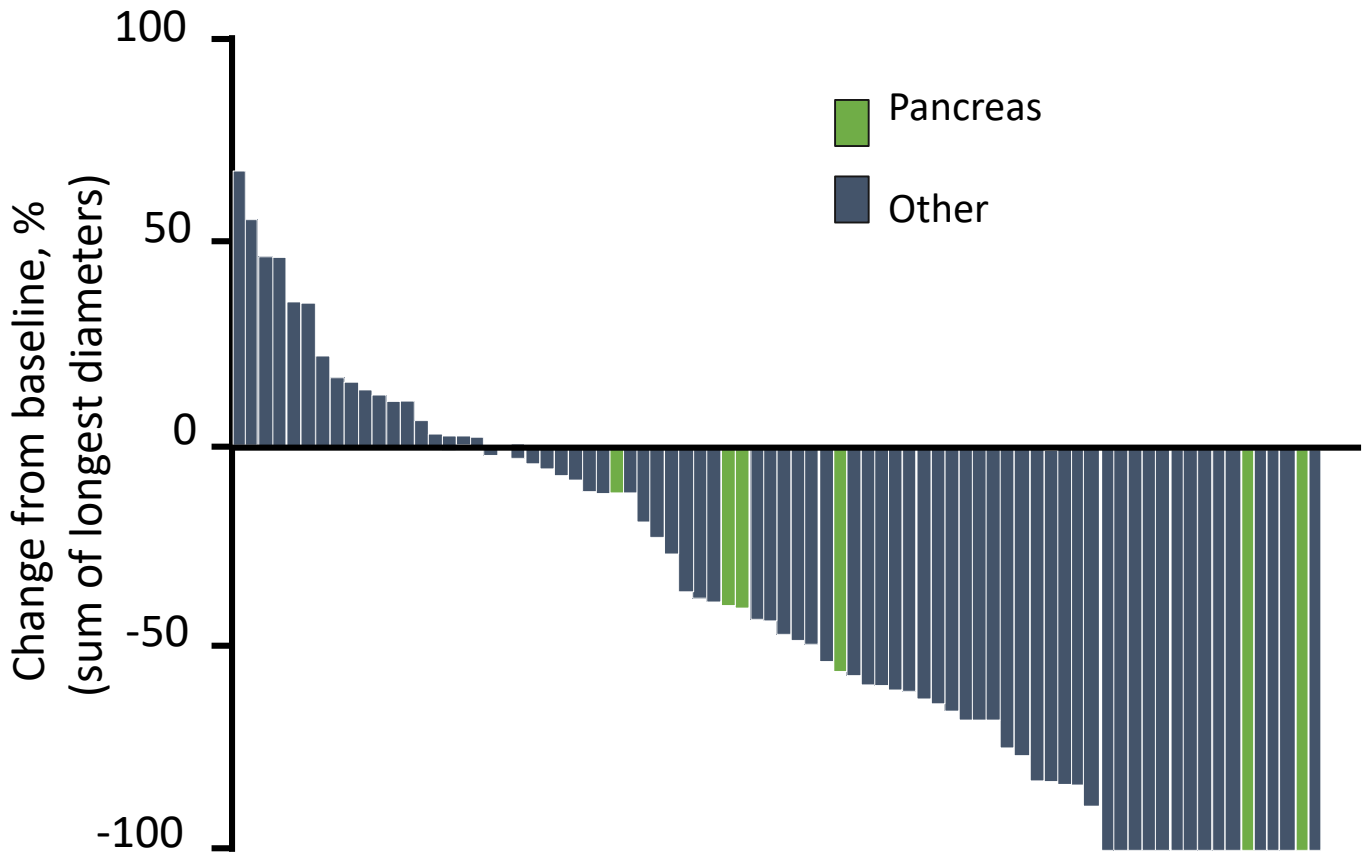


- Early studies of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death receptor (PD-1)/programmed cell death receptor ligand (PD-L1) antibodies showed minimal to no activity in advanced pancreatic cancer
- No study with single-agent immunotherapy has been successful
- Pancreatic cancer appears resistant to immunotherapy
  - Unique tumor microenvironment
  - Low levels of tumor-infiltrating T-lymphocytes
  - Lower levels of antigens to target
- One exception: ~1% of pancreatic cancers are associated with defective mismatch repair and microsatellite instability (dMMR/MSI-high)

Rosenberg A, et al. *J Gastrointest Oncol*. 2018;9(1):143-59.

Pembrolizumab in dMMR/MSI-H

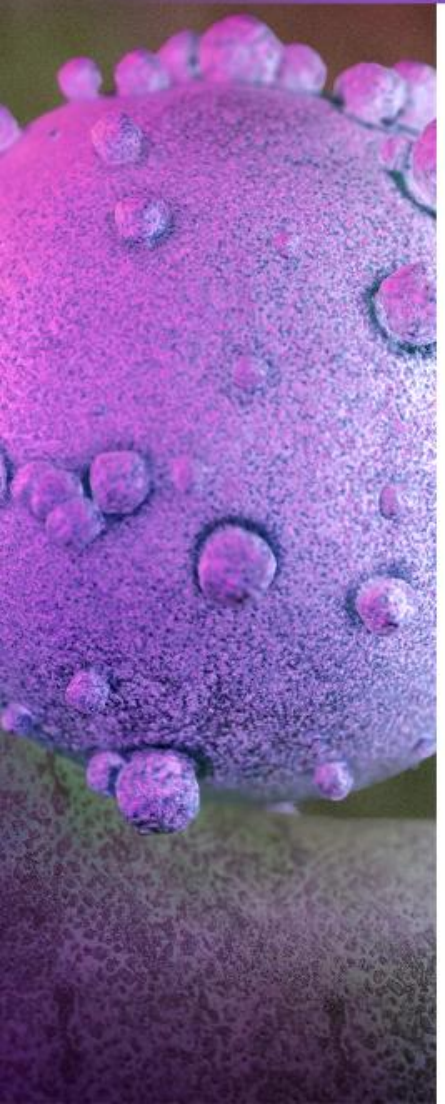
- KEYNOTE-016: phase II trial of **pembrolizumab** for patients with advanced solid tumors with dMMR
  - 5 of 6 patients with pancreatic cancer responded to pembrolizumab
- Pembrolizumab is FDA approved for advanced solid tumors with dMMR/MSI-H that have not responded to conventional therapy
- No other immunotherapy agent is approved for this indication at this time
- Multiple trials ongoing



FDA, United States Food and Drug Administration.

Humphris JL, et al. Gastroenterology. 2017;152(1):68-74.e2.;
Le. Science. 2017;357(6349):409-13.;
Pembrolizumab [prescribing information]. 2020.

Targeted Therapy



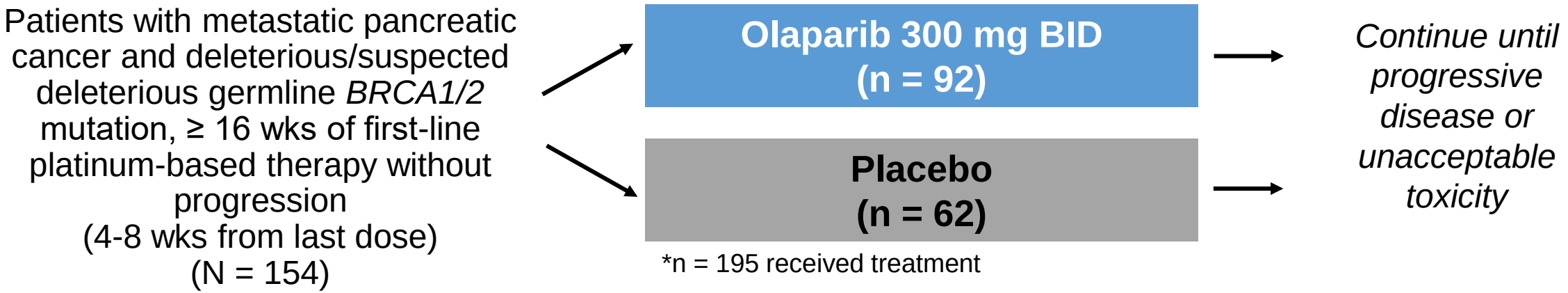
- Personalizing pancreatic cancer therapy based on biomarkers has not been highly successful

- BRCA 1/2
- Epidermal growth factor receptor (EGFR)
- Neurotrophic receptor tyrosine kinase (NTRK)

Lambert A, et al. *Ther Adv Med Oncol*. 2019;11:1-43.

BRCA 1 / 2 – POLO: Maintenance Therapy in Metastatic Pancreatic Cancer

- International, randomized, double-blind phase III trial



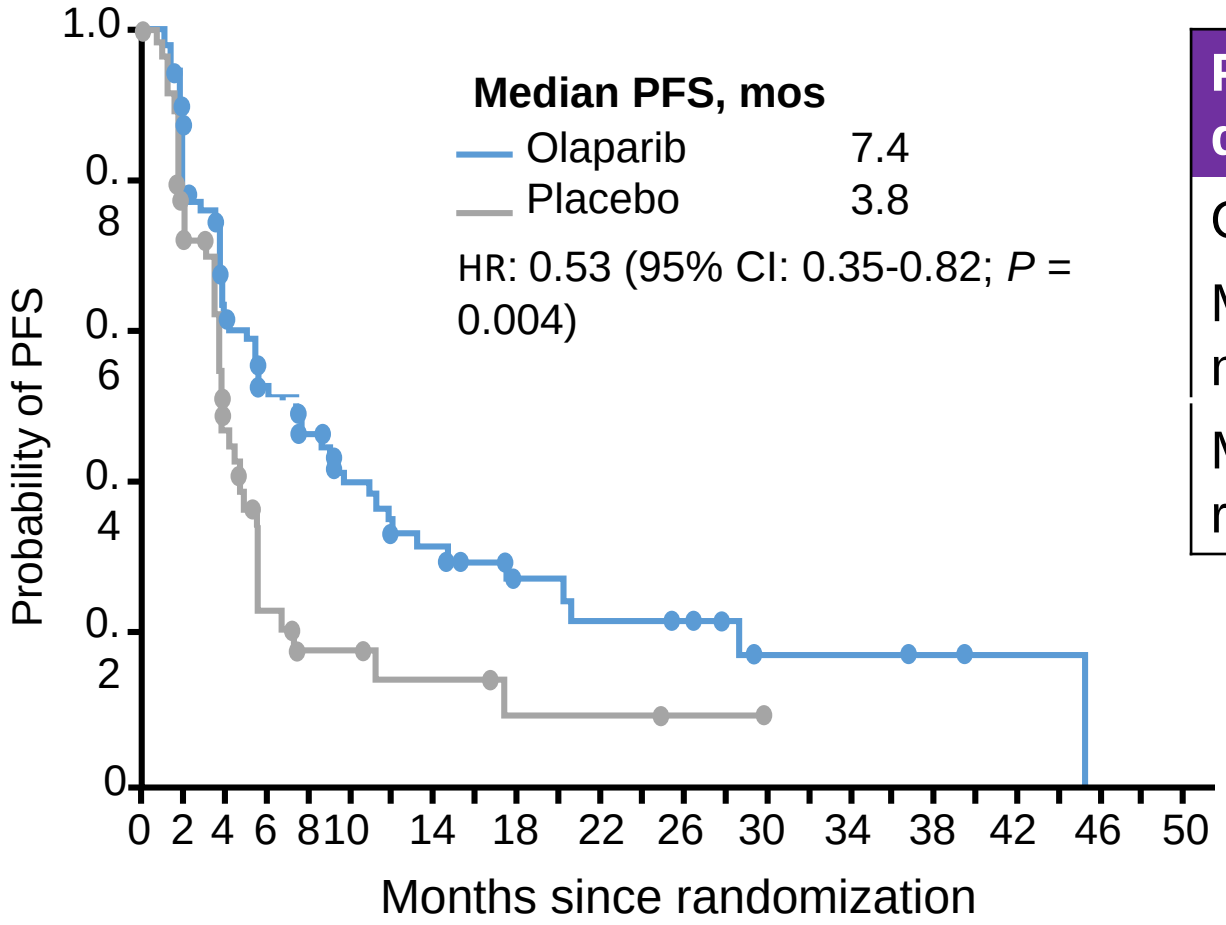
3315 patients screened; 247 had germline *BRCA* mutation (7.5%)

- Primary endpoint: PFS by blinded independent central review
- Key secondary endpoints: safety/tolerability, PFS2, ORR, OS, HRQoL

BID, twice daily; HRQoL, health-related quality of life.

Golan T, et al. *New Engl J Med*. 2019;381(4):317-27.

POLO: PFS and Response



Patients with measurable disease at baseline	Olaparib (n = 78)	Placebo (n = 52)
Objective response,* n (%)	18 (23.1)	6 (11.5)
Median time to response, months	5.4	3.6
Median duration of response, months	24.9	3.7

*2 patients in olaparib arm with ongoing complete response at data cutoff (Jan 15, 2019)

Golan T, et al. *New Engl J Med*. 2019;381(4):317-27.

POLO: Safety and QoL

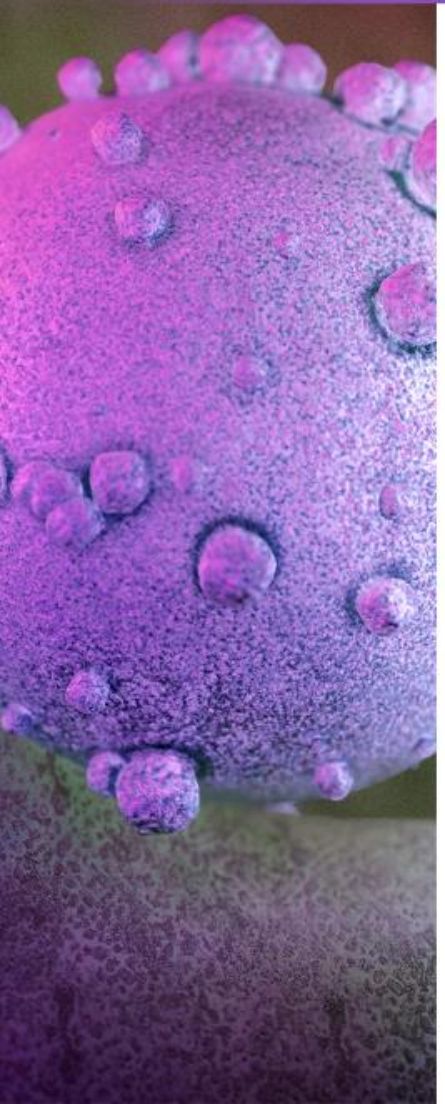
AE, %	Olaparib (n = 91)		Placebo (n = 60)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any	95.6	39.6	93.3	23.3
Fatigue/asthenia	60.4	5.5	35.0	1.7
Nausea	45.1	0	23.3	1.7
Diarrhea	28.6	0	15.0	0
Abdominal pain	28.6	2.2	25.0	1.7
Anemia	27.5	11.0	16.7	3.3
Decreased appetite	25.3	3.3	6.7	0
Constipation	23.1	0	10.0	0
Vomiting	19.8	1.1	15.0	1.7
Back pain	18.7	0	16.7	1.7
Arthralgia	15.4	1.1	10.0	0

AE, %	Olaparib (n = 91)	Placebo (n = 60)
Leading to dose interruption	35.2	5.0
Leading to dose reduction	16.5	3.3
Leading to treatment discontinuation	5.5	1.7

- Median duration of treatment, olaparib vs. placebo, months (range): 6.0 (0.8-45.3) vs. 3.7 (0.1-30.1)
- Assessment of patient-reported global HRQoL score: no clinically meaningful change from baseline in either arm
- Adjusted mean change from baseline, olaparib vs. placebo (mean + standard error): -1.20 (1.42) vs. 1.27 (1.95); *P* = 0.31

Golan T, et al. *New Engl J Med*. 2019;381(4):317-27.

EGFR



- Erlotinib + GEM vs. GEM alone

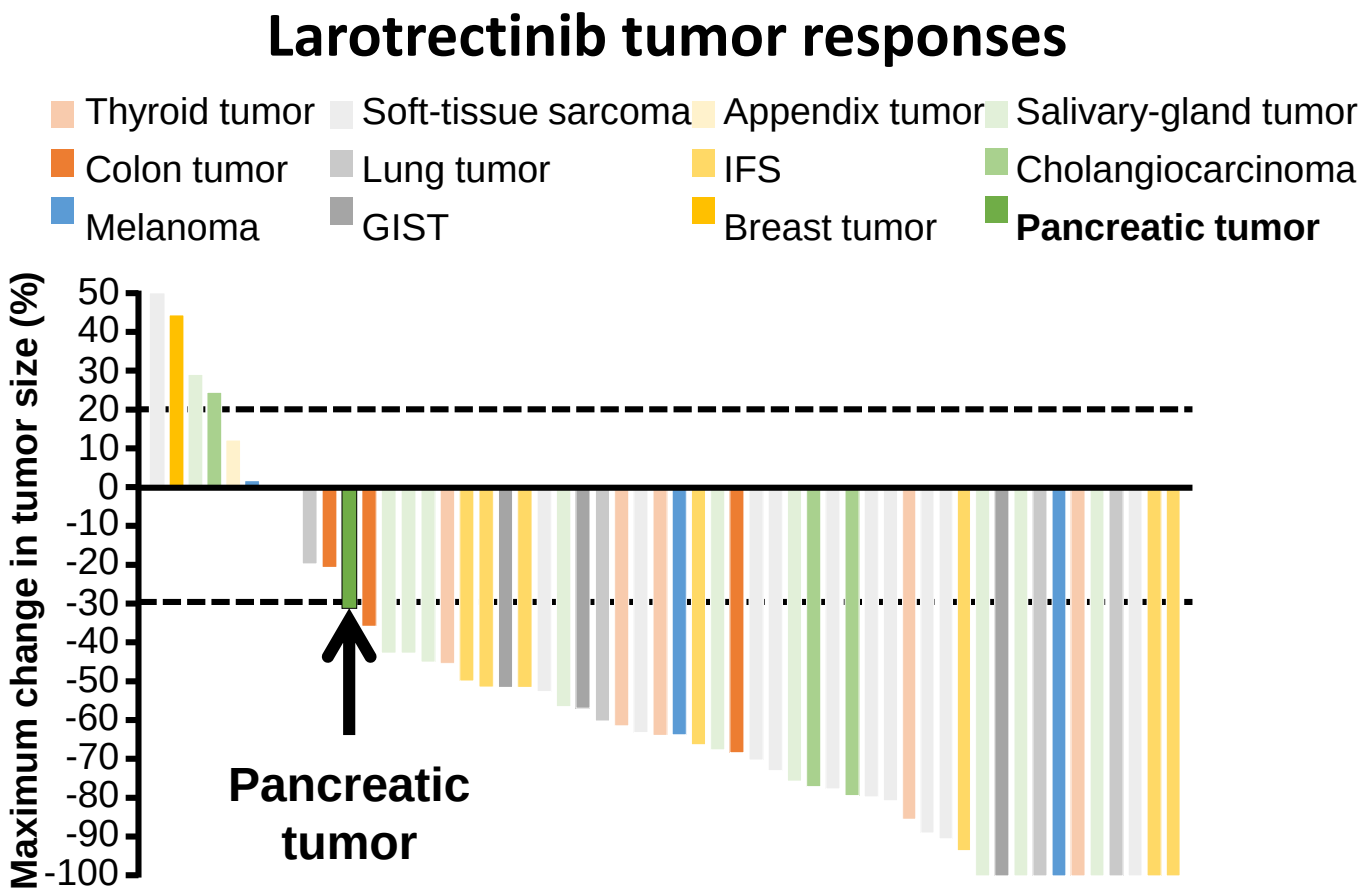
Outcome	GEM + erlotonib	GEM
N	285	284
OS	6.37	5.95
	HR = 0.81 (95% CI: 0.67 – 0.98), p = 0.03	
PFS	3.75	3.55
	HR = 0.77 (95% CI: 0.64 – 0.92), p = 0.004	
1-yr survival	23%	17%
	HR = 0.82 (95% CI: 0.69 – 0.99), p = 0.038	

- The data suggest that the benefit was seen in only a few patients
- A budget impact model found the combination was not cost effective

Moore MJ, et al. *J Clin Oncol.* 2007;25(15):1960-6.;
Soefje SA. *Am J Manag Care*. 2019;25(1 Suppl):S11-6.

NTRK Fusion-Positive Solid Cancers

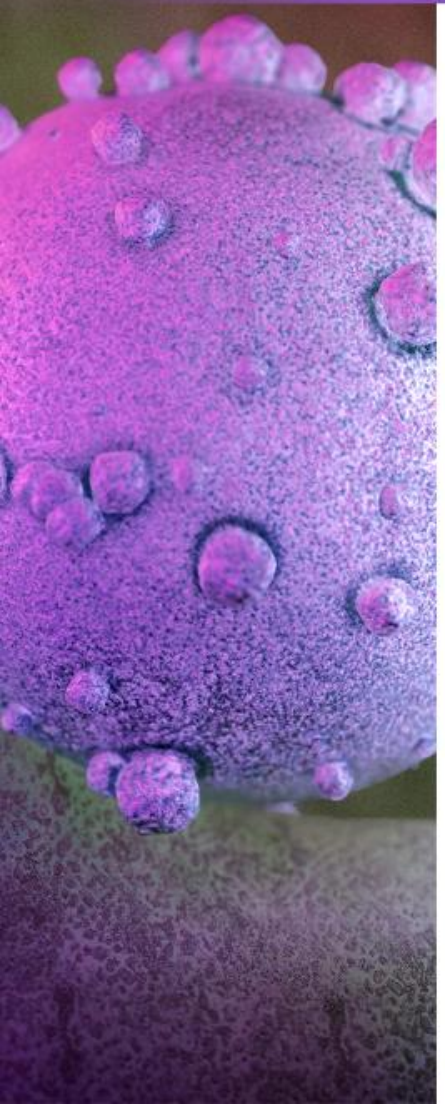
- Analysis of 3 open-label trials assessing **larotrectinib** for treating advanced solid tumors with NTRK gene fusion
  - (N = 55; 17 tumor types, most [60%] sarcomas; n = 1 pancreatic cancer)
  - ORR (investigator assessment): 80%; CR: 16%
- **Entrectinib** has been examined in 3 patients with pancreatic cancer
  - All 3 patients had improvements in quality of life and tumor response
  - One patient was still on therapy after 1 year
- Both are FDA approved for patients with advanced solid tumors with NTRK fusion positive that have not responded to conventional therapy



Drilon A, et al. *New Engl J Med*. 2018;378(8):731-9.;
Pishvaian MJ, et al. *J Clin Oncol*. 2018;36(4_suppl):521-521.

CR, complete response.

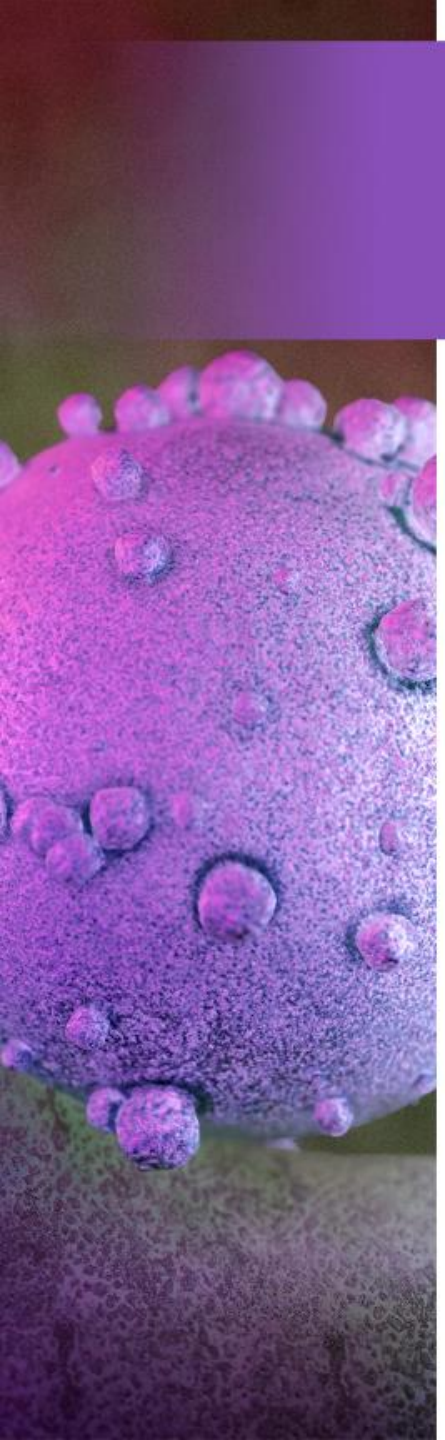
Vaccines



- Encouraging results from trials examining the use of cellular-based vaccines
- Two types of vaccines are being investigated:
  - Peptide-based cancer vaccines
  - Whole-cell vaccines
- Each has had successes and failures, but there is no clear proof they will make it into clinical practice anytime soon

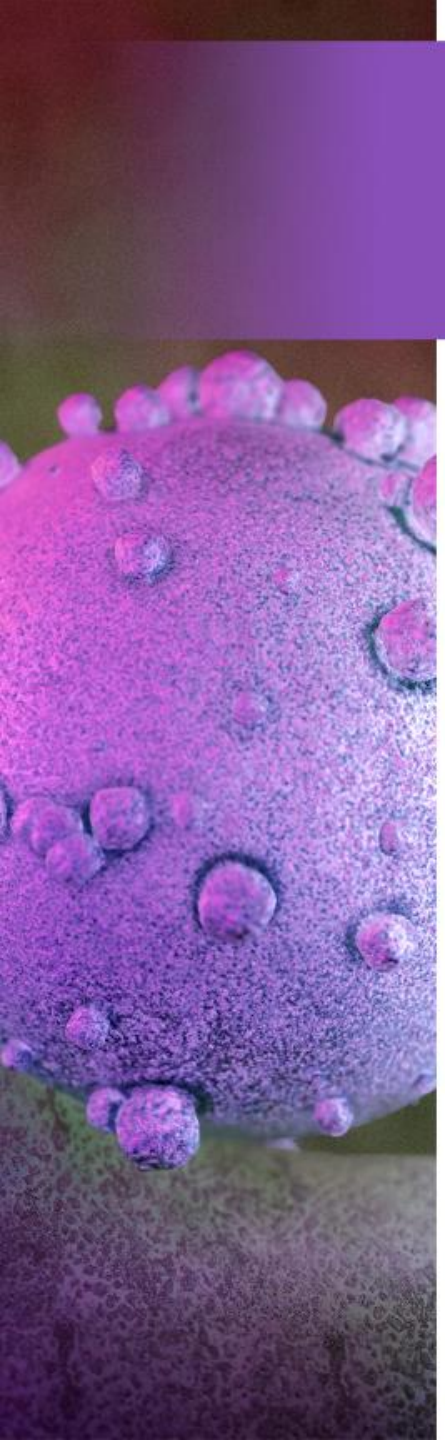
Lambert A, et al. *Ther Adv Med Oncol*. 2019;11:1-43.

Adoptive Cellular Therapy



- The patient's own T-cells are collected, activated, and expanded to attack a specific target and then reinfused
- Three types of cellular therapy products exist and are based on the method of activation
  - Tumor-infiltrating lymphocytes (TILs)
  - T-cells expressing a specific cancer T-cell receptor (TCR)
  - T-cells that express a chimeric antigen receptor (CAR)
- The CAR T-cell method appears to be most effective in pancreatic cancer
  - Early trials using the antimesothelin target have suggested activity

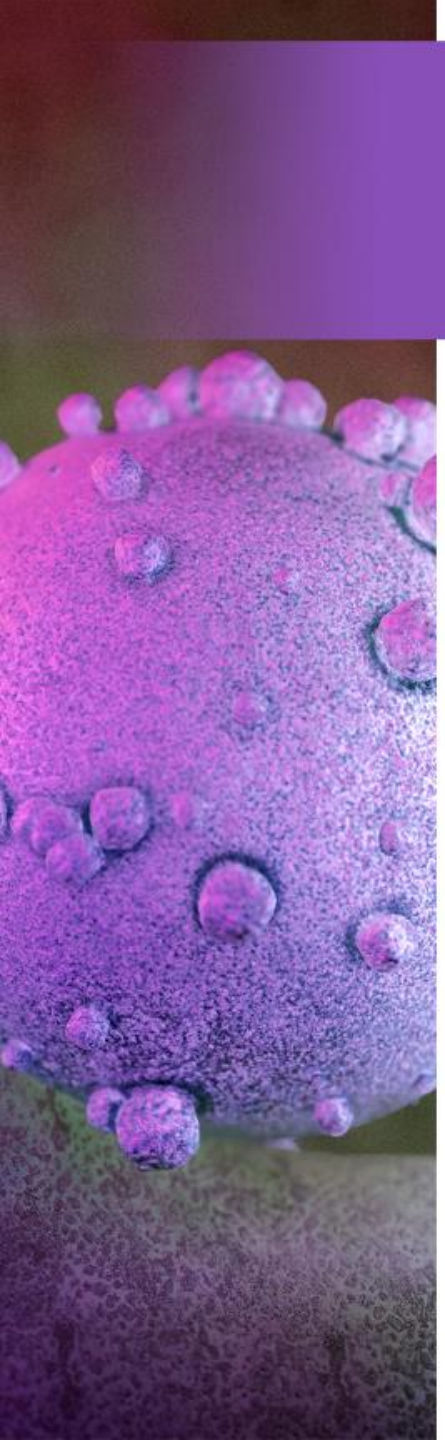
Beatty GL, et al. *Gastroenterology.* 2018;155(1):29-32.;
Lambert A, et al. *Ther Adv Med Oncol*. 2019;11:1-43.



Pharmacist Considerations – Pain Management

- Requires aggressive management
- Opioids are first-line management
- Antiepileptics, gabapentin, and pregabalin are considered for neuropathic pain
  - Disease-related pain
  - Treatment-related pain
  - *Nortriptyline and duloxetine also have analgesic efficacy*
- Corticosteroids are sometimes needed for visceral pain control
- Chemotherapy and CRT can be given for pain control
- Interventional techniques
- Alternative medicine
  - Acupuncture
  - Hypnosis

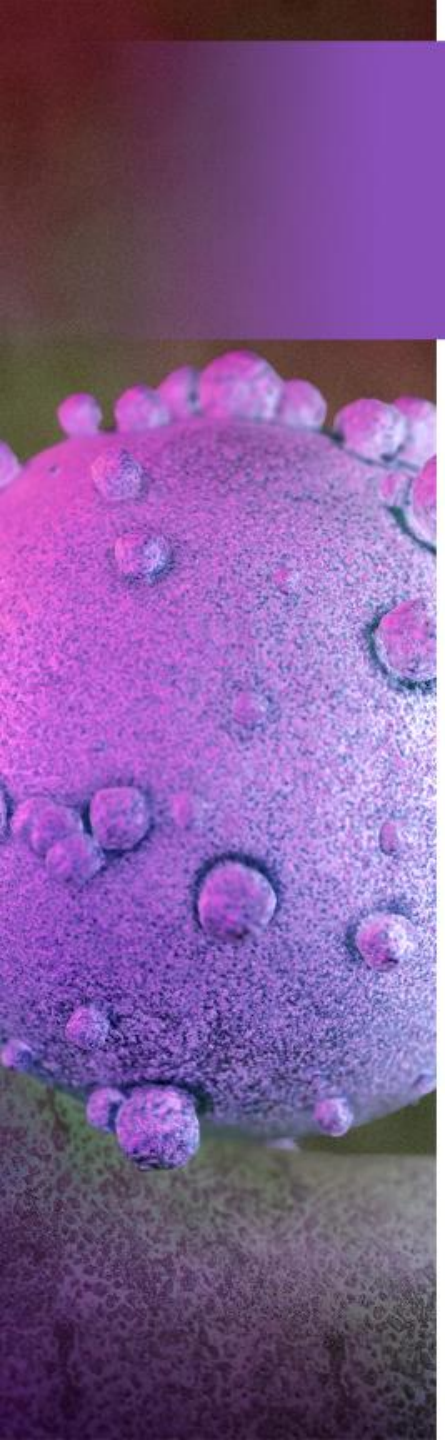
Lambert A, et al. *Ther Adv Med Oncol*. 2019;11:1-43.



Pharmacist Considerations – Anorexia and Weight Loss

- Patients experience cachexia owing to appetite loss, malnutrition, and hypercatabolism
- Weight loss leads to:
  - Weakness
  - Fatigue
  - Poor QoL
- Nutritional management is essential
  - Patients on pancreatic enzymes along with dietary counseling gain body weight
- Appetite-stimulant medications such as anamorelin may be considered in severe cases

Lambert A, et al. *Ther Adv Med Oncol*. 2019;11:1-43.

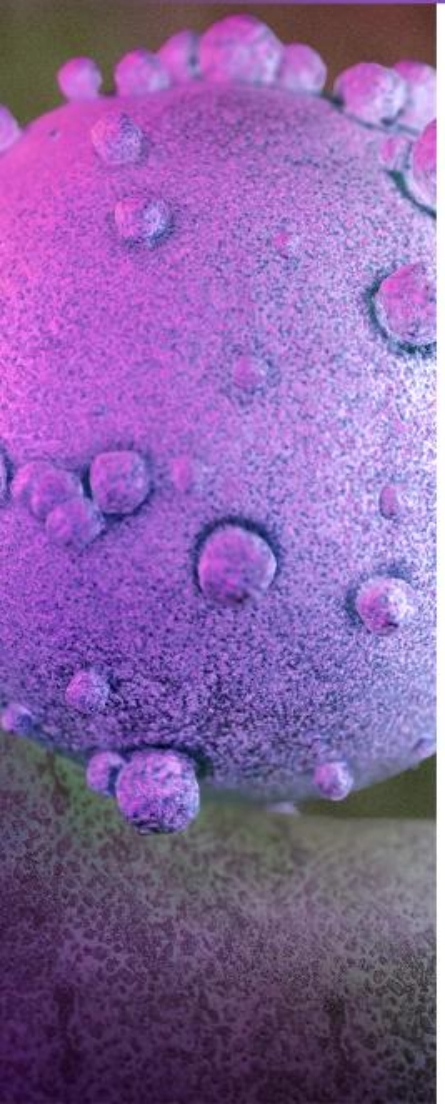


Pharmacist Considerations – Other Issues

- Neutropenia and neutropenic fever
  - Growth factors are not recommended for primary prophylaxis
    - After the development of neutropenic fever, they can be used for secondary prophylaxis
- Diarrhea
  - Instruct patients on how to deal with the diarrhea caused by irinotecan
  - Loperamide is the recommended therapy
    - Take 2 capsules at first sign of diarrhea and 1 capsule every 4 hours until diarrhea stops for 12 hours
- Peripheral neuropathy
  - Stocking/glove-type pattern progressing from tips of the fingers or toes
  - Evaluate frequently: the side effect is reversible if caught early
    - Ask patient about the buttoning of a shirt
    - Ask the patient to pick up a dime
  - If the neuropathy progress too far, it is often not reversible

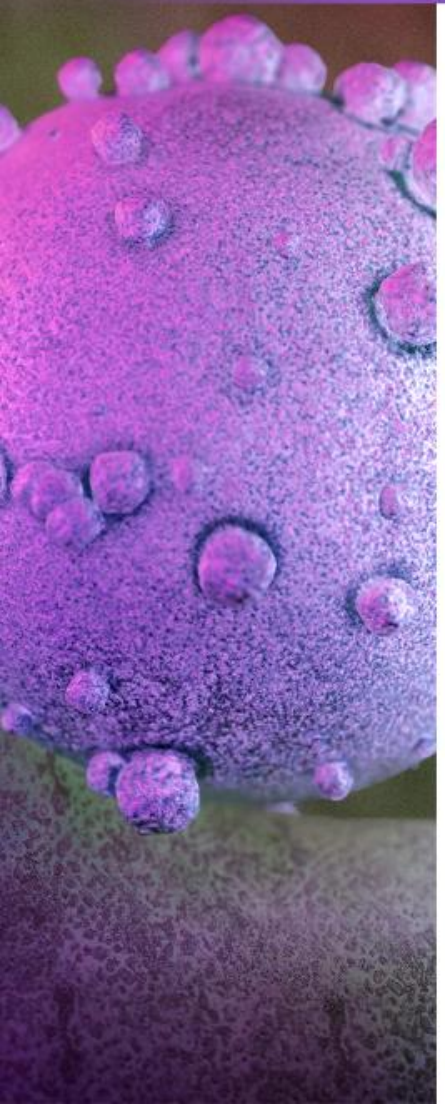
Stein A, et al. *Ther Adv Med Oncol*. 2010;2(1):51-63.

Conclusions

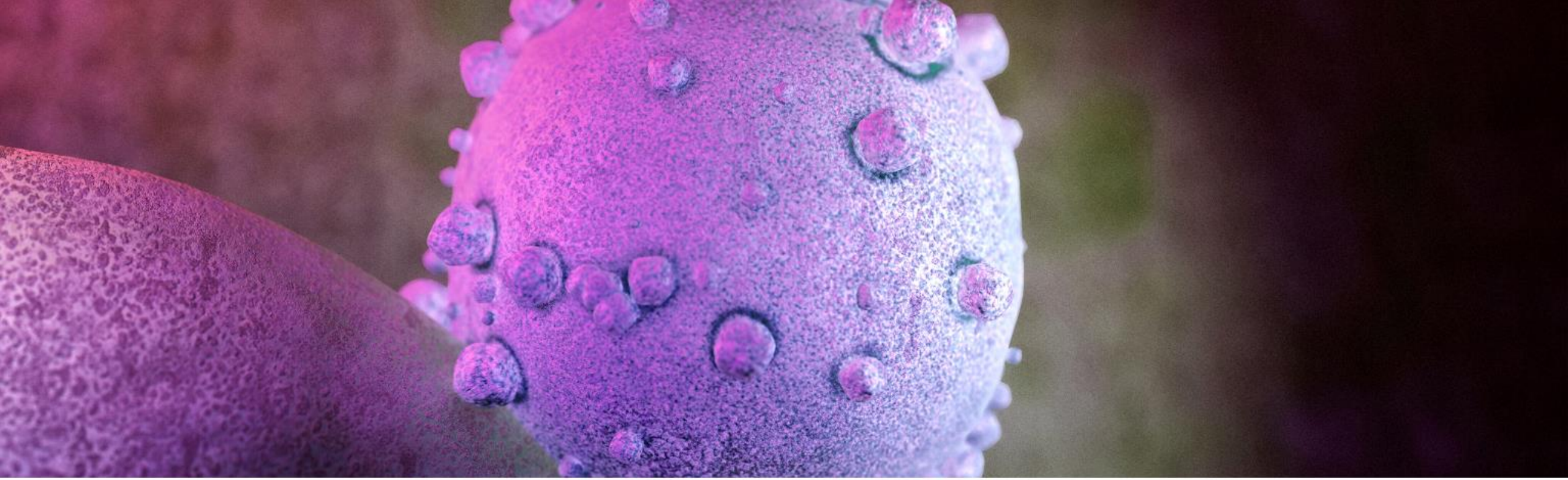


- Pancreatic cancer is very difficult to treat
- Surgery is the only curable treatment
- CRT is controversial but appears to offer no benefit
- Neoadjuvant therapy is unproven but part of standard practice for patients who may respond
- Adjuvant therapy, chemotherapy only, is the standard of care
- For advanced and metastatic disease, performance status drives decisions on therapy
- First-line therapy and performance status drive second-line therapy

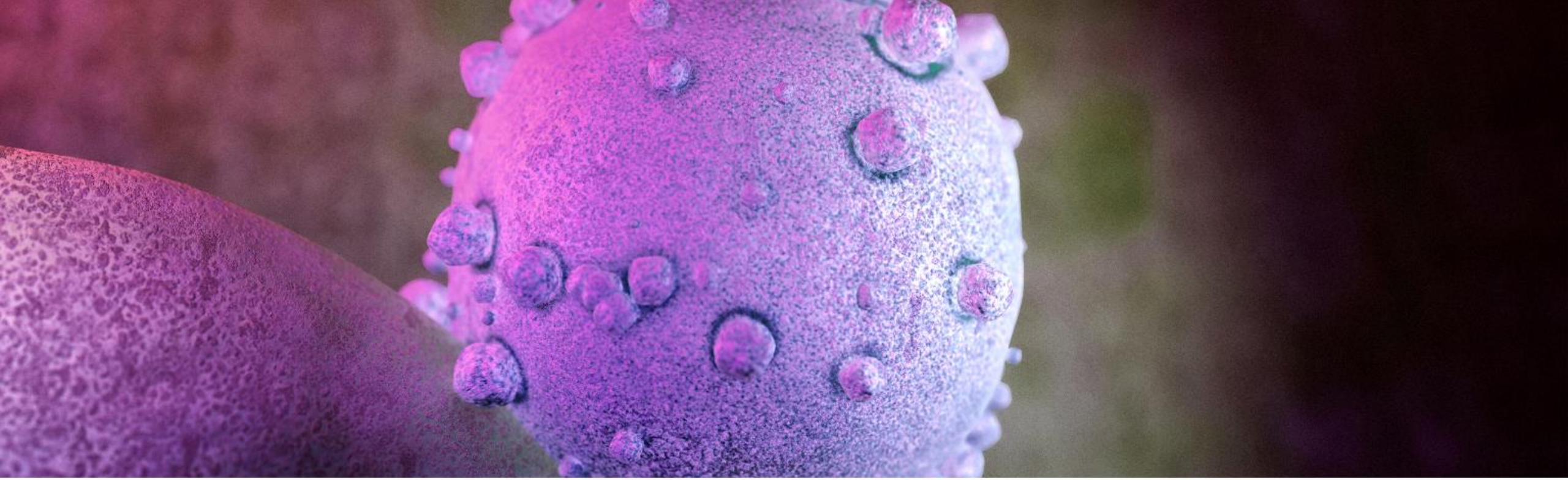
Conclusions



- Immunotherapy plays a very small role in pancreatic cancer
- Targeted therapy holds hope but still has not proven effective
  - PARP
  - NTRK
  - EGFR
- Other therapies hold promise but are very early in development
  - CAR T-cell
  - Vaccines
- Pharmacists' main impact is to help with symptom management and toxicity management



Questions and Answers



Thank You!