

BRIDGING THE SAFETY GAP:

Dose Modification and AE Management Strategies to Optimize Outcomes With Chemotherapy in
PANCREATIC CANCER



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Bridging the Safety Gap: Dose Modification and AE Management Strategies to Optimize Outcomes with Chemotherapy in Pancreatic Cancer

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PROGRAM OVERVIEW

First-line chemotherapy options for patients with pancreatic cancer, including advanced or metastatic stages, have been shown to increase overall survival. However, associated toxicity and debilitating adverse effects compromise benefits. Dose modification can help maintain treatment efficacy while mitigating these side effects. This program reviews dose modification strategies and best practices for patients with metastatic pancreatic cancer through multiple case discussions and a review of clinical evidence.

TARGET AUDIENCE

This activity is designed to meet the educational needs of community oncologists, advanced practitioners, and oncology nurses who care for patients with pancreatic cancer.

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Elucidate the implications of chemotherapy dose modification strategies on the potential effectiveness and safety of chemotherapy for patients with pancreatic cancer
- Explain best practices in chemotherapy dose modification to reduce adverse event burden and improve time on chemotherapy for patients with pancreatic cancer
- Incorporate evidence-based approaches to proactively manage, monitor, recognize, and mitigate chemotherapy-induced adverse events, with a focus on gastrointestinal toxicities, for patients with pancreatic cancer

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Efrat Dotan, MD	Consulting fees: Jazz Pharmaceuticals, Lutris Pharma, AbbVie, Amgen, Ipsen, Merus, TME Therapeutics Contracted research: BMS, Paradigm Health, AstraZeneca, Ipsen

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Agenda

Pre-Read Materials	<p>Dose Modifications in Pancreatic Cancer: A Primer for the Community Oncology Team</p> <ul style="list-style-type: none"> • Efficacy and Safety Outcomes of First-line Chemotherapy • Chemotherapy Dose Modifications • Chemotherapy-induced Diarrhea
5 minutes	Introduction & Moderator Instructions
15 minutes	<p>Dose Modifications to Optimize Chemotherapy in Metastatic Pancreatic Cancer (mPDAC)</p> <ul style="list-style-type: none"> • First-line Chemotherapy for mPDAC <ul style="list-style-type: none"> ○ Clinical Efficacy and Safety Summary • Chemotherapy Dose Modification Strategies <ul style="list-style-type: none"> ○ Animation & Analysis: <i>Modifying Chemotherapy Dosing in Pancreatic Cancer—Starting Dose, Clinical Considerations, and Best Practices in the Community Setting</i> ○ Dose Modifications Due to Side Effects • <i>UTG1A1</i> Genotyping and Irinotecan Use
5 minutes	Audience Q&A #1
30 minutes	Interactive Case Discussion
5 minutes	Conclusions Audience Q&A #2

Bridging the Safety Gap: Dose Modification and AE Management Strategies to Optimize Outcomes With Chemotherapy in Pancreatic Cancer



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Disclosures

- **Dr Abrams** discloses the following:
 - **Consulting fees:** AstraZeneca, Eisai
 - **Other:** HistoSonics (Medical Affairs Team)
- During the course of this lecture, faculty may mention the use of medications for both US Food and Drug Administration (FDA)-approved and non-FDA-approved indications
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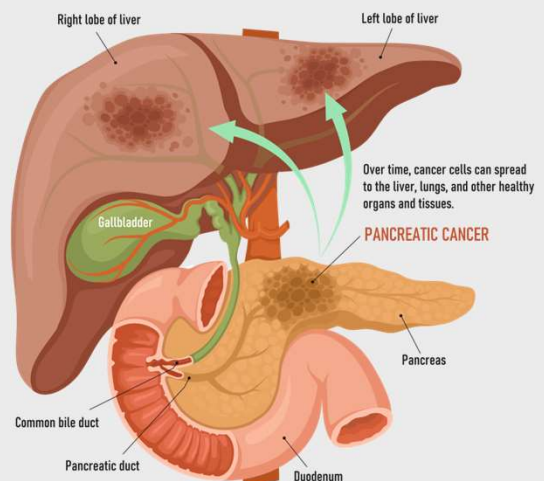
Learning Objectives

- Elucidate the implications of chemotherapy dose modification strategies on the potential effectiveness and safety of chemotherapy for patients with pancreatic cancer
- Explain best practices in chemotherapy dose modification to reduce adverse event burden and improve time on chemotherapy for patients with pancreatic cancer
- Incorporate evidence-based approaches to proactively manage, monitor, recognize, and mitigate chemotherapy-induced adverse events, with a focus on gastrointestinal toxicities, for patients with pancreatic cancer

Pancreatic Ductal Adenocarcinoma (PDAC)

PDAC is associated with aggressive progression, poor prognosis, and low survival rates

- Accounts for >90% of pancreatic cancers
- 5-year OS rate: 5%–10%
- 7th leading cause of cancer-related deaths worldwide; incidence is estimated to rise
- Poor prognosis due to early systemic spread, local aggressiveness, poor treatment efficacy
- ~50% of patients diagnosed with metastatic PDAC (mPDAC)
 - Chemotherapy is of palliative intent

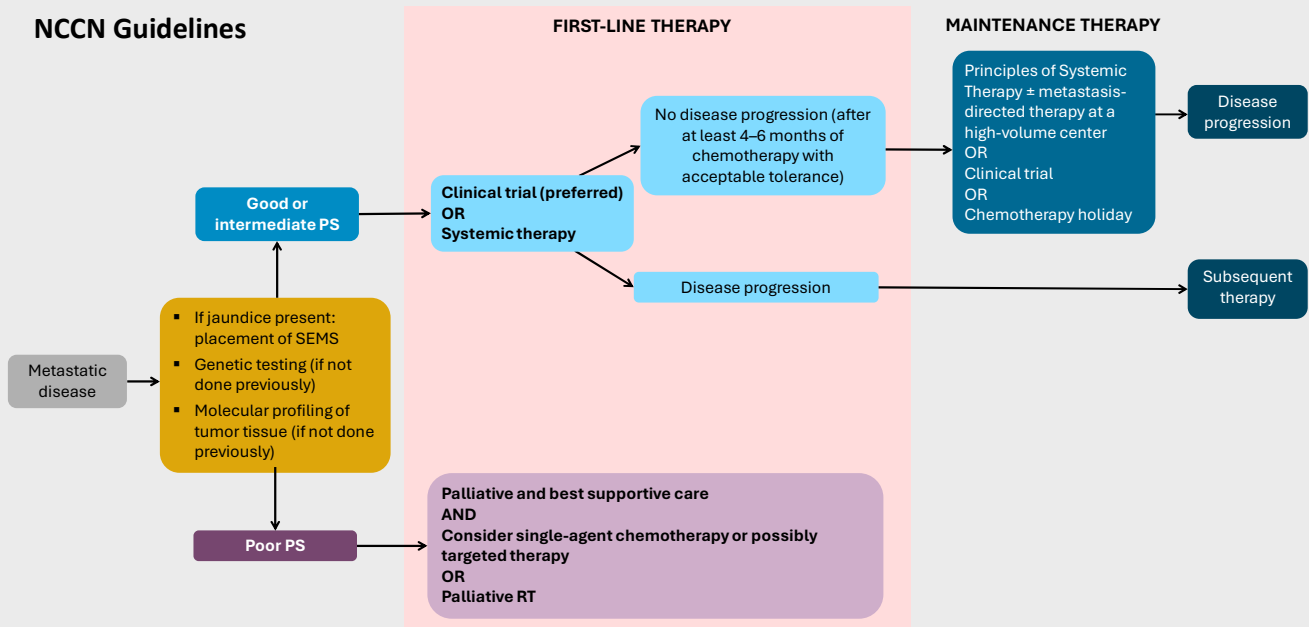


OS = overall survival.

Garajová I, et al. *Curr. Oncol.* 2023, 30, 9587–9601. Brown MB, et al. *Drugs.* 2025;85:255-262.

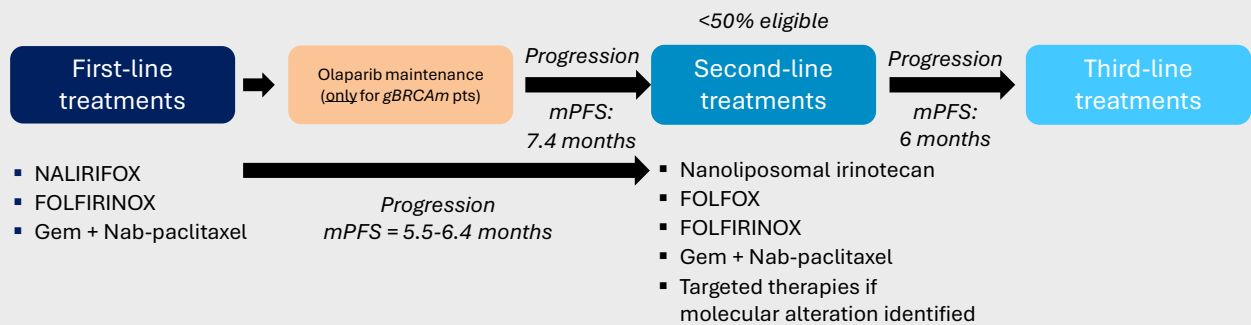
Metastatic Disease Therapy

NCCN Guidelines



PS = performance status; RT = radiation therapy; SEMS = self-expandable metal stent.
 NCCN. *Pancreatic Adenocarcinoma* (Version 2.2025). <https://www.nccn.org/guidelines/guidelines-detail?id=1455>. Published 2025. Accessed March 10, 2026.

Treatment Strategy for mPDAC



gBRCAm = germline BRCA mutation; mPFS = median progression-free survival.
 Casolino R, et al. *Camb Prism Precis Med*. 2023;1:e14.

First-line Chemotherapy for mPDAC



FOLFIRINOX

First-line chemotherapy for mPDAC

- FOL = folinic acid (leucovorin), F = fluorouracil (5-FU), IRIN = irinotecan, OX = oxaliplatin
- Given in outpatient infusion center and at home (via infusion pump)
- Each cycle is repeated every 14 days (2 weeks)
- Up to 12 cycles given for up to 6 months, depending on response and tolerability
- Typically prescribed for patients ≤ 76 years old with ECOG 0 or 1
- **Oxaliplatin 85 mg/m²** IV infusion given over 2 hours on day 1
- **Leucovorin 400 mg/m²** IV infusion given over 2 hours on day 1
- **Irinotecan 180 mg/m²** IV infusion given over 90 minutes on day 1
- **Fluorouracil 400 mg/m²** IV bolus usually given over 3–5 minutes on day 1
- **Fluorouracil 2,400 mg/m²** continuous infusion given via home-infusion pump over 46 hours beginning day 1

ChemoExperts. Treatment Name: FOLFIRINOX (Fluorouracil + Leucovorin + Irinotecan + Oxaliplatin). Jan. 25, 2021. <https://www.chemoexperts.com/folfirinox.html>. Accessed April 7, 2026. Hongxuan T, et al. *Scientific Reports*. 2018;8:8666.

Gemcitabine + Nab-paclitaxel (GEM-NABP)

First-line chemotherapy for mPDAC

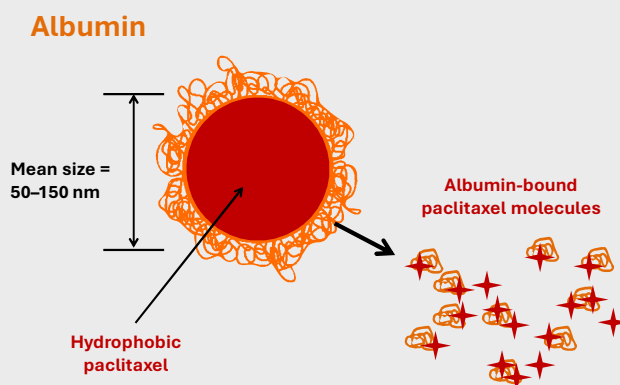
- Given in outpatient infusion center
- Administered over 15 days on days 1, 8, and 15 (1 cycle)
- Each cycle is repeated every 28 days
- In mPDAC, treatment is continued until it no longer works or unacceptable side effects occur; otherwise, each cycle may be repeated up to 6 times (6 months)
- Typically prescribed for patients ≤ 75 years old with ECOG 0 or 1
- **Nab-paclitaxel 125 mg/m²** IV infusion given over 30–40 minutes on days 1, 8, and 15
- **Gemcitabine 1,000 mg/m²** IV given immediately after over 30 minutes on days 1, 8, and 15

Nab = nanoparticle albumin bound.

Paclitaxel protein-bound particles for injectable suspension, albumin-bound (Abraxane®). Prescribing information (PI) 2022. ChemoExperts. Treatment name: Gemcitabine + abraxane®. <https://www.chemoexperts.com/gemcitabine-abraxane.html>. Accessed April 7, 2026.

Nab-paclitaxel

- Nab-paclitaxel is a colloidal suspension of 130 nanometer particles homogenized with human serum albumin
- Individual albumin-bound paclitaxel molecules dissociate in circulation in a concentration-dependent manner
- Formulation allows for the delivery of paclitaxel to tumors at a 4.5-fold increase across endothelial cells via albumin receptors
- Preclinical studies demonstrated higher intratumor concentrations of nab-paclitaxel compared to conventional paclitaxel (CrEL-paclitaxel)



CrEL = Cremophor EL (polyoxyethylated castor oil).

Cucinotto I, et al. *J Drug Deliv.* 2013;905091. Joerger M. *Cancer Chemother Pharmacol.* 2016;77(2):221-233.

NALIRIFOX

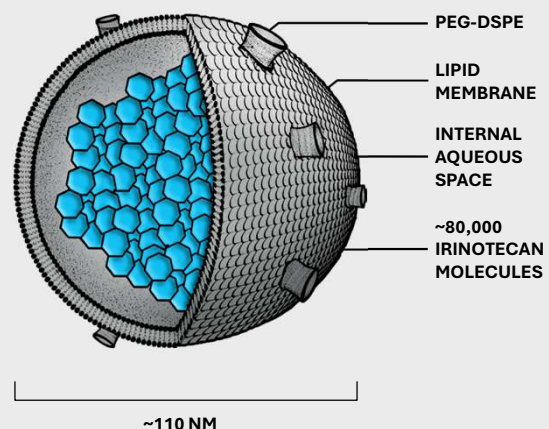
First-line chemotherapy for mPDAC

- NAR-IRI = Nanoliposomal irinotecan, F = fluorouracil (5-FU)/folinic acid (leucovorin), OX = oxaliplatin
- Given in outpatient infusion center and at home (via infusion pump)
- Each cycle is repeated every 14 days (2 weeks) on days 1 and 15
- Treatment continued until it no longer works or unacceptable side effects occur
- Typically prescribed for patients ≤ 75 years old with ECOG 0 or 1
- **Liposomal irinotecan 50 mg/m²** IV infusion given over 90 minutes on day 1
- **Oxaliplatin 60 mg/m²** IV infusion given over 2 hours on day 1
- **Leucovorin 400 mg/m²** IV infusion given over 30 minutes on day 1
- **Fluorouracil 2,400 mg/m²** continuous infusion given via home-infusion pump over 44–46 hours beginning day 1 and ending on day 3

Irinotecan liposome injection (Onivyde®). PI 2024. ChemoExperts. Treatment name: Nalirifox (liposomal irinotecan [Onivyde®] + folinic acid + fluorouracil + oxaliplatin). <https://www.chemoexperts.com/nalirifox-liposomal-irinotecan-onivyde-folinic-acid-fluorouracil-oxaliplatin.html#tip4>. Accessed April 7, 2026.

Liposomal irinotecan

- Irinotecan encapsulated in a liposome results in a longer circulation and half-life
 - 95% of irinotecan remains encapsulated in circulation for up to 169.5 hours post dose
 - Half-life: 25.8 hours following administration
- Tumor-associated macrophages uptake the liposomes and release irinotecan molecules via phagocytosis
- Preclinical models achieved similar intratumoral exposure of SN-38, irinotecan's active metabolite, at a 5-fold lower dose than irinotecan hydrochloride



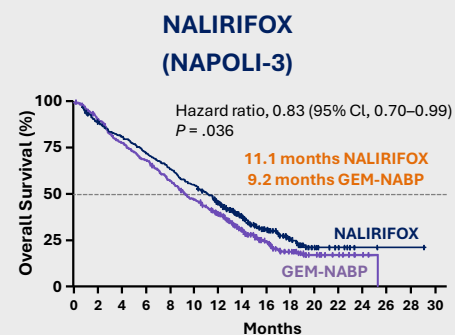
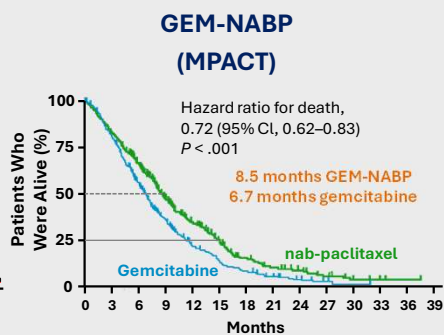
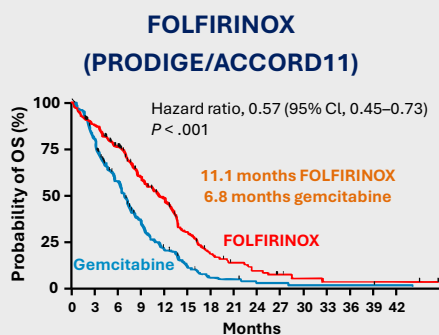
PEG-DSPE = polyethylene glycol-distearoylphosphatidylethanolamine.

Irinotecan liposome injection (Onivyde®). PI 2024. Drummond DC, et al. *Cancer Res.* 2006;66(6):3271-3277. Kelly C, et al. *J Drug Deliv.* 2011;2011:727241.

Clinical Efficacy and Safety Summary



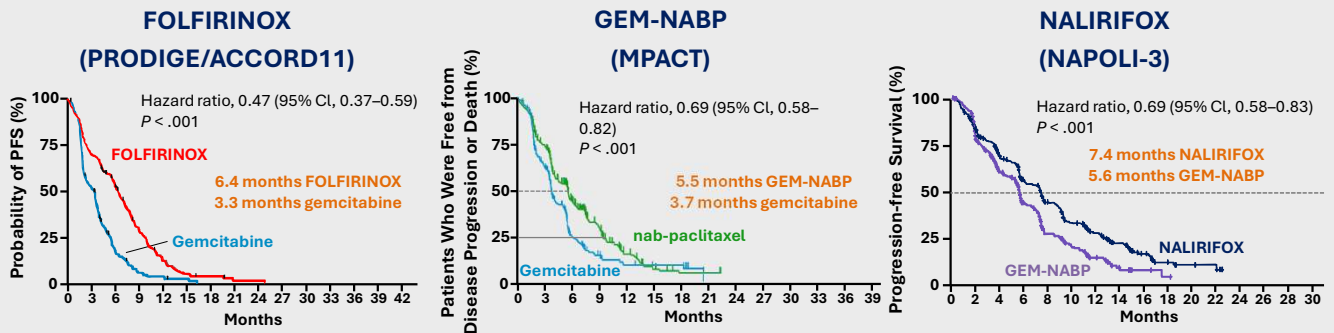
Median OS With First-line Chemotherapy for mPDAC



OS = overall survival.

Conroy T, et al. *New Engl J Med.* 2011;364:1817-1825. Von Hoff DD, et al. *New Engl J Med.* 2013;369:1691-1703. Wainberg Z, et al. *Lancet.* 2023;402:1272-1281.

Median PFS With First-line Chemotherapy for mPDAC



PFS = progression-free survival.

Conroy T, et al. *New Engl J Med.* 2011;364:1817-1825. Von Hoff DD, et al. *New Engl J Med.* 2013;369:1691-1703. Wainberg Z, et al. *Lancet.* 2023;402:1272-1281.

General Adverse Effects

Irinotecan

- Diarrhea
- Neutropenia
- Neutropenic fever
- Nausea
- Vomiting
- Mucositis
- Colitis
- Thromboembolism
- Lung toxicities (shortness of breath or cough)

Oxaliplatin

- Hypersensitivity reactions
- Peripheral neuropathy
- Cold sensitivity
- Lung toxicities (shortness of breath or cough)
- Low white blood cells, platelets, red blood cells
- Constipation
- Vomiting or nausea
- Fatigue
- Mouth sores
- Change in liver function

Leucovorin

- Seizures or fainting (rare)
- Anaphylactoid reactions
- Urticaria

Gemcitabine

- Myelosuppression (neutropenia, thrombocytopenia, anemia)
- Lung toxicities
- Hemolytic uremic syndrome
- Liver toxicities
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

Nab-paclitaxel

- Myelosuppression (neutropenia, thrombocytopenia, anemia)
- Peripheral neuropathy
- Fatigue
- Pyrexia
- Nausea or vomiting
- Alopecia
- Peripheral edema
- Diarrhea

Fluorouracil (5-FU)

- Neutropenia
- Low white blood cells, platelets, red blood cells
- Mucositis
- Diarrhea
- Nausea or vomiting

ChemoExperts. Treatment Name: FOLFIRINOX (Fluorouracil + Leucovorin + Irinotecan + Oxaliplatin). January 25, 2021. <https://www.chemoexperts.com/folfirinox.html>. ChemoExperts. Treatment name: Gemcitabine + abraxane®. <https://www.chemoexperts.com/gemcitabine-abraxane.html>. ChemoExperts. Treatment name: Nalirifox (liposomal irinotecan [Onivyde®] + folinic acid + fluorouracil + oxaliplatin). <https://www.chemoexperts.com/nalirifox-liposomal-irinotecan-onivyde-folinic-acid-fluorouracil-oxaliplatin.html#tip4> Accessed April 7, 2026.

Black Box Warnings

Irinotecan hydrochloride:

Diarrhea and myelosuppression

Withhold for ANC <1,000 cells/mm³

Early diarrhea symptoms can be prevented or ameliorated with atropine; late diarrhea should be treated promptly with loperamide

Liposomal Irinotecan:

Severe neutropenia and severe diarrhea

Withhold for ANC < 1,500 cells/mm³

Withhold for diarrhea of grade 2-4 severity; administer loperamide (late diarrhea of any severity); administer atropine (early diarrhea of any severity)

Nab-paclitaxel:

Severe myelosuppression

Do not administer to patients with baseline neutrophil counts <1,500 cells/mm³

Oxaliplatin:

Hypersensitivity reactions, including anaphylaxis

Can occur within minutes of administration during any cycle; immediately and permanently discontinue

ANC = absolute neutrophil.

Irinotecan (Camptosar®) PI 2024. Irinotecan liposome injection (Onivyde®). PI 2024. Paclitaxel protein-bound particles for injectable suspension, albumin-bound (Abraxane®). PI 2022. Oxaliplatin (Eloxatin®) PI 2020.

We will now watch a brief animation on
Modifying Chemotherapy Dosing in Pancreatic Cancer: Starting Dose, Clinical Considerations, and Best Practices in the Community Setting



Chemotherapy Dose Modifications for mPDAC



Modified FOLFIRINOX

- Modified FOLFIRINOX allows for decreased side effects, increased tolerability, and treatment continuity compared to conventional dosage
- Meta-analysis of 11 studies revealed a 6-month and 1-year OS of 79.7% and 47.6%, respectively, among patients receiving modified FOLFIRINOX

Most common dose reductions in modified FOLFIRINOX

	FOLFIRINOX	Modified FOLFIRINOX
Oxaliplatin	85 mg/m ²	85 mg/m ²
Leucovorin	400 mg/m ²	400 mg/m ²
Irinotecan	180 mg/m ²	150 mg/m ²
Fluorouracil	400 mg/m ² bolus	None
Fluorouracil	2,400 mg/m ²	2,400 mg/m ²

Conroy T, et al. *New Engl J Med*. 2011;364:1817-1825. Hongxuan T, et al. *Scientific Reports*. 2018;8:8666.

Dose Modifications Due to Side Effects

FOLFIRINOX

Adverse events	Reduction of dose for subsequent cycles	Adverse events	Reduction of dose for subsequent cycles
Febrile neutropenia Grade 4 neutropenia during more than 7 days Infection with concomitant grade 3–4 neutropenia	1st occurrence: reduce the dose of irinotecan to 150 mg/m ² and delete the bolus 5-FU dose 2nd occurrence: reduce also the dose of oxaliplatin to 60 mg/m ² 3rd occurrence: treatment discontinuation	Diarrhea grade 3–4 or Diarrhea + fever and/or Neutropenia grade 3–4	1st occurrence: reduce the irinotecan dose to 150 mg/m ² and delete the bolus 5-FU dose 2nd occurrence: reduce also the oxaliplatin dose to 60 mg/m ² and reduce the dose of continuous 5-FU to 75% of the original dose 3rd occurrence: treatment discontinuation
Grade 3–4 thrombocytopenia	1st occurrence: reduce the oxaliplatin dose to 60 mg/m ² and the continuous 5-FU dose to 75% of the original dose 2nd occurrence: reduce also the dose of irinotecan to 150 mg/m ² and the dose of continuous 5-FU of additional 25% 3rd occurrence: treatment discontinuation	Diarrhea ≥48 h despite high doses loperamide	No systematic reduction of the irinotecan, oxaliplatin or 5-FU doses after complete recovery, unless grade 3–4 diarrhea, or diarrhea + fever, and/or concomitant neutropenia grade 3–4

Conroy T, et al. *New Engl J Med.* 2011;364:1817-1825.

Modified GEM-NABP

- Patients receiving GEM-NABP in MPACT required a dose reduction (47% GEM dose and 41% NABP) due to rates of >grade 3 neuropathy or neutropenia
- Modification to a bi-weekly (elimination of Day 8) regimen does not reduce efficacy and improves tolerance (median OS: 10 months; median PFS: 5.4 months)

GEM-NABP dose modifications

	GEM-NABP	Modified GEM-NAP		
		1 st dose ↓	2 nd dose ↓	Additional
Nab-paclitaxel	125 mg/m ²	100 mg/m ²	75 mg/m ²	Discontinue
Gemcitabine	1,000 mg/m ²	800 mg/m ²	600 mg/m ²	Discontinue
Frequency	Days 1, 8, and 15	Days 1 and 15		----

Ahn DH, et al. *Ther Adv Med Oncol.* 2017;9 (2):75-82. Rogers JE, et al. *Cancer Med.* 2020; 9:5406-5415. Paclitaxel protein-bound particles for injectable suspension, albumin-bound (Abraxane®). PI 2022.

Dose Modifications Due to Side Effects

Dose recommendation and modifications for neutropenia and/or thrombocytopenia

Cycle Day	ANC (cells/mm ³)		Platelet count (cells/mm ³)	GEM-NABP
Day 1	<1,500	OR	<100,000	Delay doses until recovery
Day 8	500 to <1000	OR	50,000 to <75,000	Reduce 1 dose level
	<500	OR	<50,000	Withhold doses
Day 15: If day 8 doses were reduced or given without modification:				
		OR	50,000 to <75,000	Reduce 1 dose level from Day 8
		OR	<50,000	Withhold doses
Day 15: If day 8 doses were withheld:				
		OR	≥75,000	Reduce 1 dose level from Day 1
		OR	50,000 to <75,000	Reduce 2 dose levels from Day 1
		OR	<50,000	Withhold doses

Dose modifications for other adverse reactions

Adverse Reaction	Nab-paclitaxel	Gemcitabine
Febrile neutropenia: grade 3 or 4	Withhold until fever resolves and ANC ≥1,500; resume at next lower dose level	
Peripheral neuropathy: grade 3 or 4	Withhold until improves to ≤grade 1; resume at next lower dose level	No dose reduction
Cutaneous toxicity: grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal toxicity: grade 3 mucositis or diarrhea	Withhold until improves to ≤grade 1; resume at next lower dose level	

ANC = absolute neutrophil count.

Paclitaxel protein-bound particles for injectable suspension, albumin-bound (Abraxane®). PI 2022.

Modified NALIRIFOX

- 60% (n = 220) of patients receiving NALIRIFOX and 54% (n = 204) of patients receiving GEM-NABP required a dose reduction in NAPOLI-3

NALIRIFOX dose modifications

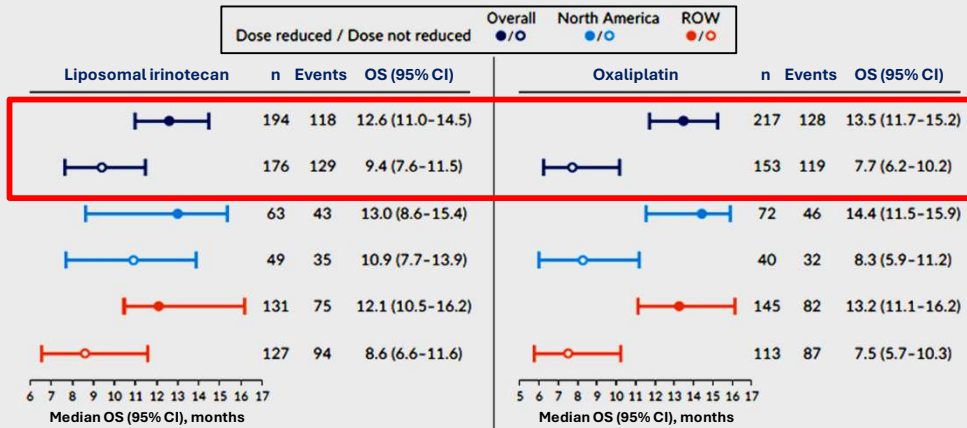
	NALIRIFOX	Modified NALIRIFOX		
		1st dose ↓	2nd dose ↓	3rd dose ↓
Liposomal irinotecan	50mg/m ²	40 mg/m ²	32.5 mg/m ²	25 mg/m ²
Oxaliplatin	60 mg/m ²	48 mg/m ²	39 mg/m ²	30 mg/m ²
Leucovorin	400 mg/m ²	400 mg/m ²	400 mg/m ²	400 mg/m ²
Fluorouracil	2,400 mg/m ²	80% of dose	65% of dose	50% of dose

Wainberg Z, et al. *Lancet*. 2023;402:1272-1281. Irinotecan liposome injection (Onivyde®). PI 2024.

Modified NALIRIFOX

- Post-hoc analysis of NAPOLI-3 revealed longer OS among patients with dose reductions of NALIRIFOX:

OS in patients with and without dose reductions of liposomal irinotecan and oxaliplatin



Patel A, et al. American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI) 2025. January 23-25, 2025; San Francisco, CA.
 Patel A, et al. Florida Society of Clinical Oncology (FLASCO) 2025. April 4-5, 2025; Orlando, FL.

Dose Modifications Due to Side Effects

NALIRIFOX

Toxicity	Occurrence	NAL-IRI adjustment in patients receiving 50 mg/m ²	Fluorouracil and oxaliplatin adjustment
Grade 3 or 4 adverse reactions	Withhold NAL-IRI. Upon recovery to ≤ grade 1, resume NAL-IRI at:		
	First	40 mg/m ²	80% of original dose
	Second	32.5 mg/m ²	65% of original dose
	Third	25 mg/m ²	50% of original dose
	Fourth	Discontinue	Discontinue fluorouracil and oxaliplatin
Grade 3 or 4 hand-foot syndrome	First	Discontinue	—
Any grade neurocerebellar toxicity	First	Discontinue	
Grade ≥2 cardiac toxicity	First	Discontinue	
Interstitial lung disease	First	Discontinue	
Anaphylactic reaction	First	Discontinue	

NAL-IRI = nanoliposomal irinotecan.
 Irinotecan liposome injection (Onivyde®). PI 2024.

UGT1A1 Genotyping and Irinotecan Use

- *UGT1A1**28 polymorphisms reduces the metabolism of lipophilic molecules, eg, bilirubin (Gilbert's syndrome) and SN-38
- *UGT1A1* deficiency relates to ↓ expression or enzymatic activity, thereby, ↓ conversion of SN-38 into water-soluble metabolites that can be eliminated through bile and urine
 - Neutropenia results from ↑ concentrations of SN-38 in plasma (and likely ↑ increased exposure to irinotecan)
 - Late-onset diarrhea results from excessive accumulation of SN-38 in the intestine
- Reduced initial dose of irinotecan should be considered for *UGT1A1**28 homozygous patients
- Commercial testing for *UGT1A1* is available, but guidelines on clinical use not established
 - Testing in patients experiencing irinotecan toxicity not recommended, as dose reduction is required

Karas S, et al. *JCO Oncol Pract.* 2022;18:270-277.

UGT1A1 Genotyping

Clinical Implications and Interventions

<i>UGT1A1</i> genotype	Effect on <i>UGT1A1</i> activity or expression	Clinical implication	Clinical intervention
*1/*1	Normal	Average risk of irinotecan toxicity	<ul style="list-style-type: none"> ▪ Use standard starting dose ▪ These patients may be able to tolerate irinotecan doses higher than the standard dose without compromising safety
*1/*28	Reduced expression	Higher risk of irinotecan toxicity	<ul style="list-style-type: none"> ▪ Use standard starting dose
*1/*26	Reduced activity		<ul style="list-style-type: none"> ▪ These patients may be able to tolerate irinotecan doses higher than the standard dose without compromising safety
*28/*28	Further reduction in expression	Highest risk of irinotecan toxicity	<ul style="list-style-type: none"> ▪ Reduce the starting dose to at least one level lower than the standard dose ▪ After cycle 1 at a reduced dose, upward titration at subsequent cycles can be considered, on the basis of individual tolerance
*6/*6	Further reduction in activity		
*6/*28	Further reduction in activity and expression		


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BRIDGING THE SAFETY GAP:
Dose Modification and AE Management Strategies to Optimize Outcomes With Chemotherapy in PANCREATIC CANCER



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- **CREATE** a free personalized office poster <https://PancreaticCancer.posterprogram.com>
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Thank You!



Bridging the Safety Gap: Dose Modification and AE Management Strategies to Optimize Outcomes With Chemotherapy in Pancreatic Cancer

Resource	Address
Resource	Address
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