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LIVE

# Advances in the Treatment of Pancreatic Cancer: Nursing Education to Optimize Clinical Practice

**September 12, 2020, 4:00 PM**
**Los Angeles, California**

This program is supported by an educational grant from Celgene Corporation.

# Speaker and Disclosure Information

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**Gayle Jameson, MSN, ACNP-BC, AOCN,** has disclosed that she has received consulting fees and fees for non-CME/CE services from Celgene.

# Agenda

- Program Overview and Baseline Assessment
- Overview of Advanced Pancreatic Ductal Adenocarcinoma
- Current Therapeutic Options for Metastatic Pancreatic Cancer
  - First-line Treatment
  - Genetic Testing and Targeted Therapy for Pancreatic Cancer
  - Second-line Treatment
- Palliative Care for Patients With Pancreatic Cancer: Symptom Management and Prevention
- Emerging Strategies
- Closing Remarks and Question and Answer Session

# Outcomes Analysis: What Did You Learn?

- Some questions in this activity will be presented twice:
  once before the content, and then again later in the activity


- All responses will only be measured in aggregate (ie, your individual responses will not be identified)
- Thank you for helping us assess the impact of this educational activity

# Let’s Vote!

## How many patients with pancreatic cancer do you provide care for in a typical year?

1. < 5
2. 6-10
3. 11-15
4. 16-20
5. > 20

# Case Scenario 1: Patient Recently Diagnosed With Metastatic Pancreatic Cancer

- 76-yr-old man with stage IV ductal adenocarcinoma of the pancreas metastatic to the lungs
- PMH: type 2 diabetes, hypertension, atrial fibrillation
- KPS 70%, ECOG PS 2
- CA 19-9: 191 U/mL
- Germline/somatic testing: microsatellite stable, no *BRCA/PALB2* mutation or *NTRK* fusion detected

# Which of the following therapeutic strategies would you consider the best approach for this patient?

1. 5-FU/LV + nanoliposomal irinotecan
2. FOLFIRINOX
3. Gemcitabine
4. Gemcitabine + erlotinib
5. Gemcitabine + cisplatin
6. Gemcitabine + nab-paclitaxel
7. Uncertain

- 76-yr-old man with stage IV ductal adenocarcinoma of the pancreas metastatic to lungs
- PMH: type 2 diabetes, hypertension, atrial fibrillation; KPS 70%, ECOG PS 2; CA 19-9: 191 U/mL
- Microsatellite stable, no *BRCA/PALB2* mutation or *NTRK* fusion detected

## After 5 cycles of gemcitabine + nab-paclitaxel, the patient develops grade 3 chemotherapy-induced neuropathy. Which of the following management approaches would be best for this patient?

1. Continue treatment at current dose; administer antiseizure medication
2. Withhold gemcitabine until symptoms resolve to grade ≤ 1, then resume at next lower dose level
3. Withhold nab-paclitaxel until symptoms resolve to grade ≤ 1, then resume at next lower dose level
4. Withhold both agents until symptoms resolve to grade ≤ 1, then resume treatment at lower dose levels
5. Switch to FOLFIRINOX
6. Uncertain

- 76-yr-old man with stage IV ductal adenocarcinoma of the pancreas metastatic to lungs
- PMH: type 2 diabetes, hypertension, atrial fibrillation; KPS 70%, ECOG PS 2; CA 19-9: 191 U/mL
- Microsatellite stable, no *BRCA/PALB2* mutation or *NTRK* fusion detected

# Case Scenario 1:
# Patient Progressing on First-line Therapy

- While receiving gemcitabine + nab-paclitaxel, the patient's CA 19-9 levels dropped and a CT scan showed improvement in tumor burden
- However, after 6 cycles, disease progression was observed on CT scan; his KPS is 80%, ECOG 1

- 76-yr-old man with stage IV ductal adenocarcinoma of the pancreas metastatic to lungs
- PMH: type 2 diabetes, hypertension, atrial fibrillation; KPS 70%, ECOG PS 2; CA 19-9: 191 U/mL
- Microsatellite stable, no *BRCA/PALB2* mutation or *NTRK* fusion detected
- Treated with gemcitabine + nab-paclitaxel

# Which of the following therapeutic strategies would you consider the best approach for this patient?

1. Remain on current regimen; increase dose of nab-paclitaxel
2. Switch to 5-FU/LV
3. Switch to 5-FU/LV + nanoliposomal irinotecan
4. Switch to FOLFIRINOX
5. Switch to FOLFOX
6. Switch to pembrolizumab
7. Switch to olaparib
8. Uncertain

- 76-yr-old man with stage IV ductal adenocarcinoma of the pancreas metastatic to lungs
- PMH: type 2 diabetes, hypertension, atrial fibrillation; KPS 70%, ECOG PS 2; CA 19-9: 191 U/mL
- Microsatellite stable, no *BRCA/PALB2* mutation or *NTRK* fusion detected
- Treated with gemcitabine + nab-paclitaxel; initial response but progressive disease after 6 cycles; KPS now 80%/ECOG 1

# Overview of Advanced Pancreatic Ductal Adenocarcinoma

# Pancreatic Cancer: Scope of the Problem

- Projected **57,600 new cases** of pancreatic cancer in United States in 2020, with **47,050 deaths**; 5-yr OS is **9%**[1]
- Stage for stage, pancreatic cancer is associated with the **lowest survival rates** of any major cancer type[2]
- Within the next decade, pancreatic cancer is expected to rise to the second leading cause of cancer-related mortality in the United States (after lung cancer)[3]
- The **vast majority of patients (> 80%) are inoperable** at time of diagnosis[1]

1. American Cancer Society. Cancer facts & figures 2020. 2. Siegel. CA Cancer J Clin. 2020;70:7.
3. Rahib. Cancer Res. 2014;74:2913.

Slide credit: clinicaloptions.com

# Why Is Pancreatic Cancer so Lethal?

- Lack of early detection tools; no validated screening
- Symptoms occur during later stages of the disease
- Tumor has the ability to “hide” from the immune system
- Complex tumor biology/microenvironment
  - Numerous mutations
  - Stroma

Slide credit: clinicaloptions.com

# Staging in Pancreatic Cancer

| Clinical Staging |
| --- |
| Resectable |
| Borderline resectable |
| Unresectable (locally advanced or metastatic) |

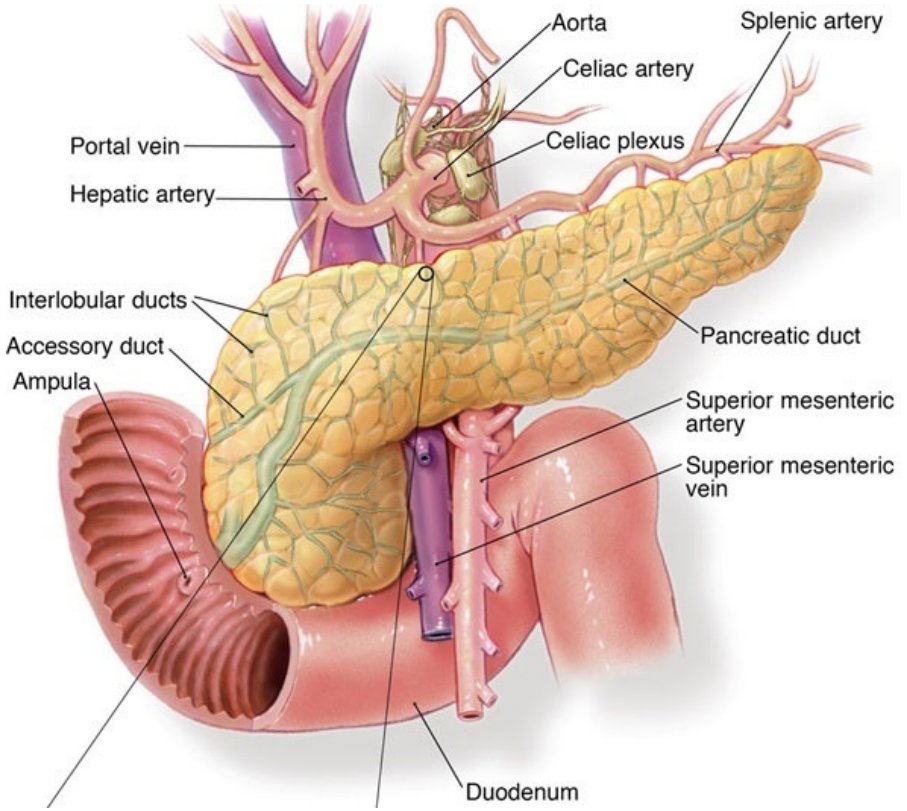
| AJCC Pathologic Staging | |
| --- | --- |
| Stage 0 | Tis, N0, M0 |
| Stage IA | T1, N0, M0 |
| Stage IB | T2, N0, M0 |
| Stage IIA | T3, N0, M0 |
| Stage IIB | T1-T3, N1, M0 |
| Stage III | T1-T4, N ≥ 2, M0 |
| Stage IV | Any T, any N, M1 |

AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017:337. ACS Pancreatic Cancer Stages.

Slide credit: clinicaloptions.com

# Advanced Pancreatic Ductal Adenocarcinoma

- Often has no early signs or symptoms[1]
- Presenting signs and symptoms can include
  - Weight loss: 85%
  - Jaundice: 55%
    - Tumor in head of pancreas can obstruct the biliary system
  - Steatorrhea: 25%
  - Vague abdominal pain: 79%
  - Epigastric pain: 71%
  - Nausea: 51%
  - Depression: > 70%; highest of any GI cancer[2]




1. Porta. Clin Transl Oncol. 2005;5:189. 2. Mayr. BMC Cancer. 2010;10:569.

Slide credit: clinicaloptions.com

# Role of CA 19-9 in Pancreatic Cancer

- Lewis blood group antigen (elevated in up to 90% of patients)[1]
- If nonsecretor, CA 125 or CEA may serve as an alternative marker[2]
- **Not** a screening test[1]
- Predictive value: decline correlates with response and OS[3]
- Analysis of MPACT (phase III trial of gemcitabine ± nab-paclitaxel for patients with metastatic pancreatic cancer, N = 861)[3]
  - CA 19-9 measured at baseline and Wk 8
  - Improved OS with any treatment when any CA 19-9 decline (80%) vs no decline: **11.1 vs 8.0 mos**
  - In gemcitabine + nab-paclitaxel arm, median OS for those with decline in CA 19-9 vs those without at 8 wks: **13.2 vs 8.3 mos**

1. Poruk. Curr Mol Med. 2013;13;340. 2. Meng. Onco Targets Ther. 2017:10:4591. 3. Chiorean. Ann of Oncol. 2016;27:654.

# Pancreatic Cancer: Risk Factors

| | |
|---|---|
| **Demographic Factors** | ▪ Advancing age, male, black, Ashkenazi Jewish ancestry |
| **Known Genetic Syndromes** | ▪ Lynch syndrome (HNPCC)<br>▪ Familial breast cancer *(BRCA2)*<br>▪ Peutz–Jeghers<br>▪ Ataxia telangiectasia<br>▪ Familial atypical multiple mole melanoma<br>▪ Hereditary pancreatitis |
| **Family History** | ▪ Risk increases along with number of first-degree relatives |
| **Host/Environmental Factors** | ▪ Type 2 diabetes*<br>▪ Chronic pancreatitis<br>▪ Obesity<br>▪ Tobacco use<br>▪ Heavy alcohol consumption<br>▪ *Vitamin D: contradictory evidence* |

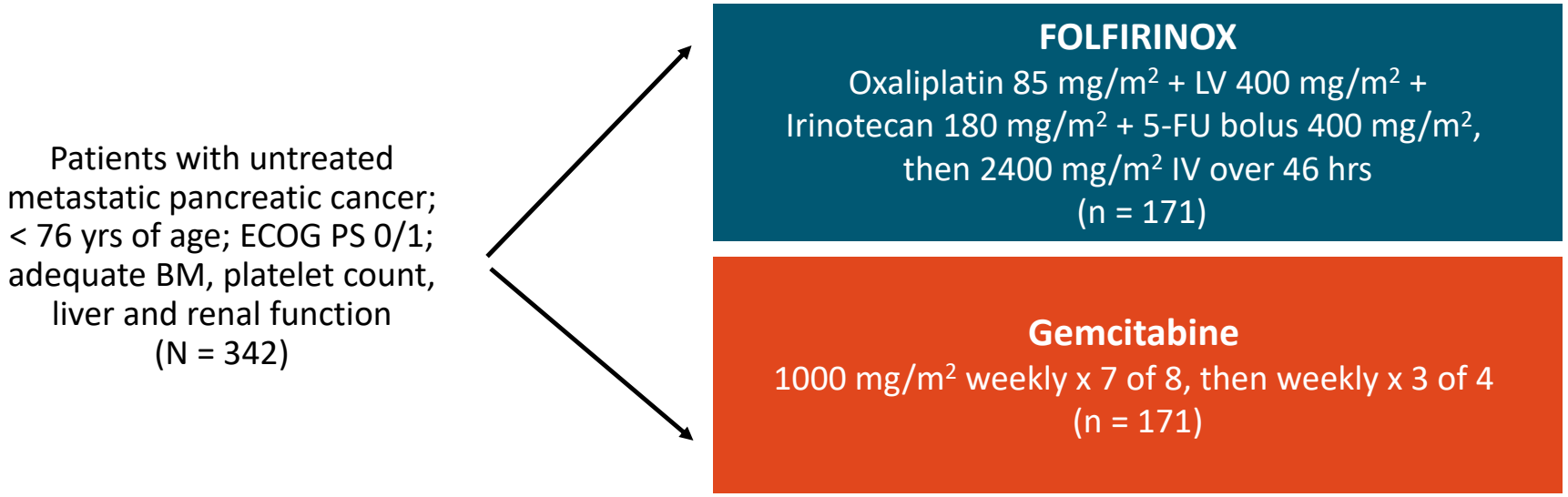
*Study of 2121 diabetic adults found that 1% of those diagnosed with diabetes at or after 50 yrs of age will be diagnosed with pancreatic cancer within 3 yrs.

ACS Pancreatic Cancer Risk Factors. Chari. Gastroenterology. 2005;129:504.

# Current Therapeutic Options for Metastatic Pancreatic Cancer: First-line Treatment

# FOLFIRINOX vs Gemcitabine for Patients With Metastatic Pancreatic Cancer

- Multicenter, randomized phase II/III trial

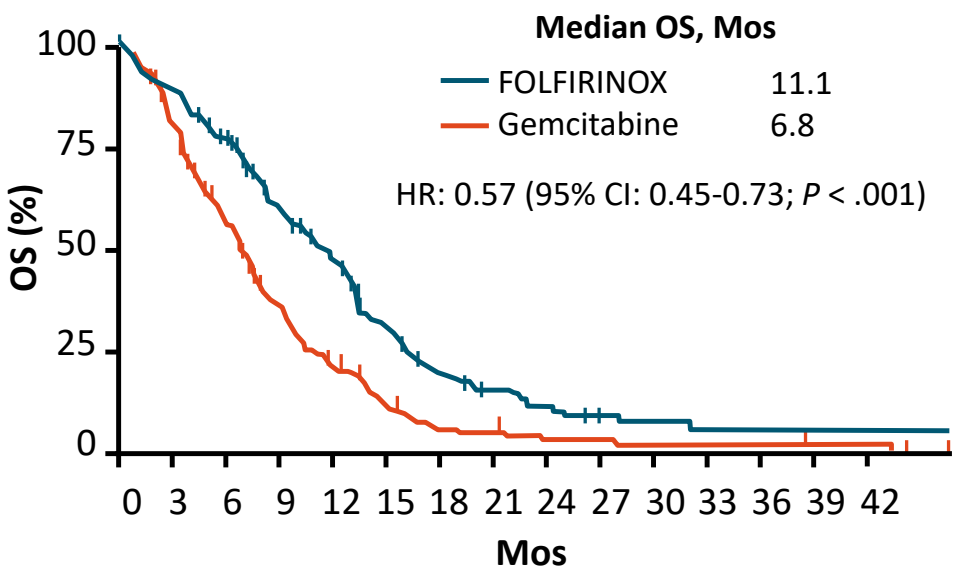


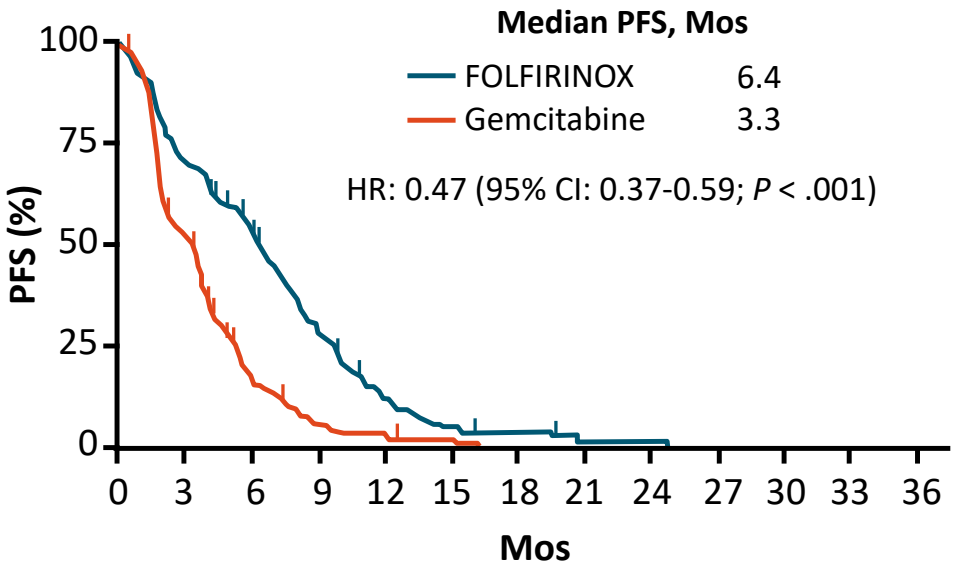

- Primary endpoints: ORR (phase II), OS (phase III)

Conroy. NEJM. 2011;364:1817.

Slide credit: clinicaloptions.com

# FOLFIRINOX vs Gemcitabine: OS and PFS




Conroy. NEJM. 2011;364:1817.

Slide credit: clinicaloptions.com

# FOLFIRINOX vs Gemcitabine: Safety

| Grade 3/4 AE, % | FOLFIRINOX (n = 171) | Gemcitabine (n = 171) | *P* Value |
|---|---|---|---|
| Hematologic | | | |
| ▪ Neutropenia | 45.7 | 21.0 | < .001 |
| ▪ Febrile neutropenia | 5.4 | 1.2 | .03 |
| ▪ Thrombocytopenia | 9.1 | 3.6 | .04 |
| Nonhematologic | | | |
| ▪ Fatigue | 23.6 | 17.8 | NS |
| ▪ Vomiting | 14.5 | 8.3 | NS |
| ▪ Diarrhea | 12.7 | 1.8 | < .001 |
| ▪ Sensory neuropathy | 9.0 | 0.0 | < .001 |
| ▪ Elevated ALT | 7.3 | 20.8 | < .001 |

Conroy. NEJM. 2011;364:1817.

Slide credit: clinicaloptions.com

# Management of Disease-Related Symptoms and Treatment-Related Adverse Events

- Nurses are vital to the shared decision-making model
- Critical for nurses to understand treatment options as they educate and empower patients in their healthcare decisions
- Nurses have a key role in educating, assessing, and caring for patients with disease-related symptoms and treatment-related adverse events
  - Needed for optimal patient outcomes

# Management of Key AEs: FOLFIRINOX

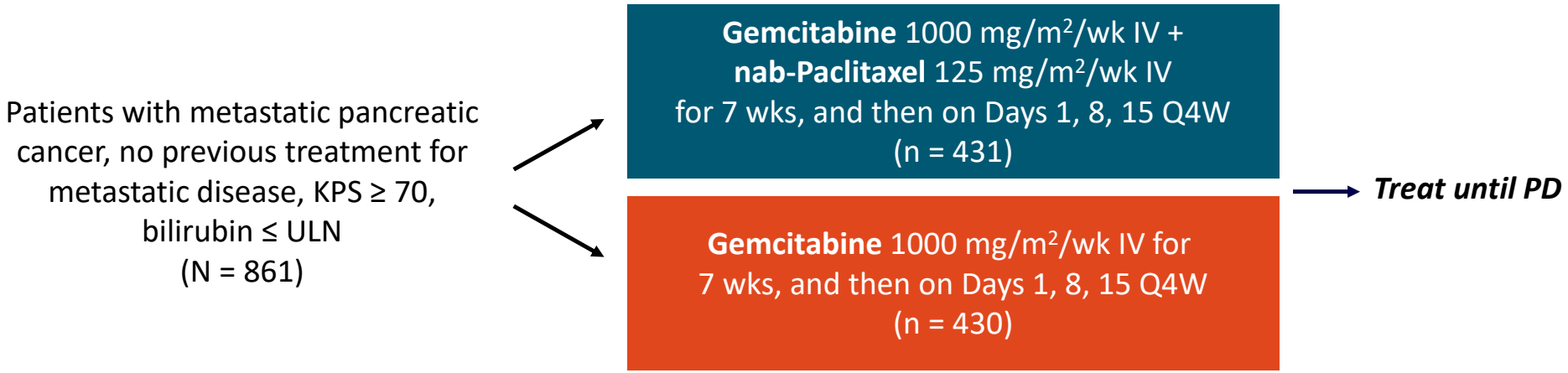
| AE | Key Management Considerations |
|---|---|
| Neutropenia/febrile neutropenia/thrombocytopenia | ▪ Decrease dose of 5-FU or oxaliplatin; omit irinotecan for febrile neutropenia<br>▪ Delay treatment until neutrophils ≥ 1.5 x $10^9$/L after grade 4 neutropenia |
| Diarrhea | ▪ Decrease dose of ≥ 1 component<br>▪ Diarrhea occurring > 24 hrs after injection may be prolonged and life threatening; treat promptly with loperamide, fluids, and electrolytes |
| Infusion reactions | ▪ Slow infusion time, provide atropine and/or proton pump<br>▪ Desensitization protocols |

1. Marsh. Cancer Med. 2015;4:853. 2. Oxaliplatin PI. 3. Irinotecan PI.

Slide credit: clinicaloptions.com

# MPACT: Gemcitabine ± nab-Paclitaxel for Patients With Metastatic Pancreatic Cancer

- Multicenter, open-label, randomized phase III trial

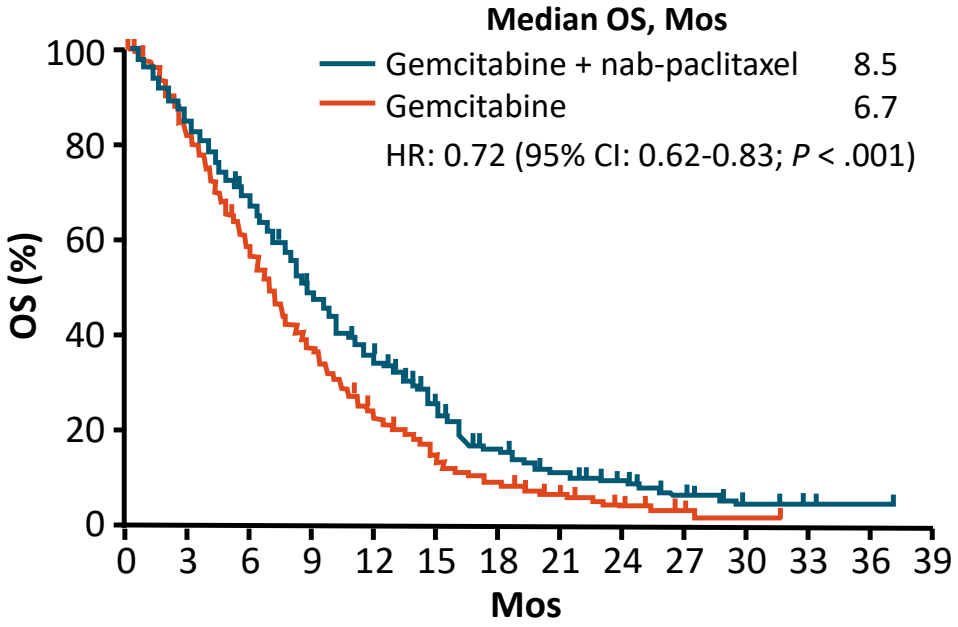


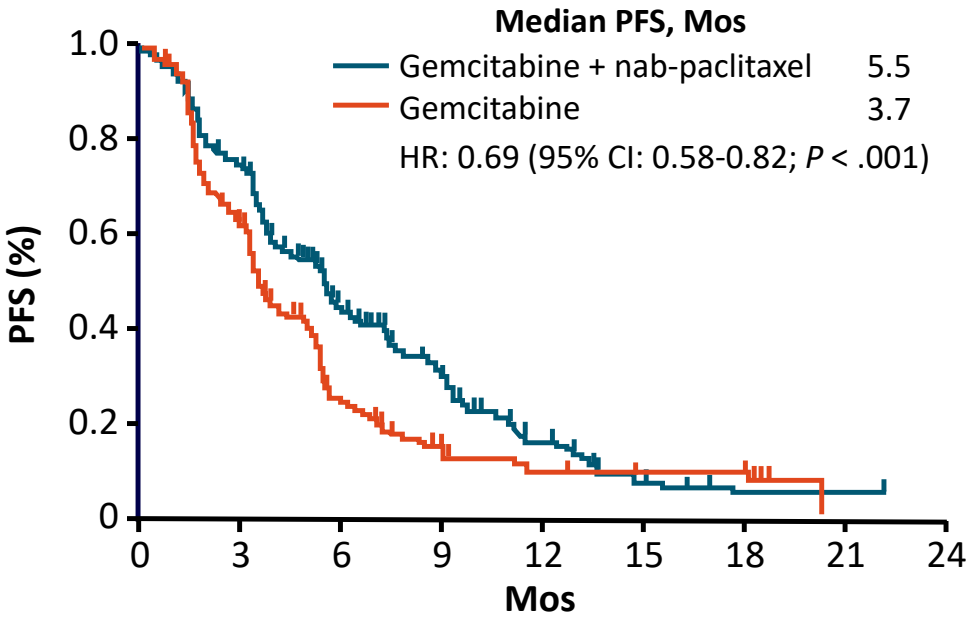

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, safety

Von Hoff. NEJM. 2013;369:1691.

Slide credit: clinicaloptions.com

# MPACT: OS and PFS




Von Hoff. NEJM. 2013;369:1691.

Slide credit: clinicaloptions.com

# MPACT: Safety

| Event, % | Gemcitabine + nab-Paclitaxel (n = 421) | Gemcitabine (n = 402) |
|---|---|---|
| AE leading to death | 4 | 4 |
| Hematologic AEs grade ≥ 3 | | |
| ▪ Neutropenia | 38 | 27 |
| ▪ Leukopenia | 31 | 16 |
| ▪ Thrombocytopenia | 13 | 9 |
| ▪ Anemia | 13 | 12 |
| Receipt of growth factors | 26 | 15 |
| Febrile neutropenia | 3 | 1 |
| Nonhematologic AEs grade ≥ 3 in ≥ 5% of patients | | |
| ▪ Fatigue | 17 | 7 |
| ▪ Peripheral neuropathy | 17 | 1 |
| ▪ Diarrhea | 6 | 1 |

Von Hoff. NEJM. 2013;369:1691.

Slide credit: clinicaloptions.com

# Management of Key AEs: Gemcitabine + nab-Paclitaxel

| AE | Key Management Considerations |
|---|---|
| Peripheral neuropathy | ▪ **Withhold therapy for grade 3/4 peripheral neuropathy; resume *nab-paclitaxel* at next lower dose level when neuropathy improves to grade ≤ 1 (no modification for gemcitabine)** |
| Neutropenia/febrile neutropenia/thrombocytopenia | ▪ Dose reduction or delays at Days 8 and/or 15 based on severity of neutropenia and prior dose reductions |
| Gastrointestinal toxicity | ▪ For grade 3/4: withhold until grade ≤ 1<br>▪ Resume at next lower dose level |
| Cutaneous toxicity | ▪ For grade 2/3: reduce to next lower level<br>▪ Discontinue if toxicity persists |

Scheithauer. J Gastrointest Oncol. 2016;7:469. nab-Paclitaxel PI.

Slide credit: clinicaloptions.com

# Frontline Regimens for Patients With Metastatic Pancreatic Cancer

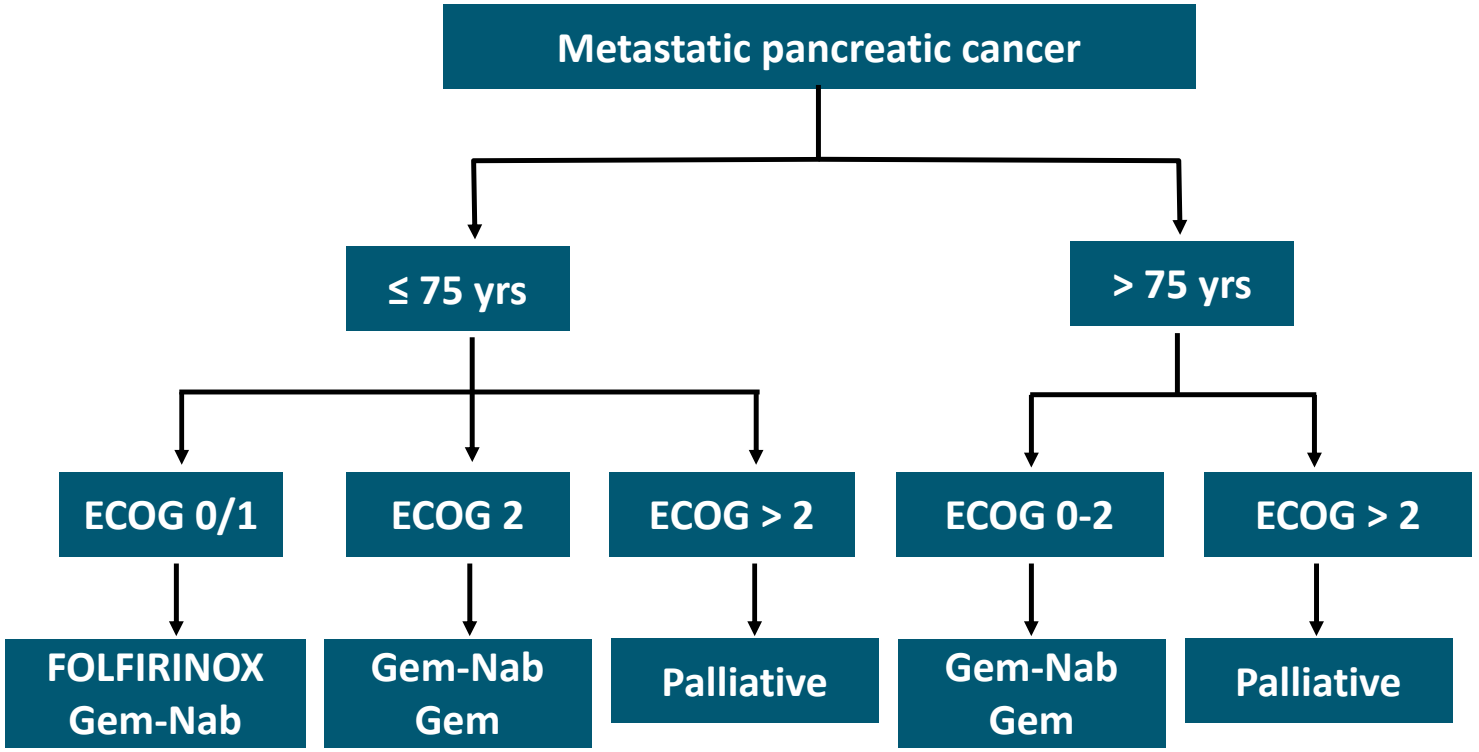
| Trial Characteristics and Outcomes* | FOLFIRINOX vs Gem (N = 342)[1] | nab-Pac + Gem vs Gem (N = 861)[2] |
|---|---|---|
| Median age, yrs (range) | 61 (25-76) | 62 (27-86) |
| Male, % | 62 | 57 |
| Region (NA/WE/EE/A), % | 0/100 (France)/0/0 | 62/9/15/14 |
| ECOG PS/KPS (0/100, 1/80-90, 2/60-70), % | 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 |
| ORR, % | 32 vs 9 | 23 vs 7 |
| Disease control rate, % | 70 vs 51 | 48 vs 33 |
| Median PFS, mos | 6.4 vs 3.3 | 5.5 vs 3.7 |
| Median OS, mos | 11.1 vs 6.8 | 8.5 vs 6.7 |

*A randomized trial comparing these two regimens has not been performed.

1. Conroy. NEJM. 2011;364:1817. 2. Von Hoff. NEJM. 2013;369:1691.

Slide credit: clinicaloptions.com

# Choice of Chemotherapy Regimen Based on Age and Performance Status

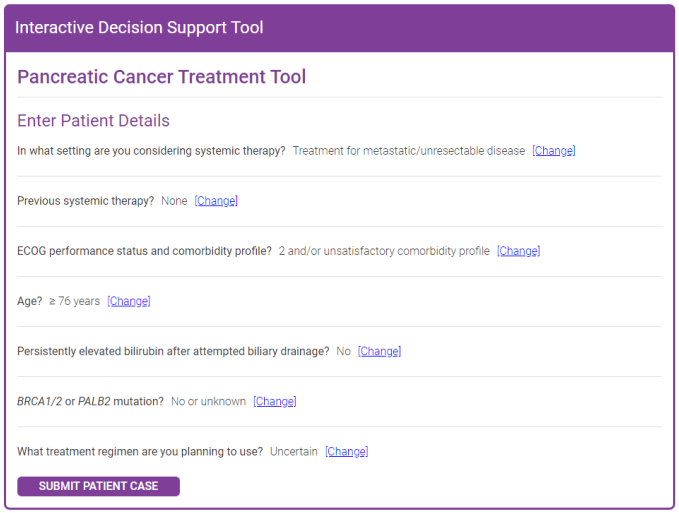


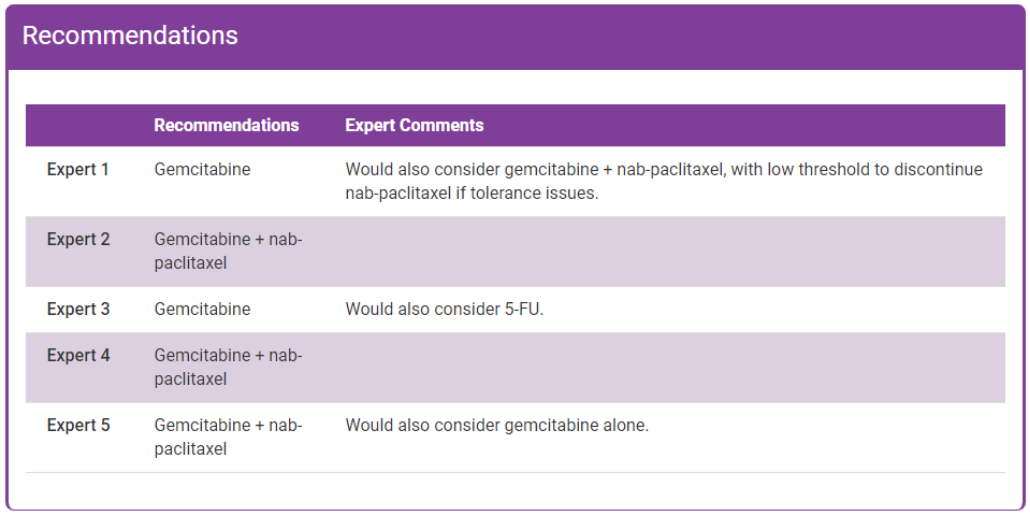

Higuera. World J Gastroenterol. 2016;22:764.

Slide credit: clinicaloptions.com

# Online Treatment Decision Tool for Pancreatic Cancer

- Enter specific patient/disease characteristics by answering a series of multiple choice questions to get recommendations for your specific case from 5 experts
  - Andrew H. Ko, MD; Elena Gabriela Chiorean, MD; Dan Laheru, MD; Michael J. Pishvaian, MD, PhD; and Andrea Wang-Gillam, MD, PhD




**Available at: www.clinicaloptions.com/PancreaticTool**

Slide credit: clinicaloptions.com

# Revisiting Case Scenario 1: Patient Recently Diagnosed With Metastatic Pancreatic Cancer

- 76-yr-old man with stage IV ductal adenocarcinoma of the pancreas metastatic to the lungs
- PMH: type 2 diabetes, hypertension, atrial fibrillation
- Performance status: KPS 70%, ECOG 2
- CA 19-9: 191 U/mL
- Germline/somatic testing: microsatellite stable, no *BRCA/PALB2* mutation or *NTRK* fusion detected

# Which of the following therapeutic strategies would you now consider the best approach for this patient?

1. 5-FU/LV + nanoliposomal irinotecan
2. FOLFIRINOX
3. Gemcitabine
4. Gemcitabine + erlotinib
5. Gemcitabine + cisplatin
6. Gemcitabine + nab-paclitaxel
7. Uncertain

- 76-yr-old man with stage IV ductal adenocarcinoma of the pancreas metastatic to lungs
- PMH: type 2 diabetes, hypertension, atrial fibrillation; KPS 70%, ECOG PS 2; CA 19-9: 191 U/mL
- Microsatellite stable, no *BRCA/PALB2* mutation or *NTRK* fusion detected

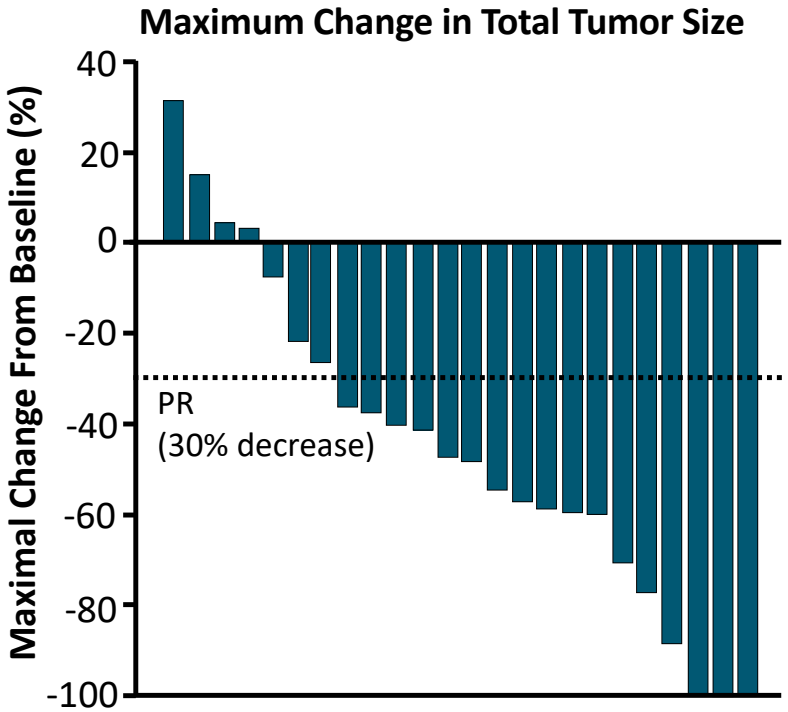
## After 5 cycles of gemcitabine + nab-paclitaxel, the patient develops grade 3 chemotherapy-induced neuropathy. Which of the following management approaches would be best for this patient?

1. Continue treatment at current dose; administer anti-seizure medication
2. Withhold gemcitabine until symptoms resolve to grade ≤ 1, then resume at next lower dose level
3. Withhold nab-paclitaxel until symptoms resolve to grade ≤ 1, then resume at next lower dose level
4. Withhold both agents until symptoms resolve to grade ≤ 1, then resume treatment at previous dose levels
5. Switch to FOLFIRINOX
6. Uncertain

- 76-yr-old man with stage IV ductal adenocarcinoma of the pancreas metastatic to lungs
- PMH: type 2 diabetes, hypertension, atrial fibrillation; KPS 70%, ECOG PS 2; CA 19-9: 191 U/mL
- Microsatellite stable, no *BRCA/PALB2* mutation or *NTRK* fusion detected

# nab-Paclitaxel + Gemcitabine + Cisplatin for Patients With Metastatic Pancreatic Cancer

- Open-label phase Ib/II study in which treatment-naive patients with metastatic pancreatic cancer received **nab-paclitaxel + gemcitabine + cisplatin** (25, 37.5, or 50 mg/m$^2$) (N = 25)




- MTD of cisplatin (phase II dose), 25 mg/m$^2$
- **Median OS: 16.4 mos**; median PFS: 10.1 mos
- Response
  - CR: n = 2 (8%; 1° endpoint of 25% CR not met)
  - ORR: 71%; disease control rate: 88%
- Most common grade ≥ 3 AEs: thrombocytopenia (68%), anemia (32%), neutropenia (24%)

Jameson. JAMA Oncol. 2019;[Epub ahead of print].

Slide credit: clinicaloptions.com

# Genetic Testing and Targeted Therapy for Pancreatic Cancer

# Case Scenario 2:
# Patient Achieving CR With Initial Therapy

- 56-yr-old man with stage IV PDAC metastatic to the lungs
- KPS 100%
- Family history: sister with breast cancer, mother had ovarian cancer
- Patient germline testing: *BRCA2* mutation
- He begins FOLFIRINOX chemotherapy and completes 12 cycles; CT scan shows CR

# Which of the following therapeutic strategies would you consider the best approach for this patient?

1. Stop treatment
2. Continue FOLFIRINOX with current dosing
3. Continue FOLFIRINOX with modified dosing
4. Switch to maintenance capecitabine
5. Switch to maintenance olaparib
6. Uncertain

- 56-yr-old man with stage IV PDAC metastatic to the lungs
- Performance status: KPS 100%
- Family history: sister with breast cancer, mother had ovarian cancer; patient germline testing: *BRCA2* mutation
- Begins FOLFIRINOX chemotherapy and completes 12 cycles; CR

# Germline and Somatic Testing: Recommendations and Therapeutic Implications

- National guidelines now recommend **germline (inherited gene) testing for ALL patients** diagnosed with pancreatic cancer, regardless of family history[1]
  - A study of 3030 patients with pancreatic cancer identified **high-risk gene mutations** *BRCA1, BRCA2, CDKN2A, TP53, MLH1,* and *ATM* in **5.5% of all pancreatic cancer patients**, including 7.9% with a family history and 5.2% without a family history of pancreatic cancer[2]
- Somatic (tumor tissue) may identify potential actionable mutations

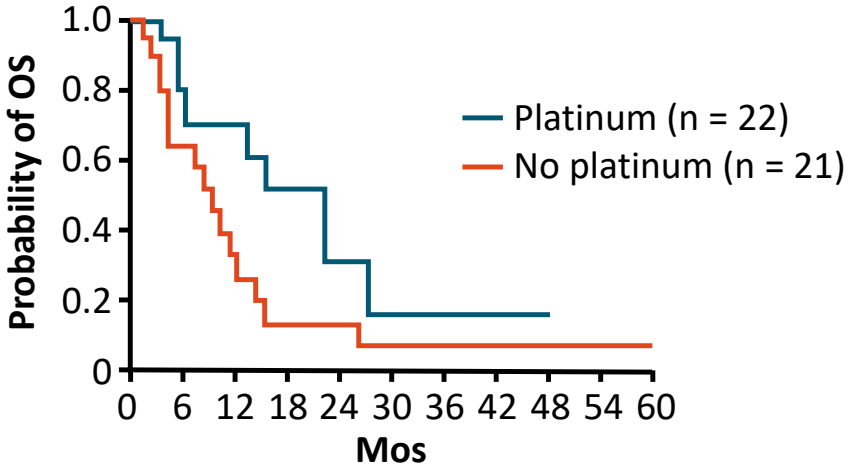
| Subtype | Examples | Potential Therapy |
|---|---|---|
| Immunogenic | MSI/MMR defects | Pembrolizumab (eg, anti–PD-1 mAbs) |
| DNA damage response (defective DNA repair) | *BRCA1/2, PALB2, ATM, CHEK2* mutations | Platinum agents, PARP inhibitors |
| Rare genetic abnormalities | *NTRK* fusions | TRK inhibitors (eg, larotrectinib, entrectinib) |

1. Stoffel. J Clin Oncol. 2019;37:153. 2. Hu. JAMA. 2018;319:2401.

Slide credit: clinicaloptions.com

# Earlier Studies in *BRCA*-Mutated Pancreatic Cancer

- Retrospective analysis of platinum-based therapy for patients with advanced pancreatic cancer with *BRCA1/2* mutation
  - **Superior OS** (22 vs 9 mos; *P* = .039) for patients with *BRCA1/2* mutations treated **with platinum** vs non-platinum chemotherapy regimens[1]



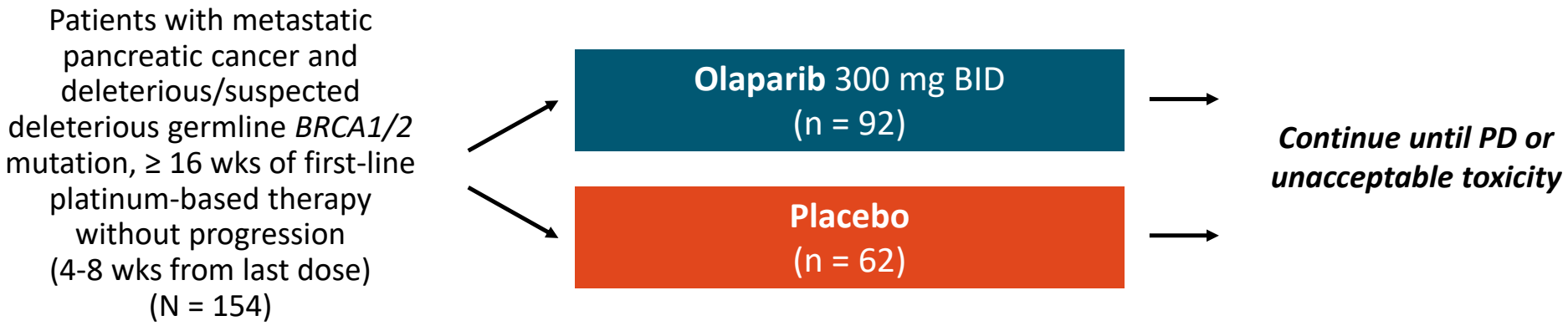

- Activity of PARP inhibitors (eg, olaparib) in patients with *BRCA* mutations; several ongoing/early phase trials
  - PARP inhibitors impair BER, inhibit SSBR/DSBR
  - Phase II study of olaparib for patients with germline *BRCA 1/2* mutation and prior gemcitabine: ORR in 5 of 23 (21.7%) patients[2]

1. Golan. Br J Cancer. 2014;111:1132. 2. Kaufman. JCO. 2015;33:244.

Slide credit: clinicaloptions.com

# POLO: Maintenance Olaparib vs Placebo After First-line Platinum-Based Therapy in Metastatic Pancreatic Cancer

- International, randomized, double-blind phase III trial

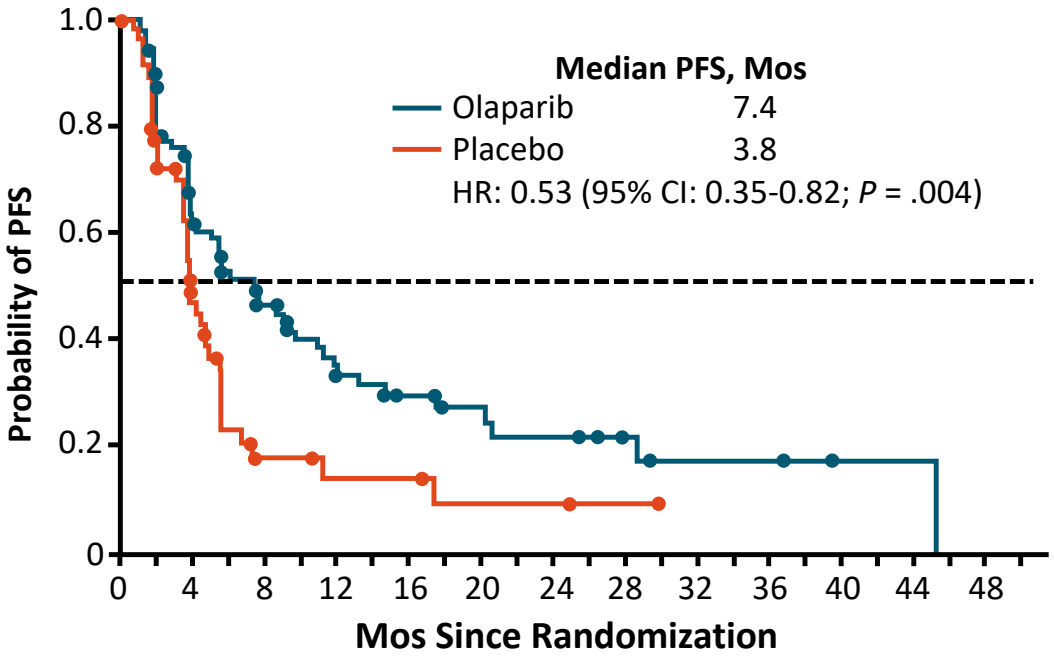



- 3315 patients screened; 247 had germline *BRCA* mutation (7.5%)
- Primary endpoint: PFS by blinded independent central review
- Key secondary endpoints: safety/tolerability, PFS2, ORR, OS, HRQoL

Golan. NEJM. 2019;381:317.

Slide credit: clinicaloptions.com

# 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, mos | 5.4 | 3.6 |
| Median duration of response, mos | 24.9 | 3.7 |

*Modified RECIST v1.1; 2 patients in olaparib arm with ongoing CR at data cutoff (January 15, 2019).

Golan. NEJM. 2019;381:317.

# POLO: Safety and QoL

| Adverse Event, % | 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 |

| Adverse Event, % | 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: 6.0 mos (range: 0.8-45.3) vs 3.7 mos (range: 0.1-30.1)
- Assessment of patient-reported global HRQoL score: no clinically meaningful change vs BL in either arm
  - Adjusted mean change from BL, olaparib vs placebo: -1.20 (SE: 1.42) vs 1.27 (SE: 1.95); *P* = .31

Golan. NEJM. 2019;381:317.

Slide credit: clinicaloptions.com

# Maintenance Therapy for Patients With Advanced Pancreatic Cancer

- Patients who have response or stable disease after 4-6 mos of chemotherapy may be considered for maintenance therapy

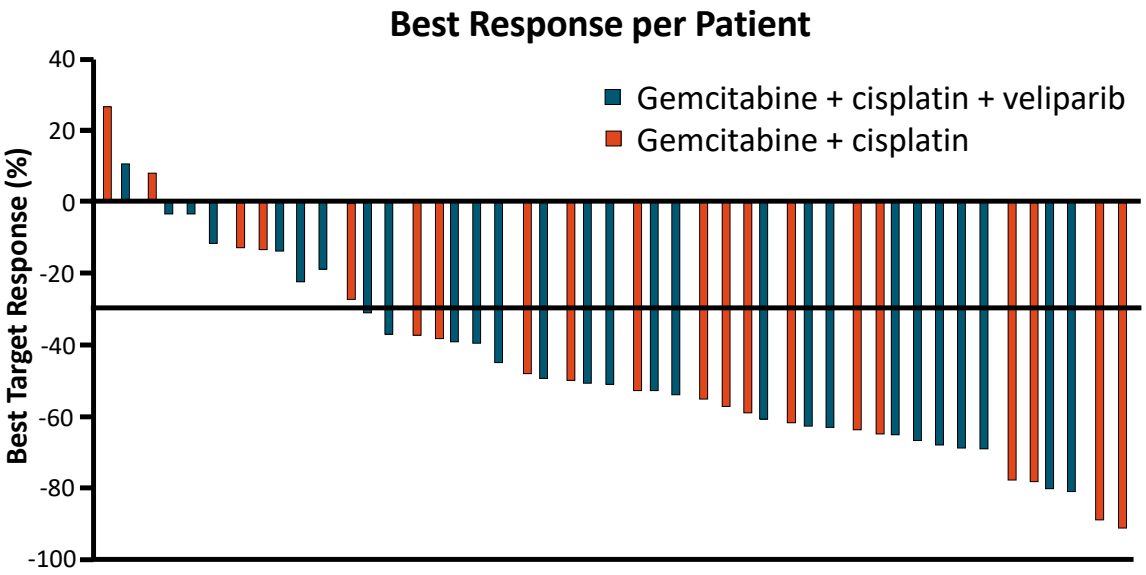
| First-line Regimen | Potential Maintenance Regimen |
|---|---|
| Platinum-based therapy and germline *BRCA1/2* mutation | ▪ Olaparib |
| FOLFIRINOX | ▪ FOLFOX<br>▪ FOLFIRI<br>▪ Capecitabine |
| Gemcitabine + nab-paclitaxel | ▪ Modified gemcitabine + nab-paclitaxel schedule<br>▪ Gemcitabine monotherapy |

Olaparib PI.

Slide credit: clinicaloptions.com

# Gemcitabine + Cisplatin ± Veliparib for Pancreatic Cancer With Germline *BRCA/PALB2* Mutation

- Randomized phase II study in which untreated locally advanced or metastatic PDAC with germline *BRCA/PALB2* mutations received **gemcitabine + cisplatin ± veliparib** (N = 50)




| Outcome | Gem + Cis + Vel (n = 27) | Gem + Dis (n = 23) | *P* Value |
|---|---|---|---|
| RR, % | 74.1 | 65.2 | .55 |
| DCR, % | 100 | 78.3 | .02 |
| Median OS, mos | 15.5 | 16.4 | .6 |
| Median PFS, mos | 10.1 | 9.7 | .73 |

- Grade 3/4 hematologic AEs numerically more common with gemcitabine + cisplatin + veliparib vs gemcitabine + cisplatin (81% vs 73%)

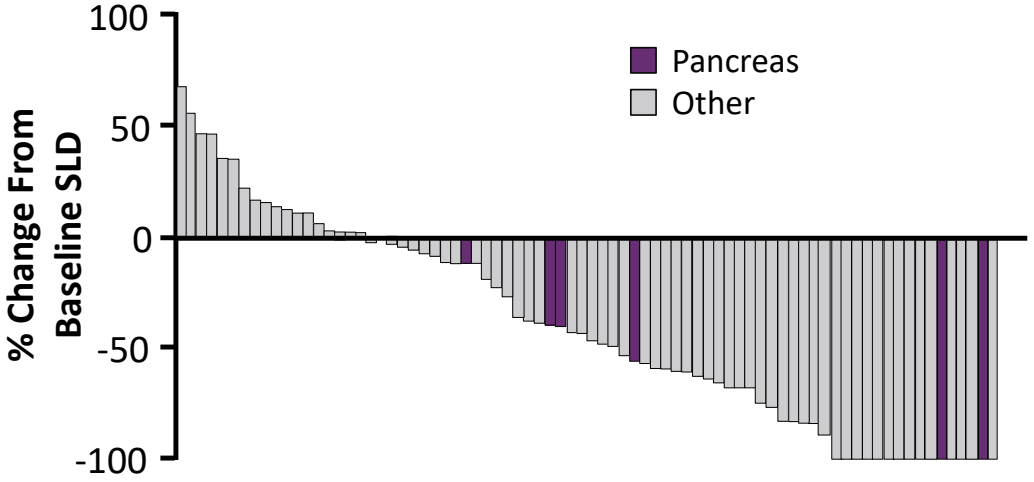
O'Reilly. ASCO GI 2020. Abstr 639. O'Reilly. JCO;[Epub].

Slide credit: clinicaloptions.com

# New Findings in Immunotherapy: Pembrolizumab in MSI-H Pancreatic Cancer

- Early studies of CTLA-4 and PD-1/PD-L1 antibodies showed minimal to no activity in advanced pancreatic cancer
- However, ~ 1% of pancreatic cancers associated with defective mismatch repair (dMMR/MSI-high)[1]

- KEYNOTE-016: phase II trial of pembrolizumab for patients with advanced solid tumors with dMMR[2]
  - 5 of 6 patients with pancreatic cancer responded to pembrolizumab[2,3]



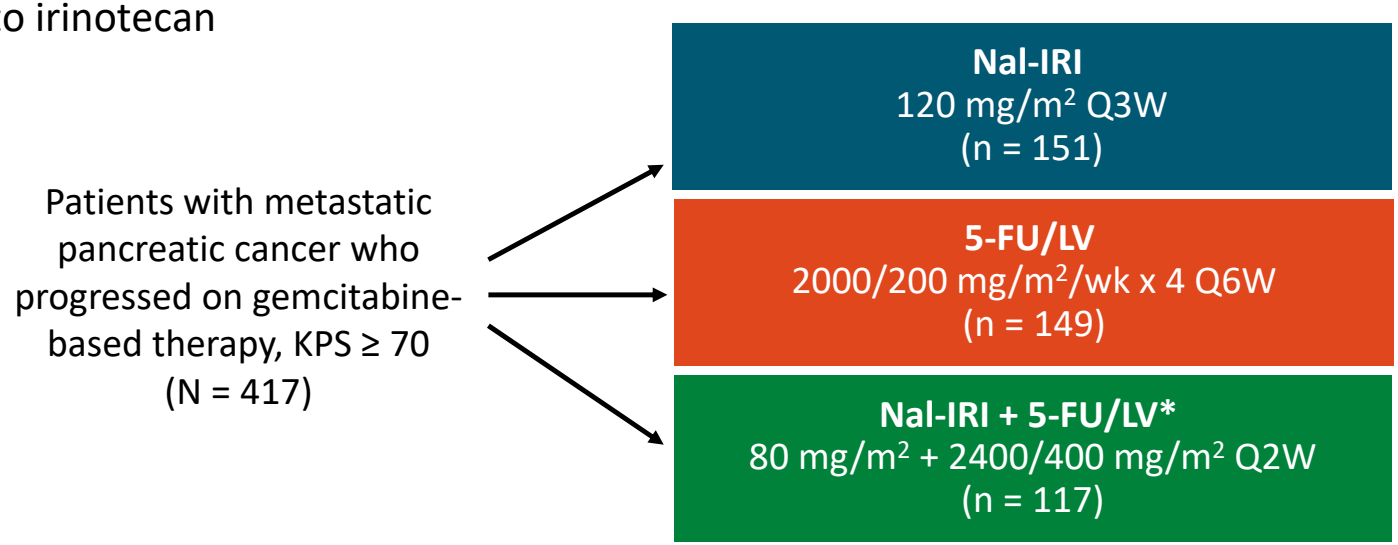

1. Humphris. Gastroenterology. 2017;152:68.e2. 2. Le. Science. 2017;357:409. 3. Pembrolizumab PI.

Slide credit: clinicaloptions.com

# Current Therapeutic Options for Metastatic Pancreatic Cancer: Second-line Chemotherapy

# NAPOLI-1: Nanoliposomal Irinotecan ± 5-FU/LV vs 5-FU/LV After Progression on Gem-Based Therapy

- Multicenter, randomized, open-label phase III trial
  - Liposomal formulation hypothetically associated with preferentially increased tumor exposure to irinotecan



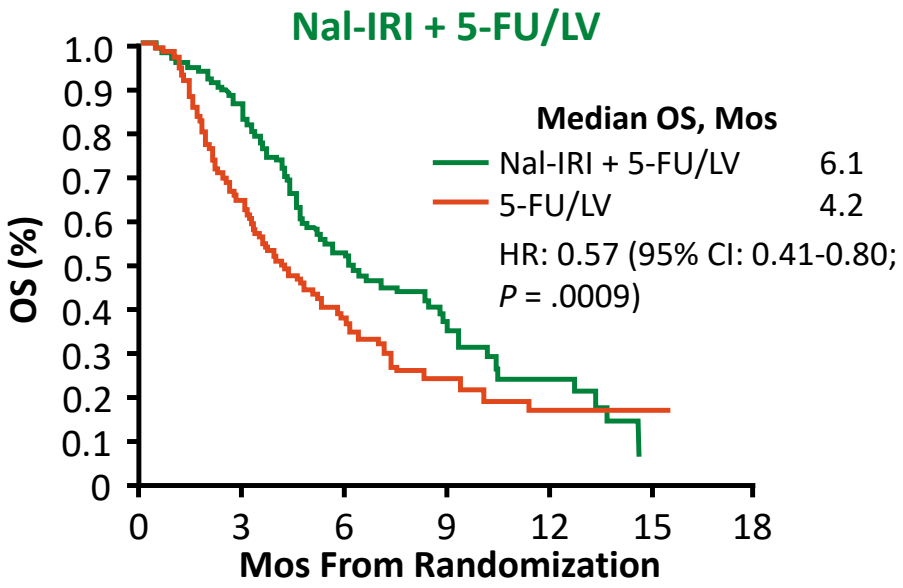

- Primary endpoint: OS

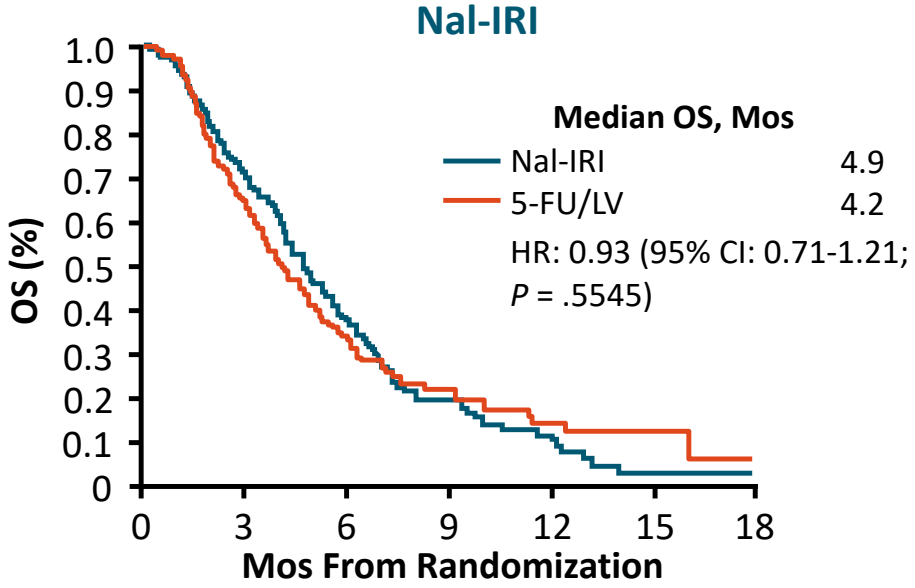
*Combination arm added after safety data were available. Patients in 5-FU/LV arm used as controls for combination arm.

Wang-Gillam. Lancet. 2016;387:545.

Slide credit: clinicaloptions.com

# NAPOLI-1: OS




| Tumor Response and Control | Nal-IRI + 5-FU/LV (n = 117) | 5-FU/LV (n = 119) | *P* Value |
|---|---|---|---|
| Median PFS, mos (95% CI) | 3.1 (2.7-4.2) | 1.5 (1.4-1.8) | .0001 |
| ORR, % (95% CI) | 16 (9.6-22.9) | 1 (0-2.5) | < .001 |
| CA 19-9 reduction, % | 36 | 12 | .0009 |

Wang-Gillam. Lancet. 2016;387:545.

Slide credit: clinicaloptions.com

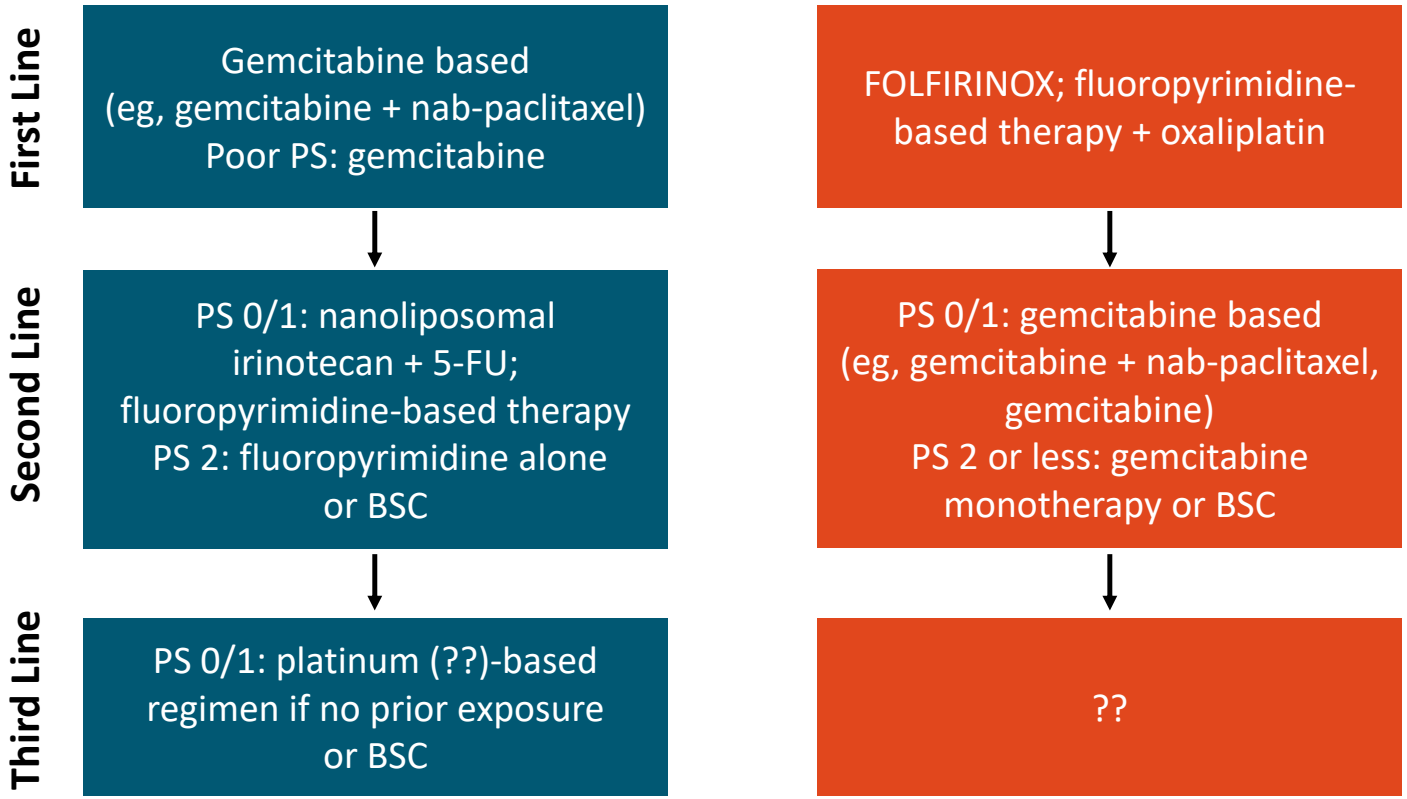
# NAPOLI-1: Safety

| AEs, % | Nal-IRI + 5-FU/LV (n = 117) | | 5-FU/LV (n = 134) | |
|---|---|---|---|---|
| | Any Grade | Grade 3/4 | Any Grade | Grade 3/4 |
| Diarrhea | 59 | 13 | 26 | 4 |
| Vomiting | 52 | 11 | 26 | 3 |
| Nausea | 51 | 8 | 34 | 3 |
| Decreased appetite | 44 | 4 | 32 | 2 |
| Fatigue | 40 | 14 | 28 | 4 |
| Neutropenia | 39 | 27 | 5 | 1 |
| Anemia | 38 | 9 | 23 | 7 |
| Hypokalemia | 12 | 3 | 9 | 2 |

Wang-Gillam. Lancet. 2016;387:545.

Slide credit: clinicaloptions.com

# Current Treatment Sequencing for Metastatic Pancreatic Cancer*




*Outside of a clinical trial.
As noted, patients with specific molecular profiles may be considered for targeted therapies.

Slide credit: clinicaloptions.com

# Revisiting Case Scenario 1: Patient Progressing on First-line Therapy

- While receiving gemcitabine + nab-paclitaxel, the patient's CA 19-9 levels dropped and a CT scan showed improvement in tumor burden
- However, after 6 cycles, disease progression was observed on CT scan; his KPS is 80%, ECOG 1

- 76-yr-old man with stage IV ductal adenocarcinoma of the pancreas metastatic to lungs
- PMH: type 2 diabetes, hypertension, atrial fibrillation; KPS 70%, ECOG PS 2; CA 19-9: 191 U/mL
- Microsatellite stable, no *BRCA/PALB2* mutation or *NTRK* fusion detected
- Treated with gemcitabine + nab-paclitaxel

# Which of the following therapeutic strategies would you now consider the best approach for this patient?

1. Remain on current regimen; increase dose of nab-paclitaxel
2. Switch to 5-FU/LV
3. Switch to 5-FU/LV + nanoliposomal irinotecan
4. Switch to FOLFIRINOX
5. Switch to FOLFOX
6. Switch to pembrolizumab
7. Switch to olaparib
8. Uncertain

- 76-yr-old man with stage IV ductal adenocarcinoma of the pancreas metastatic to lungs
- PMH: type 2 diabetes, hypertension, atrial fibrillation; KPS 70%, ECOG PS 2; CA 19-9: 191 U/mL
- Microsatellite stable, no *BRCA/PALB2* mutation or *NTRK* fusion detected
- Treated with gemcitabine + nab-paclitaxel; initial response but progressive disease after 6 cycles; KPS now 80%/ECOG 1

# Palliative Care for Patients With Pancreatic Cancer: Symptom Management and Prevention

# Palliative Care

- Dedicated palliative care, early in the disease course, concurrent with active treatment, **associated with improved outcomes** in patients with advanced cancer[1,2]
  - ↑ QoL, ↑ survival, ↑ coping skills that decrease depressive symptoms
- Referral to interdisciplinary palliative care teams is optimal[2]
- **ASCO Clinical Practice Guideline Recommendation**
  - For newly diagnosed patients with advanced cancer, early palliative care should begin within 8 wks of diagnosis

1. Greer. Palliative and Supportive Care in Oncology Symposium 2016. Abstr 104. 2. Ferrell. J Clin Oncol. 2017;35:96.

# Fatigue

- **Fatigue is the most common symptom affecting people with cancer**[1]
- Identify underlying cause and treat when possible
- Proper nutrition
- Adequate hydration; consider IV hydration
- Adequate sleep
- Diabetes management

- Regular exercise: recommend 30 min/day, 5 days/wk
- Psychological interventions[2]
- Consider Wisconsin ginseng 2000 mg BID[3]

Slide credit: clinicaloptions.com

# Pancreatic Endocrine/Exocrine Insufficiency

| | |
|---|---|
| **Symptoms** | ▪ Bloating, diarrhea, weight loss, flatulence, malnutrition<br>▪ New-onset diabetes can be associated |
| **Treatment** | ▪ Requires enzyme replacement with pancrelipase<br>  ▪ Patients are frequently not treated or are underdosed<br>  ▪ Take with first bite of food<br>▪ Dietitian or nutritionist consult may be beneficial<br>▪ Insulin/oral antihyperglycemic drugs |

Vujasinovic. Nutrients.2017;9:183.

Slide credit: clinicaloptions.com

# Additional Treatment-Related AEs and Management Strategies

| AE | Key Management Considerations |
|---|---|
| Chemotherapy-induced peripheral neuropathy (CIPN)[1-5] | ▪ No proven modalities to prevent<br>▪ Requires chemotherapy hold and/or dose modification<br>▪ Treatment: duloxetine is the only agent proven effective (studied in painful CIPN)<br>▪ Nonpharmacologic interventions are being studied (eg, cryotherapy, exercise/OT, acupuncture, scrambler therapy) |
| Nausea[6,7] | ▪ Etiology is likely multifactorial<br>▪ Treatment related: manage with antiemetics, 5HT3 receptor agonist, olanzapine<br>▪ Disease related: delayed gastric emptying (metoclopramide) |

1. Hershman. J Clin Oncol. 2014;32:1941. 2. Smith. JAMA. 2013;309:1359. 3. Peyton. Clin J Oncol Nurs. 2019;23:533-528.
4. Jameson. ASCO. 2017. Abstr TPS518. 5. Loprinzi. Support Care Cancer. 2019;24:2807. 6. Navari. NEJM. 2016;375:134.
7. Lee. Expert Rev Endocrinol Metab. 2010;5:653.

# Disease-Related Symptom Management

| Symptom | Key Management Considerations |
|---|---|
| Abdominal pain | ▪ Location depends on tumor site (head vs tail)<br>▪ Narcotics/intrathecal pumps<br>▪ Celiac plexus block<br>▪ Palliative radiation or chemoradiation |
| Biliary obstruction and jaundice | ▪ Symptoms: pruritus, change in the color of stool/urine, and jaundice<br>▪ Endoscopic biliary metal/plastic stent<br>▪ External biliary stent/PTC |
| Gastric outlet obstruction | ▪ Signs and symptoms: nausea, vomiting, and distended abdomen<br>▪ Gastrojejunostomy (good PS)<br>▪ Enteral stent |

Balaban. J Clin Oncol. 2016;34:2654.

Slide credit: clinicaloptions.com

# Disease-Related Symptom Management (*Continued*)

| Symptom | Key Management Considerations |
|---|---|
| Anorexia/early satiety/ unexplained weight loss | ▪ Referral to dietitian/nutrition services (culturally sensitive)<br>▪ Appetite stimulants |
| Venous thromboembolism | ▪ Diagnosis may precede the diagnosis of pancreatic cancer<br>▪ Low-molecular-weight heparin (preferred over warfarin) |
| **Psychosocial Concerns** | |
| Depression | ▪ Pancreatic cancer believed to have one of the highest rates of concomitant depressive disorders<br>▪ Monitor and screen for depression, anxiety; refer to psychology or psychiatry, social services<br>▪ Consider antidepressant medication |
| Insomnia | ▪ Cognitive behavioral therapy<br>▪ Sleep hygiene |

Balaban. J Clin Oncol. 2016;34:2654. Garland. Neuropsychiatr Dis Treat. 2014;10:1113.

Slide credit: clinicaloptions.com

# Emerging Strategies

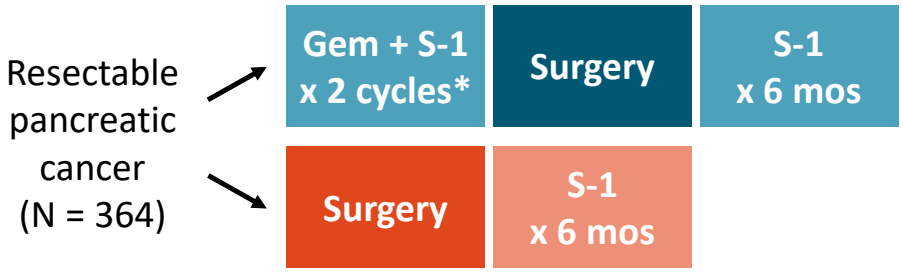
# Advances and Innovation in the Treatment of Pancreatic Cancer

- **Today, there is hope and excitement through evolving research**
  - Increased funding and interest in PDAC research
- As of January 27, 2020, there are 186 open and recruiting clinical trials for PDAC patients in the US (ClinicalTrials.gov)
- Novel ideas and new discoveries in biomarker development, diagnostic techniques, surgery, local and systemic therapies
- Novel strategies
  - Early detection and disease interception
  - Neoadjuvant and adjuvant trials
  - Novel targeted agents
  - New devices (eg, tumor treating fields, brachytherapy)
  - Dietary modification (eg, ketogenic diet)

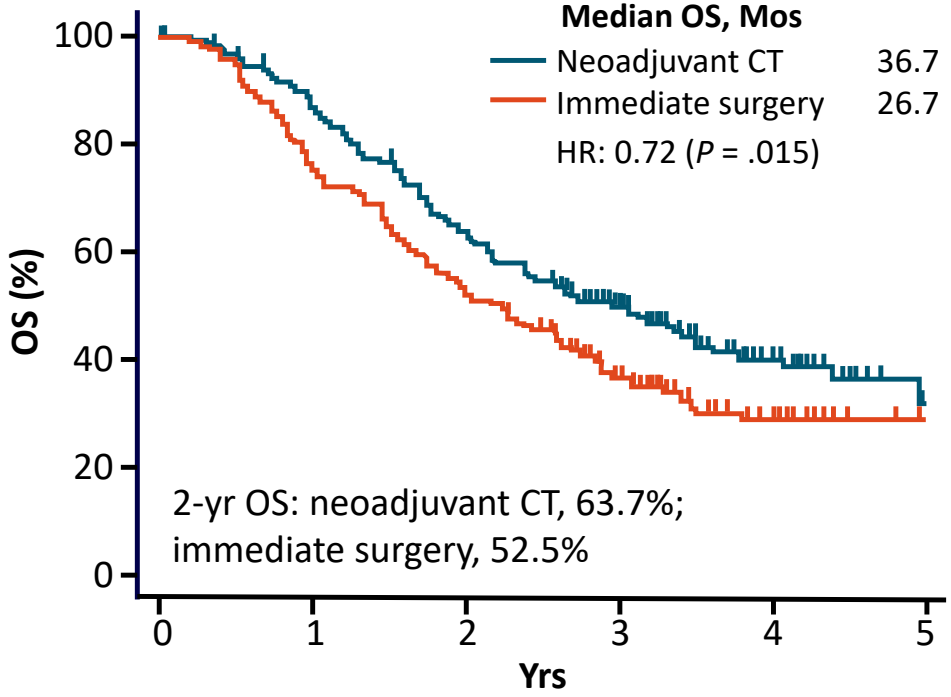
Slide credit: clinicaloptions.com

# Prep-02/JSAP-05: Neoadjuvant Chemotherapy vs Immediate Surgery

- Randomized phase II/III trial




*Gemcitabine: 1 g/m$^2$ on Days 1, 8; oral S-1: 40 mg/m$^2$ BID on Days 1-14.

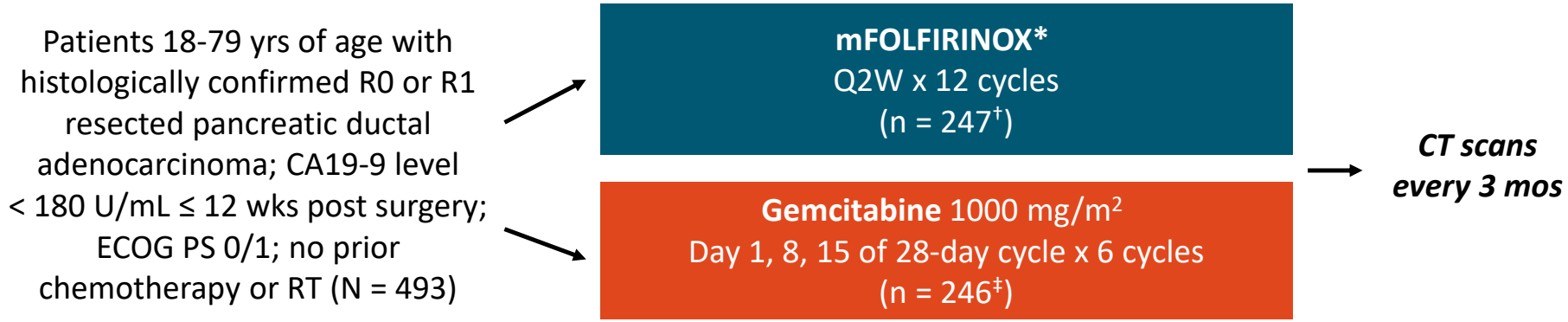



Unno. ASCO GI 2019. Abstr 189.

Slide credit: clinicaloptions.com

# PRODIGE 24/CCTG PA.6: Adjuvant mFOLFIRINOX vs Gemcitabine in Resected Pancreatic Cancer

- Multicenter, randomized phase III trial



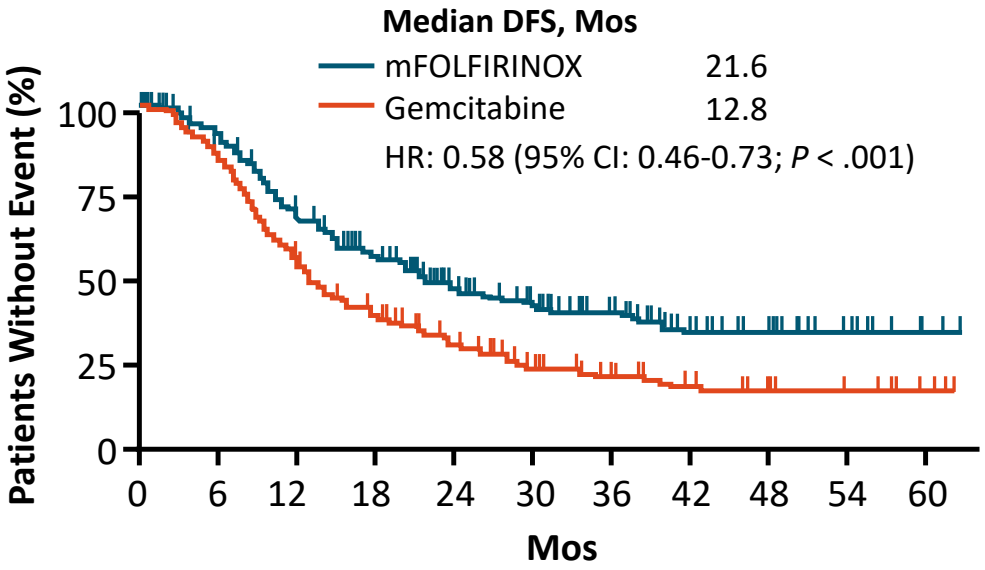

*On Day 1 of each cycle, oxaliplatin 85 mg/m$^2$, leucovorin 400 mg/m$^2$, and irinotecan 180 mg/m$^2$ (reduced to 150 mg/m$^2$ due to 20% grade 3/4 diarrhea rate in first 30 patients); continuous fluorouracil IV 2.4 g/m$^2$ over 46 hrs. †n = 238 treated. ‡n = 243 treated.

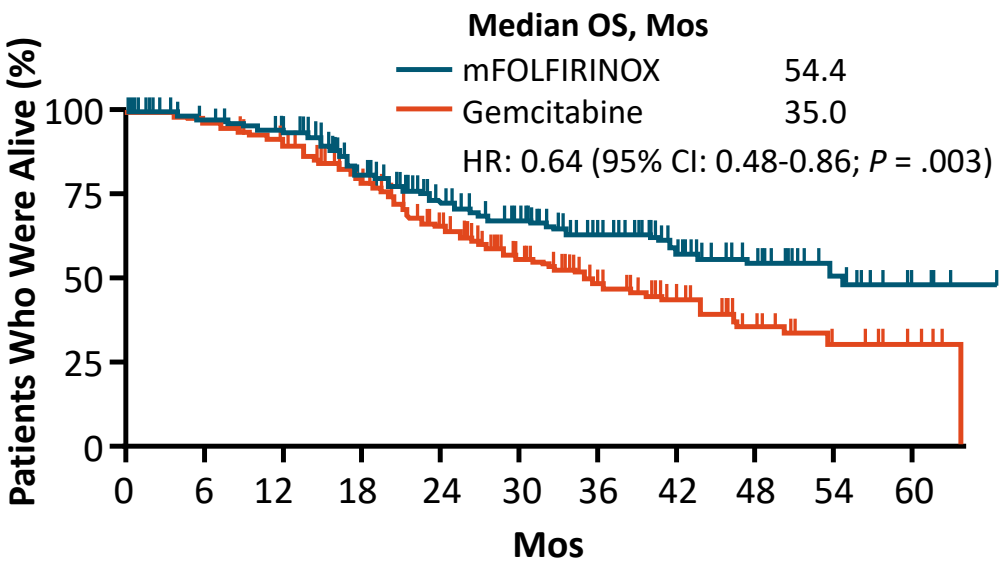
- Primary endpoint: DFS
- Secondary endpoints: toxicity, OS, cancer-specific survival, metastasis-free survival

Conroy. NEJM. 2018;379:2395.

Slide credit: clinicaloptions.com

# PRODIGE 24/CCTG PA.6: Survival Outcomes



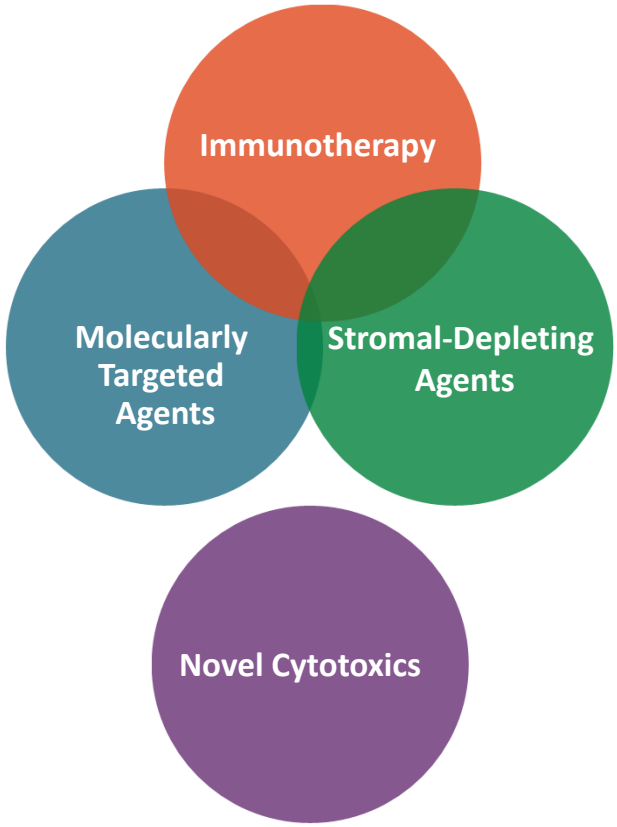

| Survival Outcome | mFOLFIRINOX (n = 247) | Gemcitabine (n = 246) |
|---|---|---|
| 3-yr DFS, % (95% CI) | 39.7 (32.8-46.6) | 21.4 (15.8-27.5) |

| Survival Outcome | mFOLFIRINOX (n = 247) | Gemcitabine (n = 246) |
|---|---|---|
| 3-yr OS, % | 63.4 (55.7-70.1) | 48.6 (40.9-55.8) |

Conroy. NEJM. 2018;379:2395.

Slide credit: clinicaloptions.com

# Classes of Novel Therapeutics Under Investigation for Pancreatic Cancer




| Trial | Strategy | MoA | Setting | Phase |
|---|---|---|---|---|
| NCT03941093 | Pamrevlumab + gemcitabine + nab-paclitaxel | Anti–connective tissue growth factor + chemo | Locally advanced | III |
| NCT03331562 | PD-1 inhibitor + vitamin D analog | | Stage IV maintenance | II |
| NCT02826486 | BL804 + pembrolizumab | CXCR4 inhibitor + PD-1 inhibitor | Stage IV refractory | II |
| NCT04203641 | L-DOS47 + doxorubicin | Microenviron. alkalinizer + chemo | Stage IV refractory | Ib/II |
| NCT03129139 | Heat shock protein inhibitor | | Stage IV refractory | I |
| NCT03440450 | FF10832 | Gemcitabine liposome injection | Stage IV refractory | I |

Slide credit: clinicaloptions.com

# Finding Positives in Negative Trials

| Trial | Design | Regimens | Median OS, Mos |
|---|---|---|---|
| **Original Trials With Current SOC Agents vs Gemcitabine** | | | |
| PRODIGE 4/ACCORD 11 | Phase III RCT | FOLFIRINOX | 11.1 |
| MPACT | Phase III RCT | Gemcitabine + nab-paclitaxel | 8.5 |
| **Recent Trials With Negative OS Findings** | | | |
| SWOG S1313 | Phase Ib/II RCT | PEGPH20 + mFOLFIRINOX | 7.7 |
| | | mFOLFIRINOX | **14.4** |
| HALO 109-301 | Phase III RCT | PEGPH20 + gemcitabine + nab-paclitaxel | 11.2 |
| | | Gemcitabine + nab-paclitaxel | **11.5** |

- Patients are living longer on these standard-of-care regimens
- **Nursing care is making a difference in symptom management and treatment tolerability!**

Conroy. NEJM. 2011;364:1817. Von Hoff. NEJM. 2013;369:1691. Ramanathan. J Clin Oncol. 2019;37:1062. Tempero. ASCO GI 2020. Abstr 638.

Slide credit: clinicaloptions.com

# Conclusions

- For earlier-stage (resectable) disease
  - Phase III evidence support FOLFIRINOX in postoperative adjuvant setting
  - Neoadjuvant therapy becoming increasingly popular
- Improving frontline and second-line treatment options for patients with metastatic disease
  - FOLFIRINOX and gemcitabine + nab-paclitaxel have demonstrated survival benefit (vs gemcitabine alone) in phase III studies
  - Evidence for second-line/salvage treatment with nanoliposomal irinotecan + 5-FU/LV following gemcitabine-based therapy

# Conclusions

- Germline testing recommended for all patients with a new diagnosis of pancreatic cancer, regardless of family history
  - Identification of germline *BRCA* mutation should prompt consideration of platinum-based therapy for patients with metastatic disease, followed by maintenance with a PARP inhibitor (olaparib) for those exhibiting good disease control
- Somatic (tumor) testing should also be considered for patients, with mutations/ genetic alterations potentially informing treatment options (eg, immune checkpoint inhibitors) or identifying patients for appropriate clinical trials
- There is hope for improved patient outcomes through expanding research of novel and innovative approaches

# Question and Answer Session