

CHEMOTHERAPY STRATEGIES IN METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (mPDAC): FIRST-LINE CHEMOTHERAPY OPTIONS

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DEVELOPED BY GI CONNECT

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EDUCATIONAL OBJECTIVES

1. Be able to differentiate the **efficacy and safety profiles** of chemotherapies for mPDAC and understand how **mode of delivery** plays a role in this
2. Be able to recognise the **cause of toxicities** and have an awareness of strategies that can be used to improve tolerability and manage side effects whilst maintaining optimal efficacy

CLINICAL TAKEAWAYS

- Pancreatic ductal adenocarcinoma (PDAC) is usually diagnosed at an advanced, incurable stage due to non-specific symptoms and has an extremely poor prognosis
- Systemic chemotherapy is the standard treatment for metastatic PDAC but molecularly targeted treatments and immunotherapies may have a role for specific patients
- Treatment selection depends on several factors, including patients' performance status and co-morbidities. These should be considered alongside the efficacy and safety profiles of the different chemotherapy regimens
- Treatment strategies can be implemented to manage toxicities associated with the different chemotherapy regimens to enable a patient to stay on treatment for optimal efficacy

PANCREATIC DUCTAL ADENOCARCINOMA

INTRODUCTION

- Pancreatic ductal adenocarcinoma (PDAC) is a highly devastating disease with poor prognosis and rising incidence and accounts for the majority (90%) of pancreatic neoplasms.¹ Typically after diagnosis, only 13% live for 5 years²
- PDAC is the third-leading cause of cancer mortality in the US and the seventh-leading cause worldwide.^{2,3} It is projected to become the second-leading cause of cancer-related mortality by 2030³
 - Approximately 1.7% of men and women will be diagnosed with pancreatic cancer at some point during their lifetime²
- In 2024, estimated numbers in the US are:
 - 66,440 new cases (3.3% of all new cancer cases)²
 - 51,750 deaths (8.5% of all cancer deaths)²
- Pancreatic cancer is difficult to diagnose due to the lack of early symptoms and 80-90% of patients have unresectable tumours due to the advanced stage at diagnosis⁴
- Surgery, chemotherapy and radiation are the primary treatment options for pancreatic cancer¹

US, United States

1. Orth M, et al. Radiat Oncol. 2019;14:141; 2. Cancer Stat Facts: Pancreatic Cancer. Available from: <https://seer.cancer.gov/statfacts/html/pancreas.html>. Accessed October 2024; 3. Park W, et al. JAMA. 2021; 326:851-862; 4. Rawla P, et al. World J Oncol. 2019;10:10-27

OVERVIEW OF TREATMENT FOR mPDAC

- Chemotherapy is the mainstay of treatment for mPDAC patients
- Enrolment in clinical trials should always be encouraged

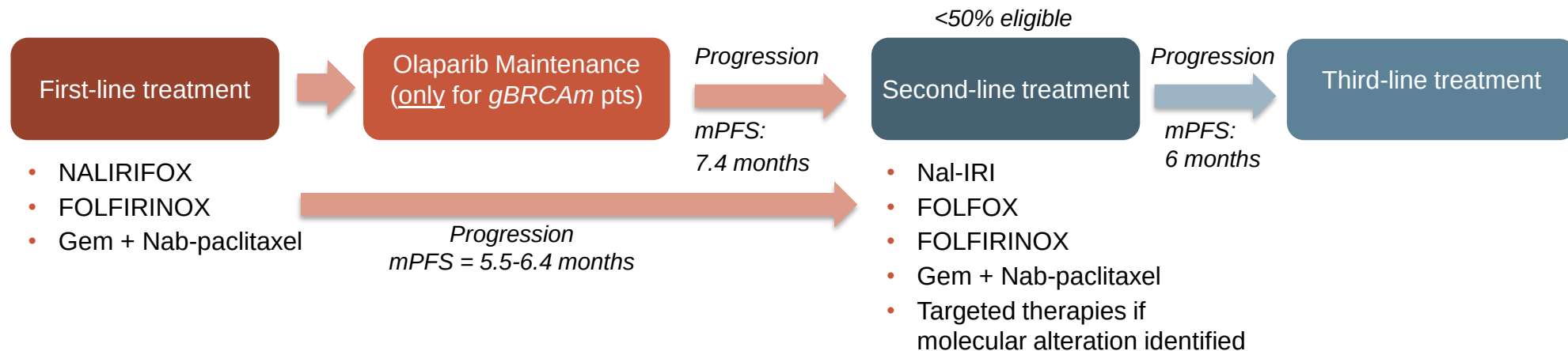


Figure adapted from Casolino 2022

gBRCAm, germline BRCA mutation; FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; FOLFOX, folinic acid (leucovorin calcium), fluorouracil, and oxaliplatin; gem, gemcitabine; mPDAC, metastatic pancreatic adenocarcinoma; mPFS, median progression-free survival; Nab, nanoparticle albumin-bound; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin

Casolino R, Biankin AV. *Camb Prism Precis Med.* 2023;1:e14

KEY STUDIES OF 1L SYSTEMIC THERAPY FOR mPDAC

Study setting	Study	Study type	Arm (N)	Primary endpoint	Primary endpoint		Secondary endpoint	Secondary endpoint		ORR (%)	Notable adverse events (Grade ≥3)
					Months	HR (95% CI)		Months	HR (95% CI)		
First-line	PRODIGE ¹ (2011)	RCT, phase 2/3	FOLFIRINOX (171)	OS	11.1	0.57 (0.45 to 0.73)	PFS	6.4	0.47 (0.37 to 0.59)	31.6	FOLFIRINOX vs Gem: neutropenia 47.5 vs 21.0%, febrile neutropenia 5.4 vs 1.2%, thrombocytopenia 9.1 vs 3.6%, diarrhoea 12.7 vs 1.8%
			Gemcitabine (171)		6.8			3.3		9.4	
First-line	MPACT ² (2013)	RCT, phase 3	Gem + NabP (431)	OS	8.5	0.72 (0.62 to 0.83)	PFS	5.5	0.69 (0.58 to 0.82)	23.0	Gem + NabP vs Gem: Neutropenia 38.0 vs. 27.0%, leukopenia 31.0 vs 16.0%, thrombocytopenia 13.0 vs 9.0%, fatigue 17.0 vs. 7.0%, and neuropathy 17.0 vs. 1.0%
			Gemcitabine (430)		6.7			3.7		7.0	
First-line	NAPOLI-3 ³ (2023)	RCT, phase 3	NALIRIFOX (383)	OS	11.1	0.83 (0.70-0.99)	PFS	7.4	0.69 (0.58-0.83)	41.8	NALIRIFOX vs Gem + NabP: hypokalaemia 15.0 vs 4.0%, diarrhoea 20.0 vs 5.0%, nausea 12.0 vs 3.0%. Lower rates of hematological AE's with NALIRIFOX: neutropenia 14.0 vs 25.0%, anaemia 11.0 vs 17.0%
			Gem + NabP (387)		9.2			5.6		36.2	
Metastatic maintenance ^a	POLO ^{4,5} (2019, 2022)	RCT, phase 3	Olaparib (92)	PFS	7.4	0.53 (0.35 to 0.82)	OS	19.0	0.83 (0.56 to 1.22)	23.1 ^b	Olaparib vs placebo: Fatigue 5.6 vs 0%, anaemia 12.2 vs 3.3%, decreased appetite 3.3 vs 0%
			Placebo (62)		3.8			19.2		11.5 ^b	

^a Patients with germline mutations in *BRCA1* or *BRCA2*, who had received at least 16 weeks of continuous platinum-based chemotherapy as the first line treatment for metastatic pancreatic cancer, were enrolled; ^bAt data cut-off 1

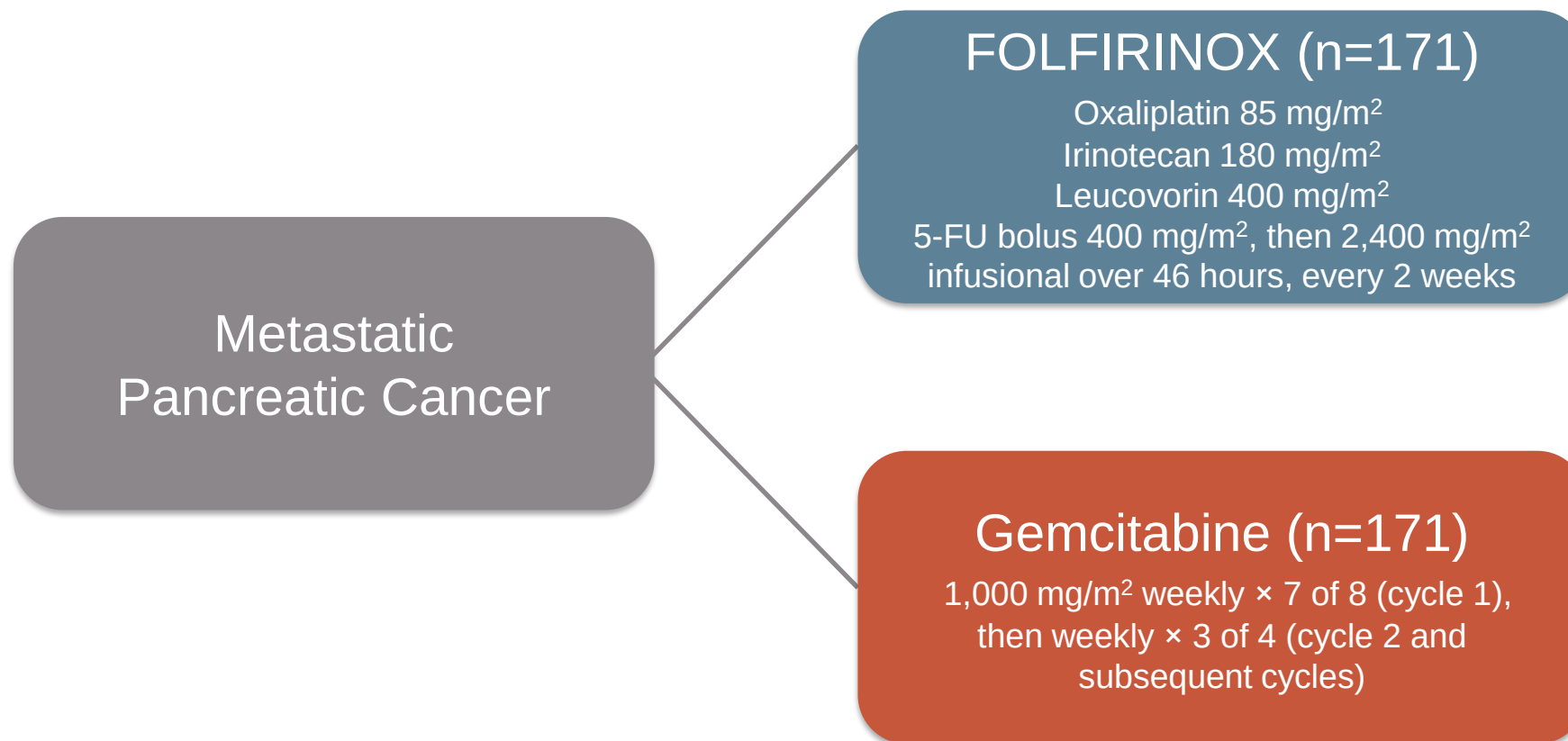
AE, adverse event; BRCA1/2, BReast CAncer 1/2 gene; CI, confidence interval; FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; Gem+ Nab-P, gemcitabine and nab (nanoparticle albumin-bound)-paclitaxel; HR, hazard ratio; mPDAC, metastatic pancreatic ductal adenocarcinoma; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial

1. Conroy T et al. N Engl J Med. 2011;364:1817-25; 2. Von Hoff D, et al. N Engl J Med. 2013;369:1691-703; 3. Wainberg Z, et al. Lancet 2023;402:1272-81;

4. Golan T, et al. N Engl J Med. 2019;381:317-27; 5. Kindler H, et al. J Clin Oncol. 2022;40:3929-39

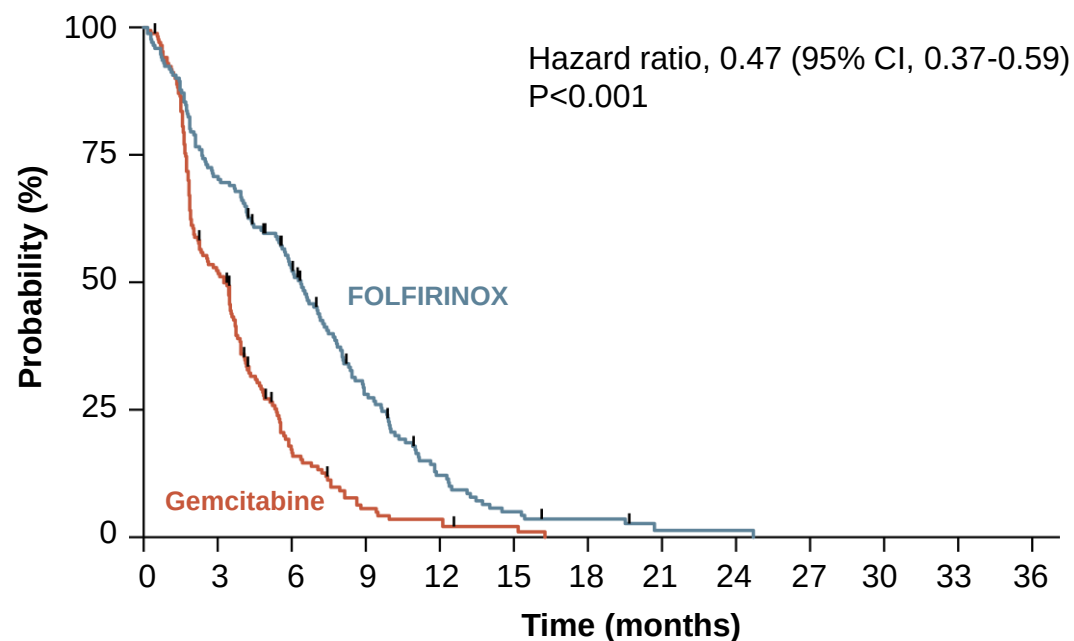
PRODIGE4/ACCORD11: STUDY DESIGN

FOLFIRINOX VS GEMCITABINE AS 1L THERAPY



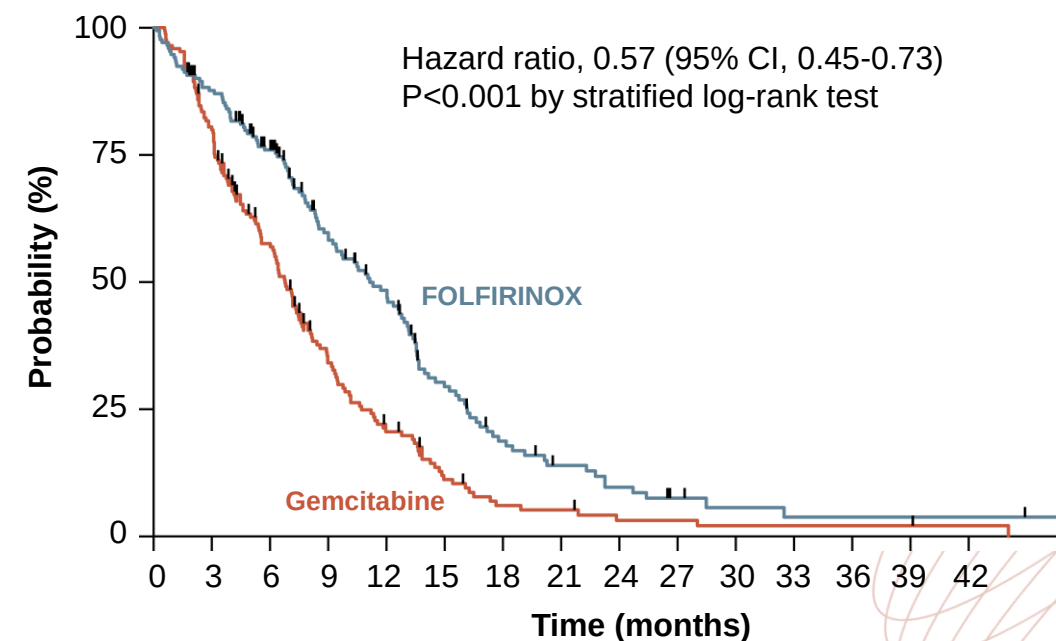
PRODIGE4/ACCORD11: FOLFIRINOX EMERGED AS A 1L OPTION

PROGRESSION-FREE SURVIVAL



No. at risk												
Gemcitabine	171	88	26	8	5	2	0	0	0	0	0	0
FOLFIRINOX	171	121	85	42	17	7	4	1	1	0	0	0

OVERALL SURVIVAL



No. at risk												
Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2

Median PFS: 6.4 mo FOLFIRINOX vs 3.3 mo gemcitabine

Median OS: 11.1 mo FOLFIRINOX vs 6.8 mo gemcitabine

1L, first-line; CI, confidence interval; FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; mo, months; OS, overall survival; PFS, progression-free survival

Conroy T, et al. N Engl J Med. 2011;364:1817-25

PRODIGE4/ACCORD11: SAFETY

MOST COMMON GRADE 3 OR 4 ADVERSE EVENTS OCCURRING IN MORE THAN 5% OF PATIENTS IN THE SAFETY POPULATION^a

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P value
Hematologic, n/N (%)			
Neutropenia	75/164 (47.5)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anaemia	13/166 (7.8)	10/168 (6.0)	NS
Non-hematologic, n/N (%)			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhoea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

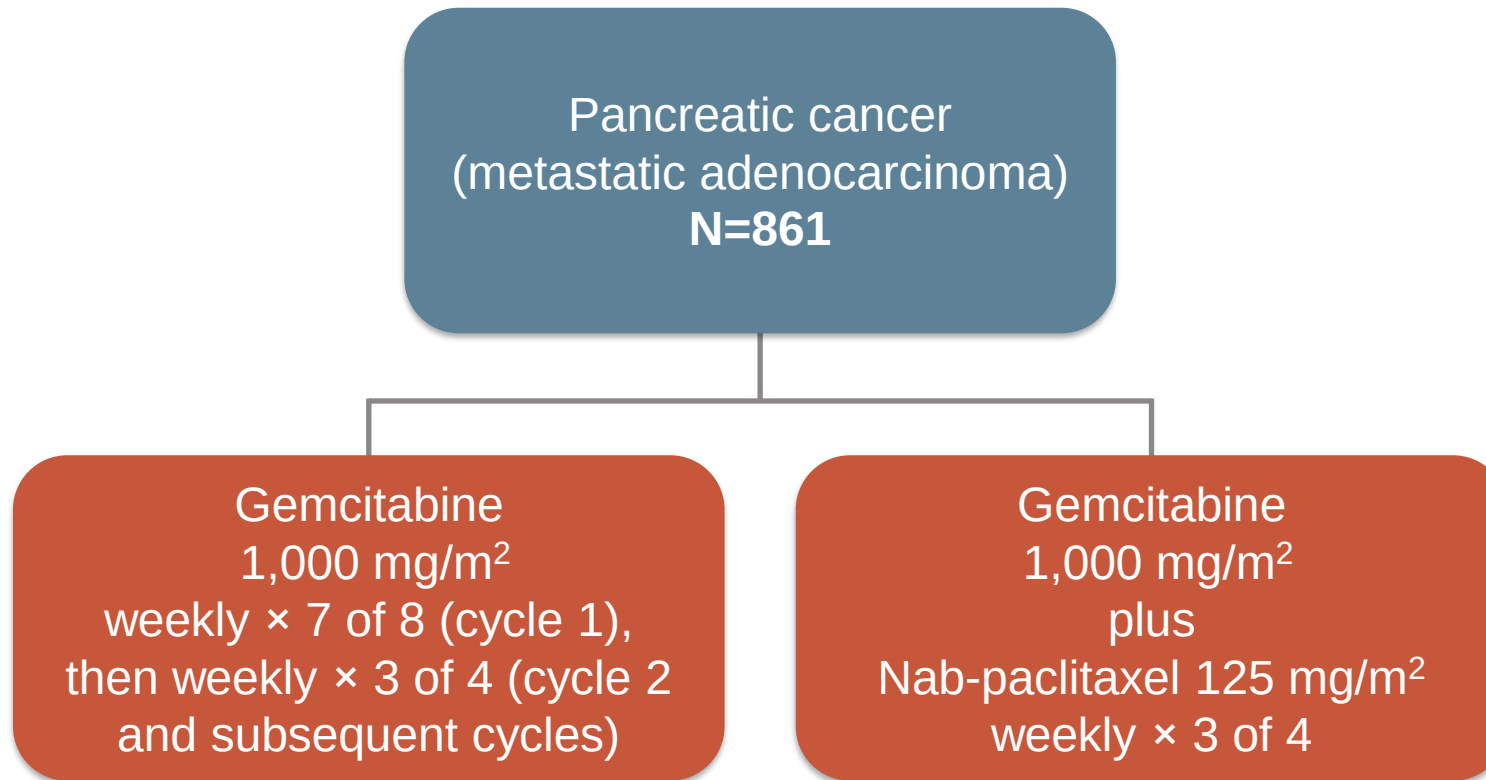
^aEvents listed are those that occurred in more than 5% of patients in either group. NS denotes not significant

FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin

Conroy T, et al. N Engl J Med. 2011;364:1817-25

MPACT: STUDY DESIGN

NAB-PACLITAXEL PLUS GEMCITABINE AS 1L THERAPY



MPACT: EFFICACY

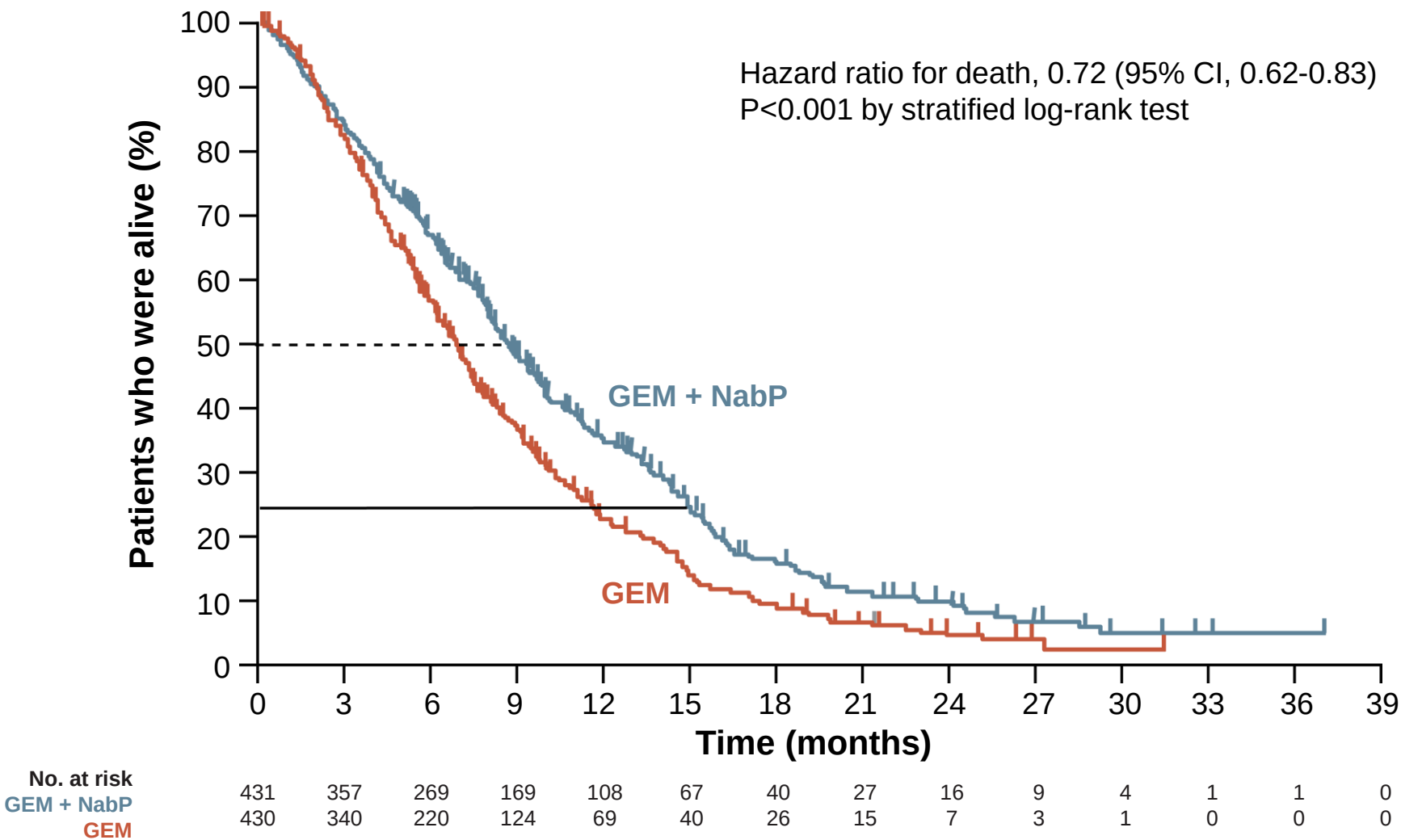
	GEM + NabP (n=431)	GEM (n=430)	Hazard ratio
Overall survival, months	8.5	6.7	0.72 (p<0.001)
One-year survival, %	35	22	
Progression-free survival, months	5.5	3.7	0.69 (p<0.001)
6-month PFS, %	44	25	
Response rate, %	23	7	p<0.001
Median treatment duration (range), months	3.9 (0.1-21.9)	2.8 (0.1-21.5)	
% protocol dose ^a			
Nab-paclitaxel	80.6	—	
Gemcitabine	75.2	84.6%	

^aProportion of administered cumulative dose relative to the planned cumulative dose

GEM, gemcitabine; HR, hazard ratio; NabP, nanoparticle albumin-bound paclitaxel; PFS, progression-free survival

Von Hoff D, et al. N Engl J Med. 2013;369:1691-703

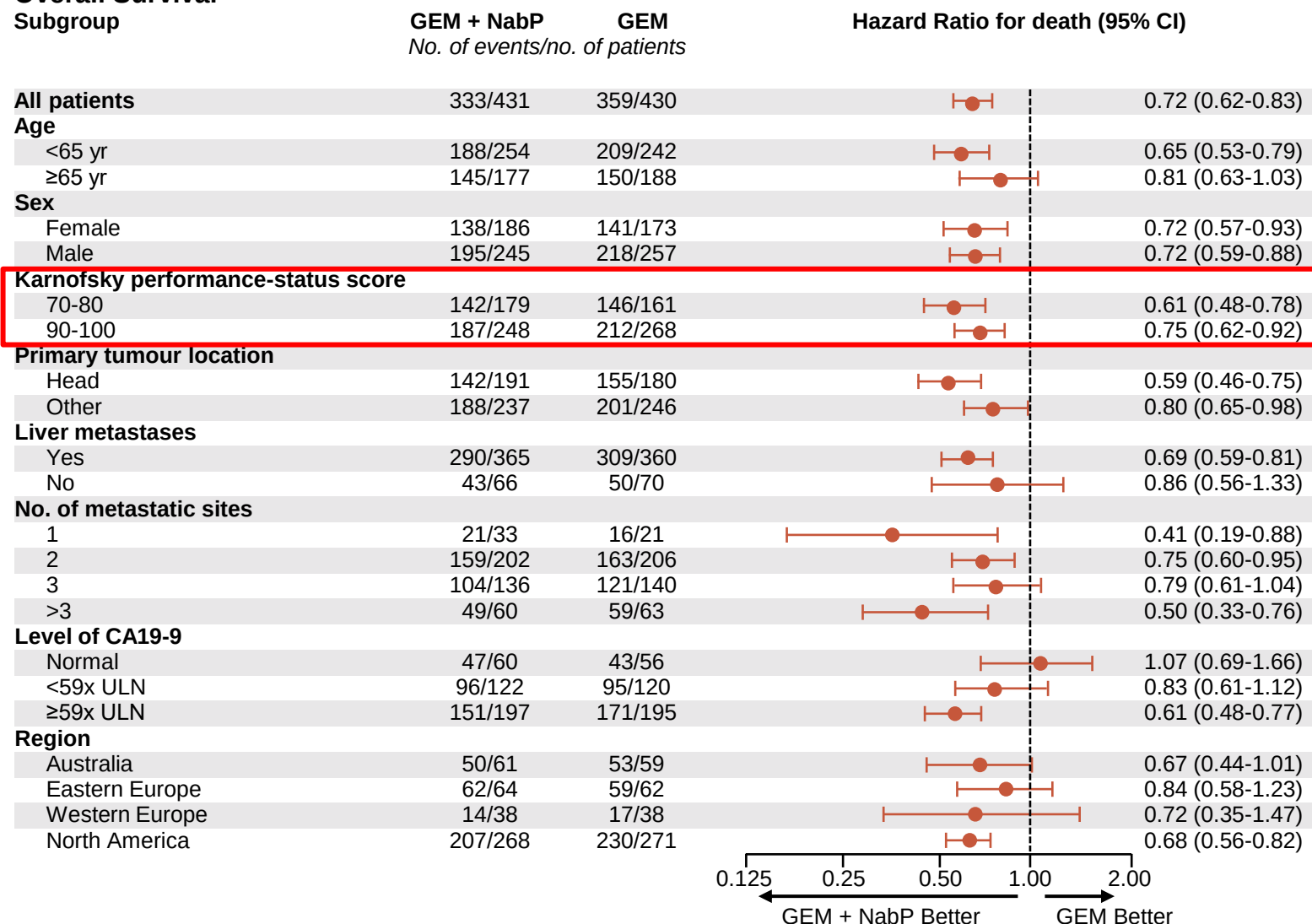
MPACT: THE ADDITION OF NabP TO GEM IMPROVES OVERALL SURVIVAL



CI, confidence interval; GEM, gemcitabine; HR, hazard ratio; NabP, nanoparticle albumin-bound paclitaxel
Von Hoff D, et al. N Engl J Med. 2013;369:1691-703

MPACT: PRE-SPECIFIED SUBGROUP ANALYSIS

Overall Survival Subgroup



CA19-9, carbohydrate antigen 19-9; CI, confidence interval; GEM, gemcitabine; NabP, nanoparticle albumin-bound paclitaxel; ULN, upper limit of normal; yr, year

Von Hoff D, et al. N Engl J Med. 2013;369:1691-703

MPACT: SAFETY

Preferred Term	GEM + NabP (n=421)	GEM (n=402)
Grade ≥3 Hematologic AE ^a , %		
Neutropenia	38	27
Leukopenia	31	16
Thrombocytopenia	13	9
Anaemia	13	12
Patients who received growth factors, %	26	15
Febrile Neutropenia, ^b %	3	1
Grade ≥3 Non-hematologic AE ^b in >5% patients, %		
Fatigue	17	7
Peripheral Neuropathy ^c	17	<1
Diarrhoea	6	<1
Grade ≥3 Neuropathy		
Median time to Onset, median days	140	113
Median time to Improvement by 1 Grade, median days	21	29
Median time to Improvement to Grade ≤1, median days	29	NR
Patients who resumed NabP, %	44	NA

- GEM + NabP group:
 - High levels of neutropenia, and thrombocytopenia
 - Significant percentage of patients with peripheral neuropathy

^a Based on lab values; ^b Based on investigator assessment of treatment-related events; ^c grouped term

AE, adverse event; GEM, gemcitabine; NabP, nanoparticle albumin-bound paclitaxel; NA, not applicable; NR, not reached

Von Hoff D, et al. N Engl J Med. 2013;369:1691-703

MODIFIED GEMCITABINE PLUS Nab-PACLITAXEL

A MODIFIED REGIMEN OF BIWEEKLY mGEM + NabP IN METASTATIC PANCREATIC CANCER PATIENTS IS TOLERABLE AND EFFECTIVE

Variable	mGEM + NabP	MPACT trial
Median PFS, months	5.4, N=57	5.5, N=431
Median OS, months	10, N=57	8.5, N=431
Grade 3 or 4 toxicity, hematological, n/N(%)		
Anaemia	8/57 (14%)	53/405 (13%)
Neutropenia	11/57 (19%)	153/405 (38%)
Thrombocytopenia	1/57 (2%)	52/405 (13%)
Growth factor support	7/57 (12%)	110/431 (26%)
Grade 3 or 4 neurotoxicity	1/57 (2%)	70/421 (17%)
Dose reduction, (%):		
Nab-paclitaxel	20%	41%
Gemcitabine	16%	47%

TWO-WEEK LOW DOSE GEM-NabP DOSING MANAGES TOXICITY AND MAINTAINS EFFICACY

Outcome	First-line GEM + NabP efficacy
Median OS (95% CI), mo	7.5 (6.51-10.33)
Median OS (95% CI) stratified by ECOG PS, mo	
0	12.7 (8.49-18.49)
1	9.6 (6.48-12.04)
2	5.3 (4.41-10.2)
3	1.6 (NE)
	P value <0.0001
Median PFS (95% CI), mo	2.8 (2.3-3.68)
Median PFS (95% CI) stratified by ECOG PS, mo	
0	5.3 (2.73-9.11)
1	2.8 (2.24-4.34)
2	1.8 (1.41-3.59)
3	1.4 (NE)
	P value = 0.0072

Outcome	Second-line GEM + NabP efficacy
Median OS (95% CI), mo	7.6 (6.12-8.26)
Median OS (95% CI) stratified by ECOG PS, mo	
0	8 (6.22-12.99)
1	7.3 (5.33-9.14)
2	6.1 (4.61 - NE)
	P value = 0.581
Median PFS (95% CI), mo	2.5 (2.14-3.85)
Median PFS (95% CI) stratified by ECOG PS, mo	
0	3.5 (2.07-7.24)
1	2.4 (2.07-2.99)
2	2.6 (1.74 - NE)
	P value = 0.362

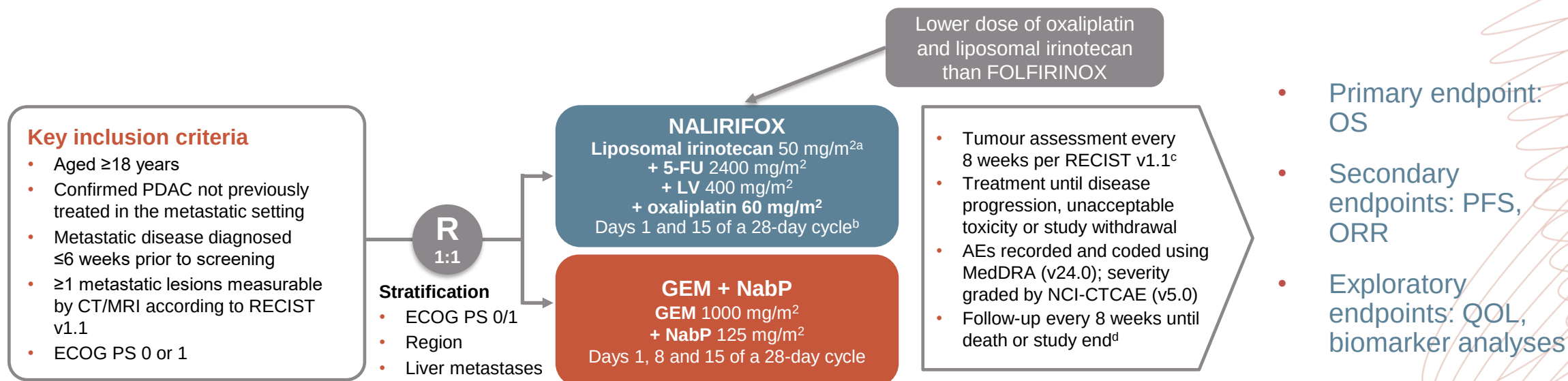
Median dosing was 600 mg/m² at fixed dose rate for GEM and 125 mg/m² for NabP given predominantly (~90%) every two weeks

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GEM-NabP, gemcitabine + nanoparticle albumin-bound paclitaxel; mo, months; NE, not estimable; OS, overall survival; PFS, progression-free survival

Rogers J, et al. Cancer Med. 2020;9:5406-15

NAPOLI-3: STUDY DESIGN

A randomised, open-label phase 3 study of liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin (NALIRIFOX) versus gemcitabine + Nab-paclitaxel in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma



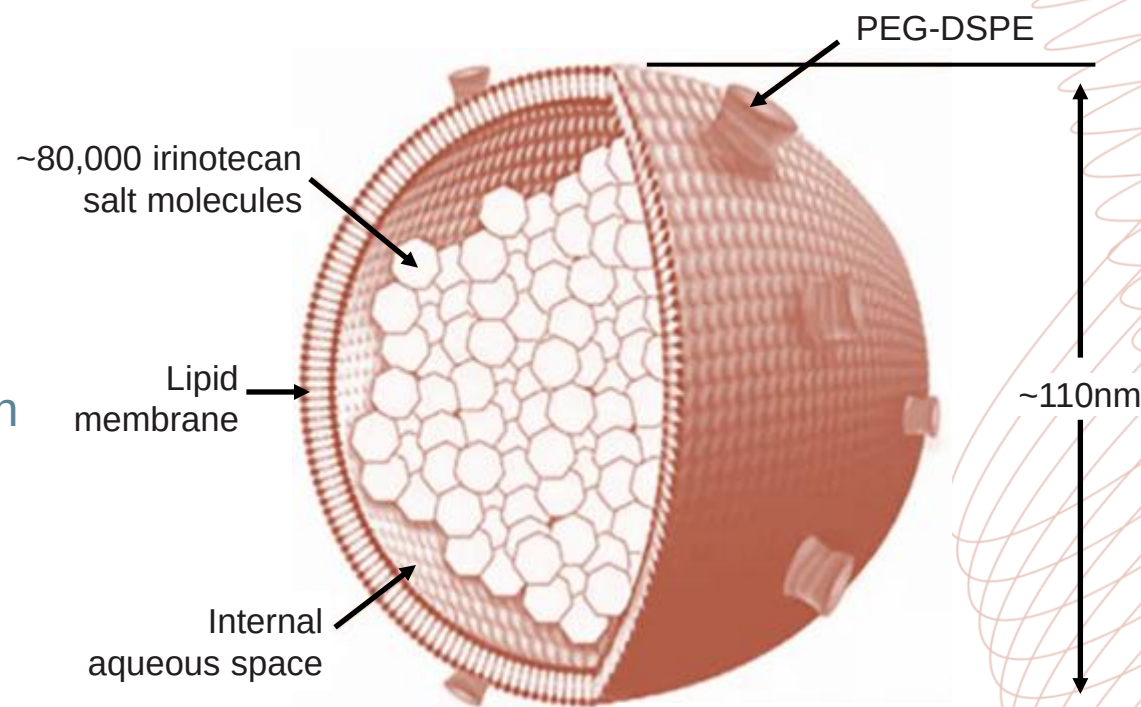
^a Dose expressed as irinotecan free base equivalent; ^b Administered sequentially as a continuous infusion over 46 hours beginning on days 1 and 15 of a 28-day cycle (dose delays and oxaliplatin discontinuation were permitted); ^c Until progressive disease; ^d The study was completed once all patients had discontinued the study treatment and at least 543 events had occurred in randomised patients

5-FU, fluorouracil; AE, adverse event; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; GEM, gemcitabine; LV, leucovorin calcium (folinic acid); MedDRA, Medical Dictionary for Regulatory Activities; MRI magnetic resonance imaging; NabP, nanoparticle albumin-bound paclitaxel; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX, Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, objective response rate; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; QoL, quality of life; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours

HOW IS NANOLIPOSOMAL IRINOTECAN (NaI-IRI) DIFFERENT TO IRINOTECAN?

- **Nanoliposomal irinotecan:** irinotecan encapsulated in liposome nanoparticles¹
- Liposome shelters irinotecan from conversion to its active metabolite (SN-38) thereby remaining in the circulation for longer than free (unencapsulated) irinotecan¹⁻³
- Leads to increases and prolonged intratumoural levels of both irinotecan and SN-38 compared with free irinotecan¹
- Median OS of 5.2 months for NaI-IRI in a phase 2 study of gemcitabine-refractory metastatic pancreatic cancer^{1,4}

Liposomal irinotecan⁵

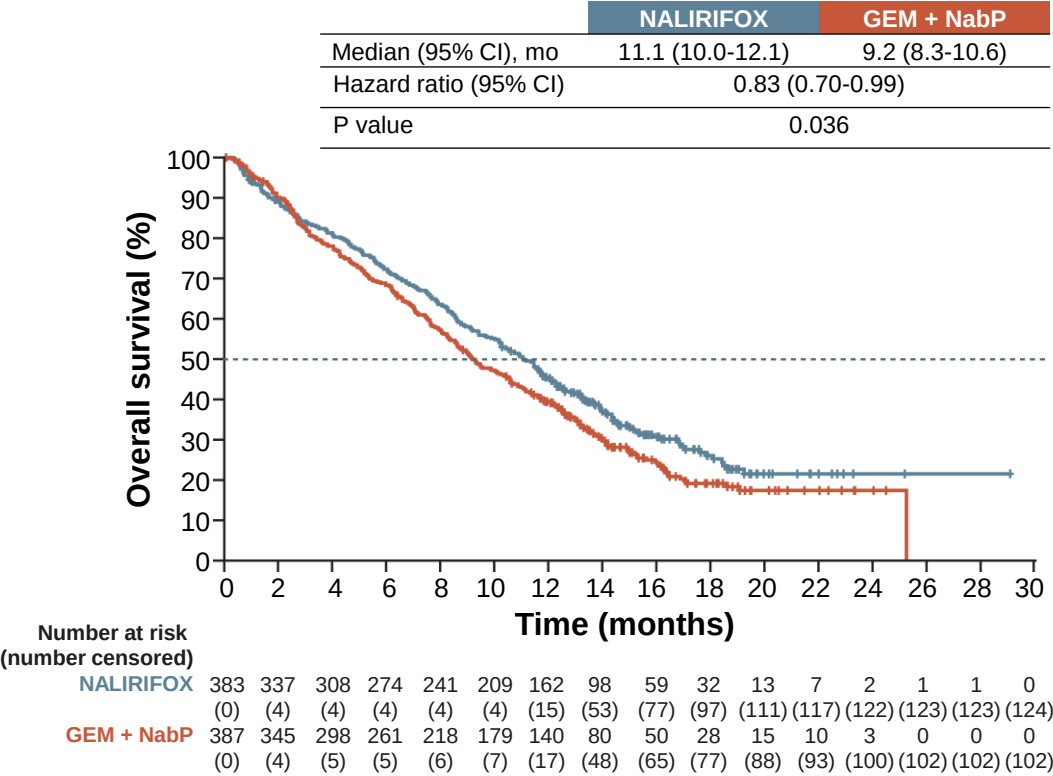


NaI-IRI, nanoliposomal irinotecan; OS, overall survival; PEG-DSPE, polyethylene glycol-distearoylphosphatidylethanolamine

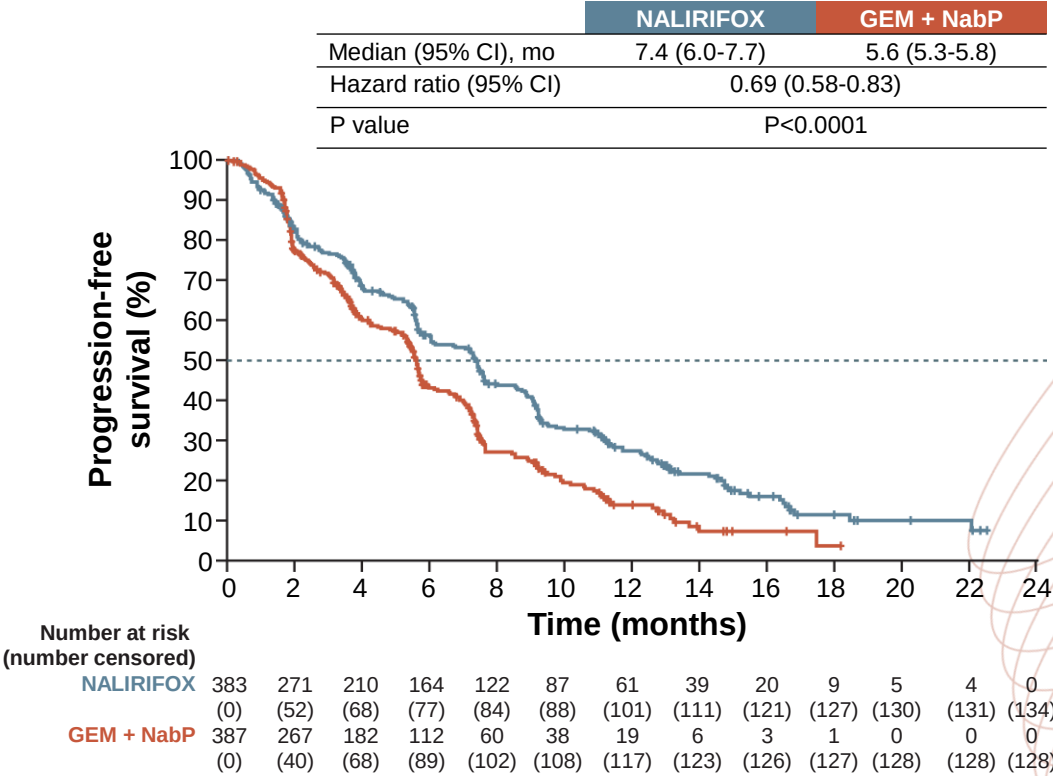
1. Wang-Gillam A, et al. Lancet 2016;387:545-57; 2. Kalra AV, et al. Cancer Res. 2014;74:7003-13; 3. Roy AC, et al. Ann Oncol. 2013;24: 1567-73; 4. Ko AH, et al. Br J Cancer. 2013;109:920-25; 5. Image: Camptothecin & Its Derivatives for Cancer Therapy | Biopharma PEG. Available at: <https://www.biochempeg.com/article/310.html>. Accessed July 2024

NAPOLI-3: NALIRIFOX MORE EFFECTIVE THAN NabP/GEM

OVERALL SURVIVAL

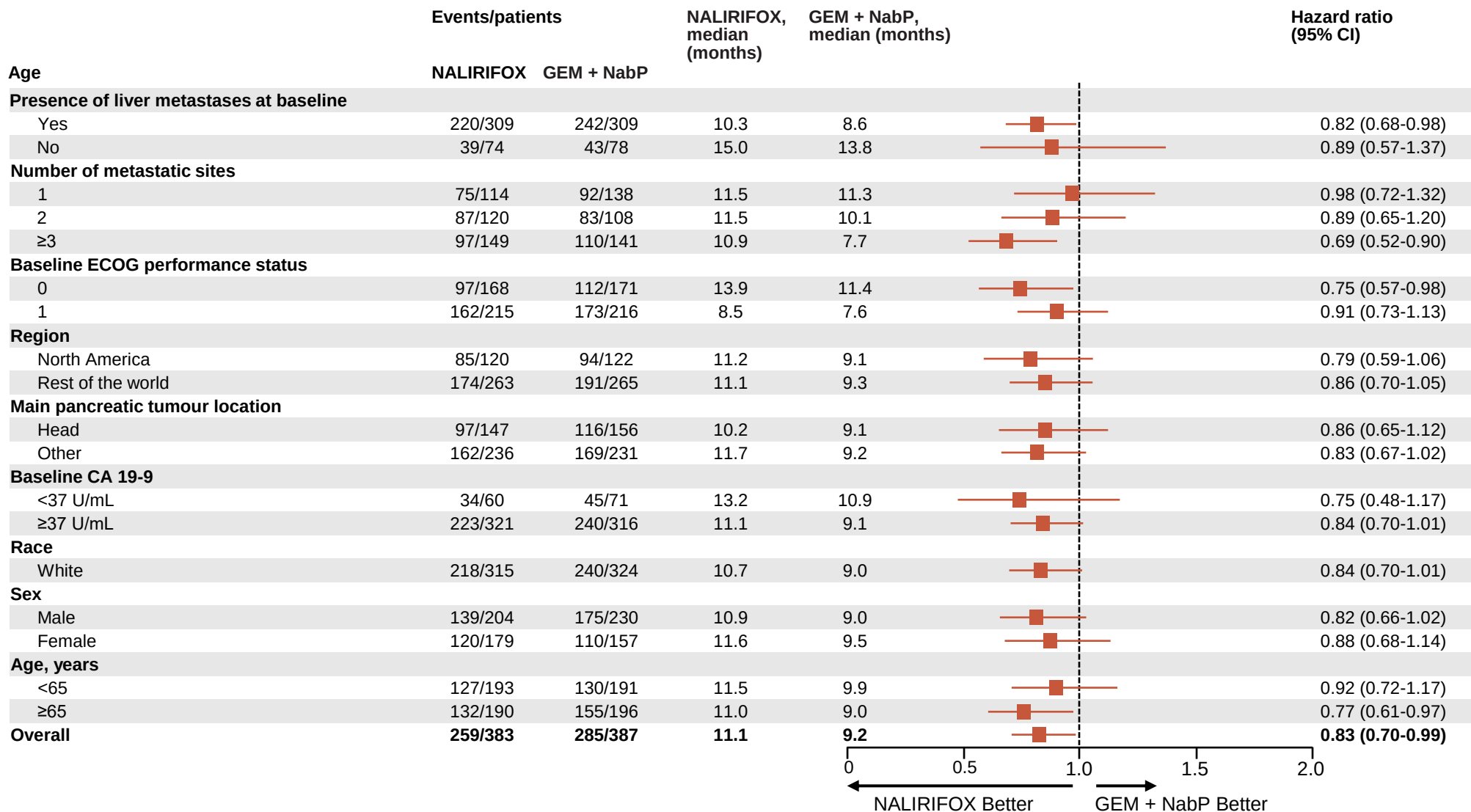


PROGRESSION-FREE SURVIVAL



CI, confidence interval; GEM, gemcitabine; mo, months; NabP, nanoparticle albumin-bound paclitaxel; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin
Wainberg Z, et al. Lancet 2023;402:1272-81

NAPOLI-3: OS SUBGROUP ANALYSES (ITT POPULATION)



CA19-9, carbohydrate antigen 19-9; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GEM, gemcitabine; ITT, intention-to-treat; NabP, nanoparticle albumin-bound paclitaxel; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX, Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; OS, overall survival

NAPOLI-3: OVERVIEW OF TEAEs IN SAFETY POPULATION

- More hematologic toxicity observed with GEM + NabP
- More diarrhoea, nausea, and vomiting observed with NALIRIFOX

TEAEs of grade 3-4 occurring in ≥5% of patients in either treatment arm	NALIRIFOX (N=370)	GEM + NabP (N=379)
Diarrhoea	75 (20%)	17 (5%)
Nausea	44 (12%)	10 (3%)
Vomiting	26 (7%)	8 (2%)
Decreased appetite	32 (9%)	10 (3%)
Hypokalaemia	56 (15%)	15 (4%)
Fatigue	23 (6%)	20 (5%)
Asthenia	33 (9%)	19 (5%)
Neutropenia	52 (14%)	93 (25%)
Neutrophil count decreased	36 (10%)	51 (14%)
Anaemia	39 (11%)	66 (17%)
Peripheral neuropathy	12 (3%)	22 (6%)
Increased γ -glutamyltransferase	23 (6%)	21 (6%)

The most common AEs (any grade) leading to dose reduction of liposomal irinotecan and oxaliplatin was diarrhoea (40% and 36% of patients with dose reductions, respectively)

Data are median (range; IQR) or n (%)

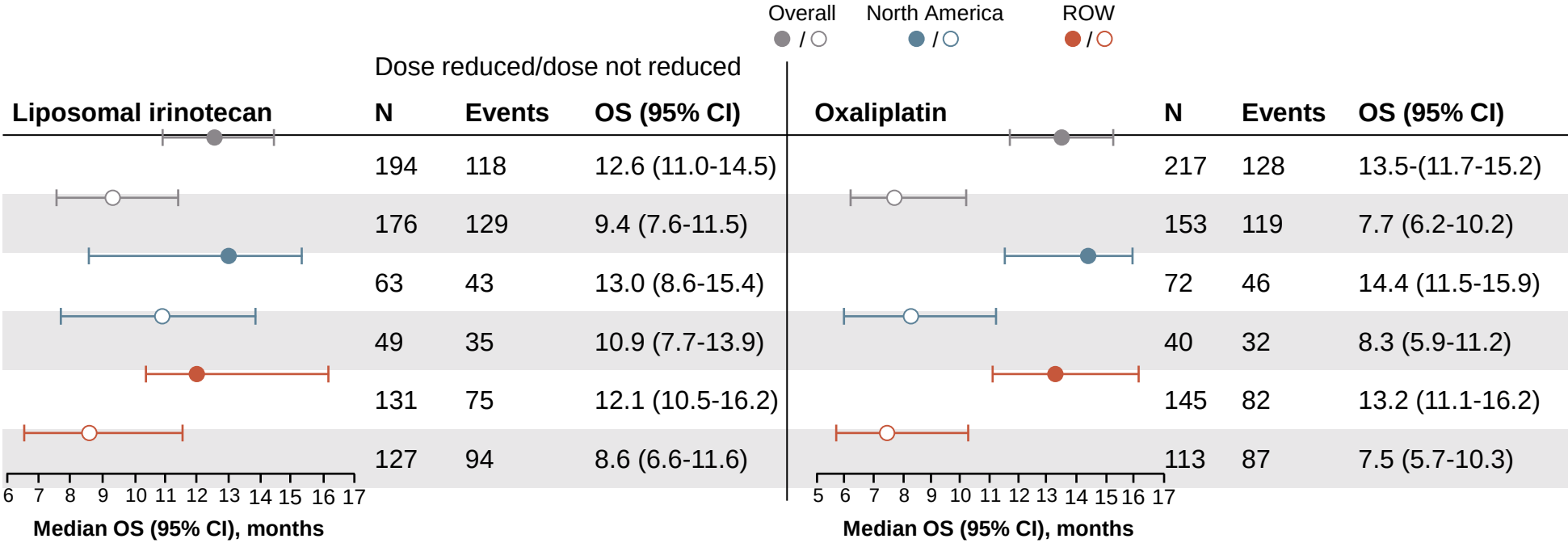
AEs, adverse events; GEM, gemcitabine; NabP, nanoparticle albumin-bound paclitaxel; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; TEAE, treatment-emergent adverse event

Wainberg Z, et al. Lancet. 2023;402:1272-81

OVERALL SURVIVAL IN PATIENTS WITH AND WITHOUT DOSE REDUCTION OF LIPOSOMAL IRINOTECAN AND OXALIPLATIN

POST HOC ANALYSIS OF NAPOLI-3 STUDY

- Liposomal irinotecan or oxaliplatin dose reductions do not adversely affect OS



CI, confidence interval; OS, overall survival; RoW, rest of world

Patel A, et al. J Clin Oncol 2025; 43, 716-716: DOI:10.1200/JCO.2025.43.4_suppl.716 (ASCO GI 2025 poster presentation)

SUMMARY OF EFFICACY AND SAFETY OF NALIRIFOX AND FOLFIRINOX

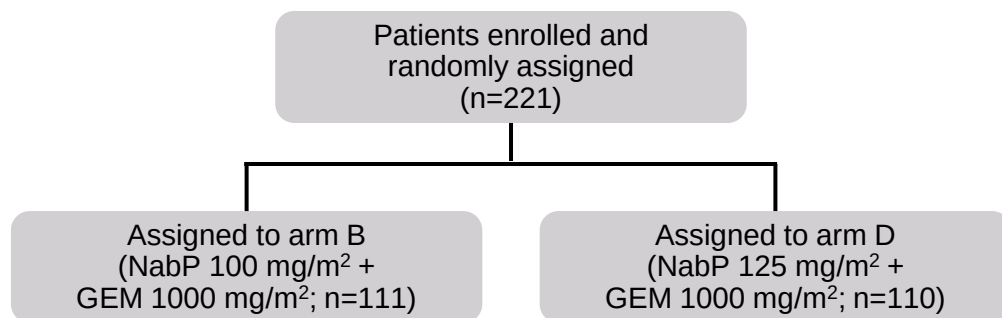
	NALIRIFOX ¹ N=370	FOLFIRINOX ² N=171
Efficacy Results		
Median OS, months	11.1	11.1
OS at 12 months, %	45.6	48.4
OS at 18 months, %	26.2	18.6
Median PFS, months	7.4	6.4
ORR, %	41.8	31.6
Safety Results		
Grade 3-4 diarrhoea, %	20.3	12.7
Grade 3-4 vomiting, %	7.0	14.5
Grade 3-4 neuropathy, %	3.2	9.0
Grade 3-4 neutropenia, %	14.1	45.7

Data presented for information purposes. Cross-trial comparison is not intended

FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; NaI-IRI, nanoliposomal irinotecan; NALIRIFOX; NaI-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

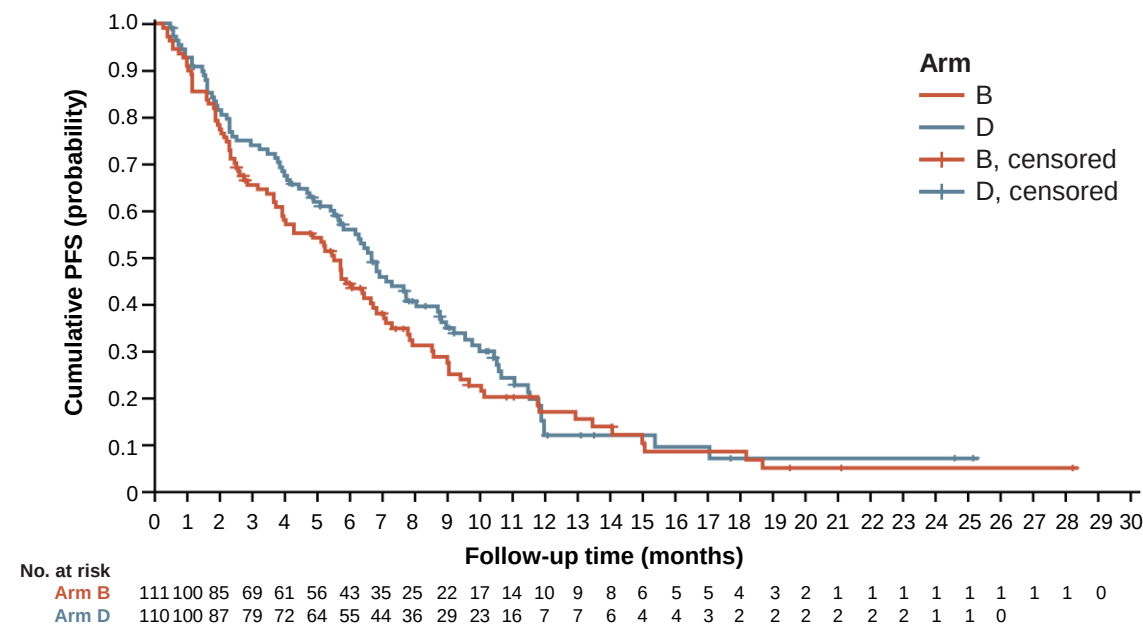
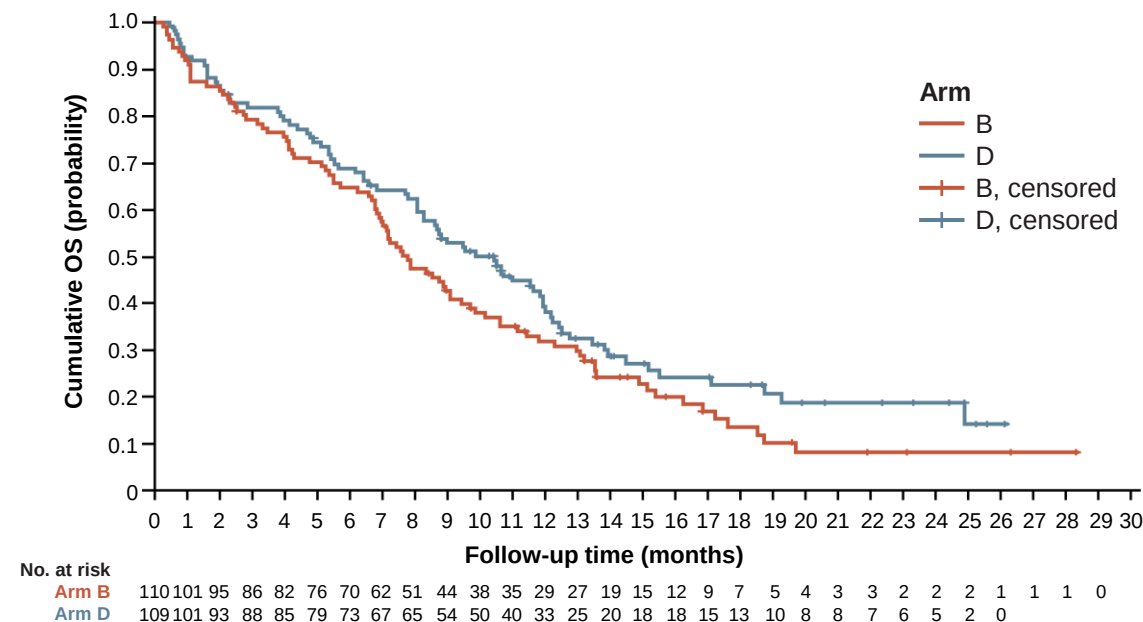
1. Wainberg Z, et al. Lancet 2023; 402:1272-81; 2. Conroy T, et al. N Engl J Med. 2011;364:1817-25

GEM + NabP IS EFFECTIVE FOR PATIENTS WITH A POOR PERFORMANCE STATUS



- Schedule 3 weeks on 1 week off
- Median age 71 and 68 (range 35-89)
- **mPFS 5.4 vs 6.6 months** (P=0.28)
- Free of disease progression at 6 months: 44% vs 58%
- **mOS 7.7m vs 9.8m** (P=0.11)
- No significant differences in AEs between the two dose regimens

AEs, adverse events; GEM, gemcitabine; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; NabP, nanoparticle albumin-bound paclitaxel
 Maccarulla T, et al. J Clin Oncol. 2019;37:230-238



POLO: PARPi AS MAINTENANCE THERAPY FOR *BRCA*m mPDAC PATIENTS POST-PLATINUM CHEMOTHERAPY

- Global, randomised, double-blind phase 3 trial

Patients with metastatic pancreatic cancer and deleterious/suspected deleterious germline *BRCA1/2* mutation, ≥16 wks of first-line platinum-based therapy without progression (4-8 wks from last dose) (N=154)



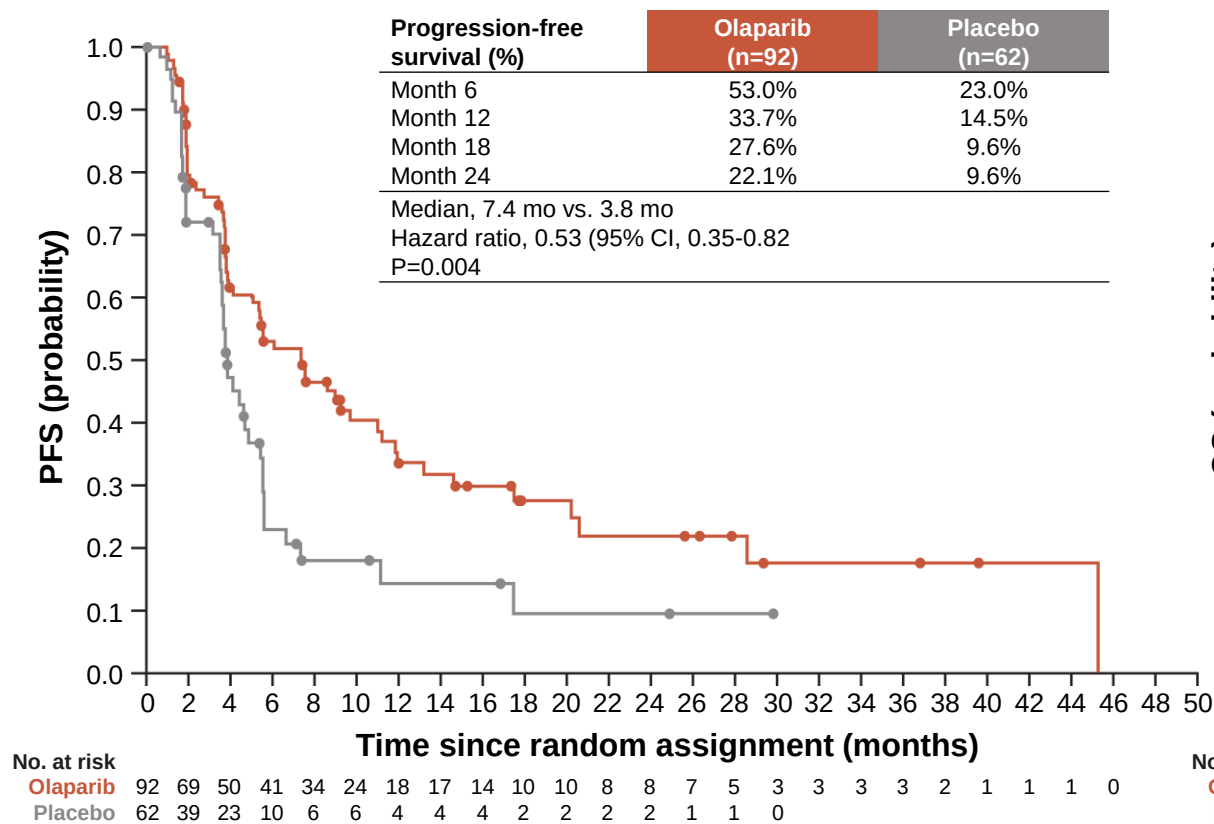
- **Primary endpoint:** PFS by blinded independent central review
- **Key secondary endpoints:** safety/tolerability, PFS2, ORR, OS, HRQoL

1L, first-line; BID, twice daily; *BRCA*, BReast CAncer 1/2 gene; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS(2), (second) progression-free survival; wks, weeks

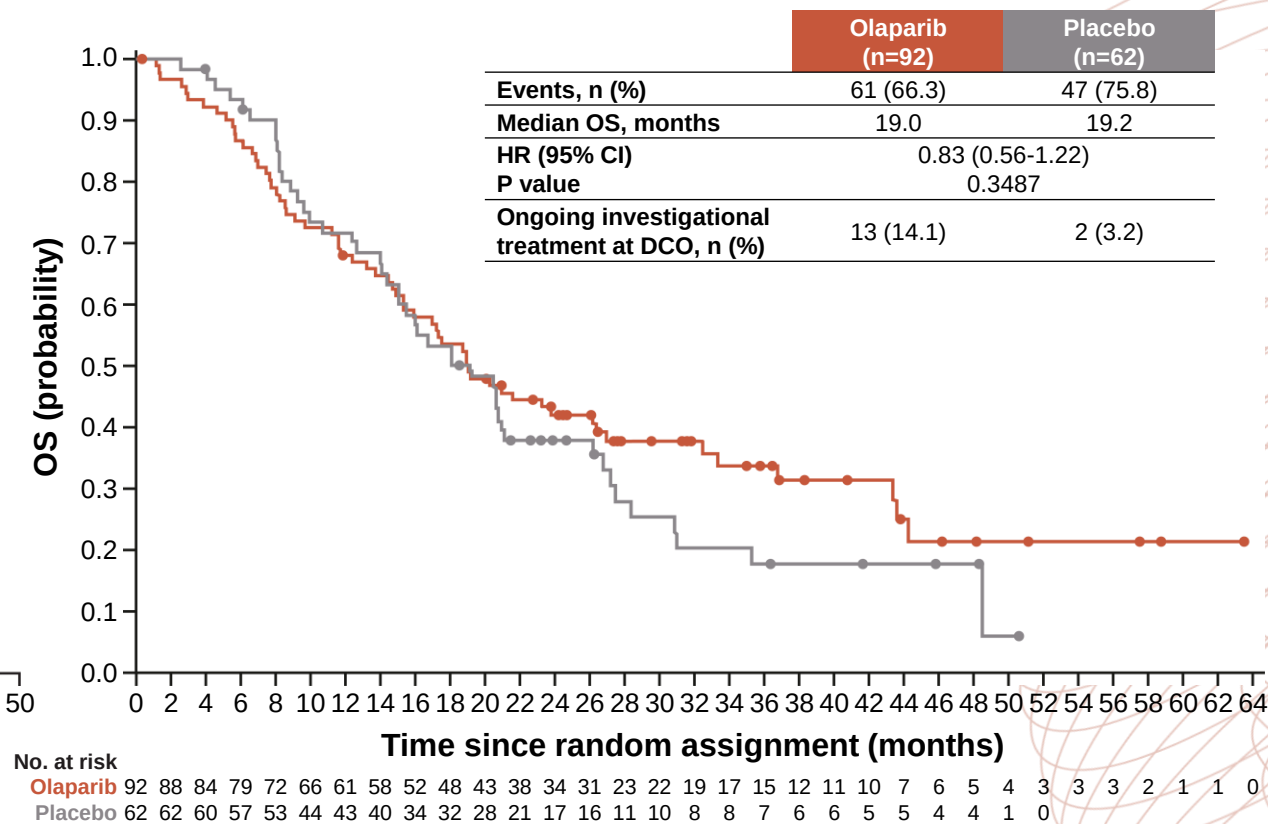
Golan T, et al. *N Engl J Med*. 2019;381:317-27; Kindler H, et al. *J Clin Oncol*. 2022;40:3929-39

POLO: PFS LONGER WITH MAINTENANCE OLAPARIB THAN PLACEBO

PROGRESSION-FREE SURVIVAL¹



OVERALL SURVIVAL²



CI, confidence interval; BRCA, BReast CAncer gene mutation; DCO, data cut-off; HR, hazard ratio; mo, months; mPDAC, metastatic pancreatic ductal adenocarcinoma; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival

1. Golan T, et al. N Engl J Med. 2019;381:317-27; 2. Kindler H, et al. J Clin Oncol. 2022;40:3929-39

TARGETED THERAPY FOR PANCREATIC ADENOCARCINOMA

Molecular Target	Targeted Therapy	NCCN panel recommendations
<i>NTRK</i> gene fusions	Larotrectinib	1 st line and subsequent treatment options for pts with <i>NTRK</i> gene fusion-positive locally advanced or metastatic pancreatic adenocarcinoma and for recurrent disease
	Entrectinib	
	Repotrectinib	Category 2B recommendation as 1 st line for patients with metastatic disease (PS 3) and subsequent therapy or therapy for recurrent disease for patients with intermediate/poor PS (PS 2-3)
<i>RET</i> gene fusions	Selpercatinib	1 st line: pts with locally advanced/metastatic disease (PS 0–2) and as subsequent therapy for pts with good PS (0–1)
<i>NRG1</i> gene fusions	Zenocutuzumab-zbco	FDA approved for advanced, unresectable, or metastatic pancreatic adenocarcinoma harboring a <i>NRG1</i> gene fusion with disease progression on or after prior systemic therapy. Awaiting incorporation into the NCCN guidelines
<i>KRAS</i> G12C mutations	Adagrasib	Subsequent therapy options for patients with any PS (category 2B for poor PS)
	Sotorasib	
<i>BRAF</i> V600E mutations	Dabrafenib/trametinib	1 st line: metastatic disease (category 2B) and as subsequent line options (category 2A) for pts with good/poor PS and <i>BRAF</i> V600E mutations
HER2-positive	Fam-trastuzumab-deruxtecan-nxki	As a subsequent therapy option only for patients with good PS and HER2 IHC 3+ expression
MSI-H/TMB-H/dMMR	Pembrolizumab	In the advanced disease setting for first-line and subsequent treatment (if no prior immunotherapy)
	Dostarlimab-gxly	As a subsequent treatment option (if no prior immunotherapy) for patients with MSI-H or dMMR locally advanced, metastatic, or recurrent pancreatic adenocarcinoma and any PS
	Nivolumab/Ipilimumab	Category 2B, subsequent therapy option for patients with good or intermediate PS and those who did not receive prior immunotherapy

BRAF, B-Raf proto-oncogene serine/threonine kinase; dMMR, deficient DNA mismatch repair; HER2, human epidermal growth factor receptor 2; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; MSI-H, microsatellite instability-high; *NTRK*, neurotrophic tyrosine receptor kinase; PDAC, pancreatic ductal adenocarcinoma; PS, performance status; *RAS*, rat sarcoma; *RET*, rearranged during transfection; TMB-H, tumour mutational burden-high

NCCN Guidelines Version 3.2024. Available at: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455>. Accessed October 2024 NCCN guidelines for pancreatic adenocarcinoma, Version 3.2024: [pancreatic.pdf \(nccn.org\)](#)

SUMMARY

- Cytotoxic chemotherapy remains the cornerstone of systemic therapy for advanced or metastatic pancreatic cancer
- NALIRIFOX is a possible new option for frontline therapy based on the NAPOLI-3 clinical trial
- Maintenance therapy after a period of chemotherapy is an option for patients with *BRCA* or *PALB2* alterations
- Treatment selection depends on several factors, including patients' performance status and co-morbidities. These should be considered alongside the efficacy and safety profiles of the different chemotherapy regimens
- Treatment strategies can be implemented to manage toxicities associated with the different chemotherapy regimens to enable a patient to stay on treatment for optimal efficacy

BRCA1/2, BReast CAncer 1/2 gene; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; PALB2, partner and localiser of BRCA2

NCCN Guidelines Version 3.2024. Available at: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1455>. Accessed October 2024



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