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

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mPDAC, metastatic pancreatic ductal adenocarcinoma

DEVELOPED BY GI CONNECT

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  - Abbvie (spouse)

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

mPDAC, metastatic pancreatic ductal adenocarcinoma

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 years[2]
- 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 2030[3]
  - Approximately 1.7% of men and women will be diagnosed with pancreatic cancer at some point during their lifetime[2]
- 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 diagnosis[4]
- Surgery, chemotherapy and radiation are the primary treatment options for pancreatic cancer[1]

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

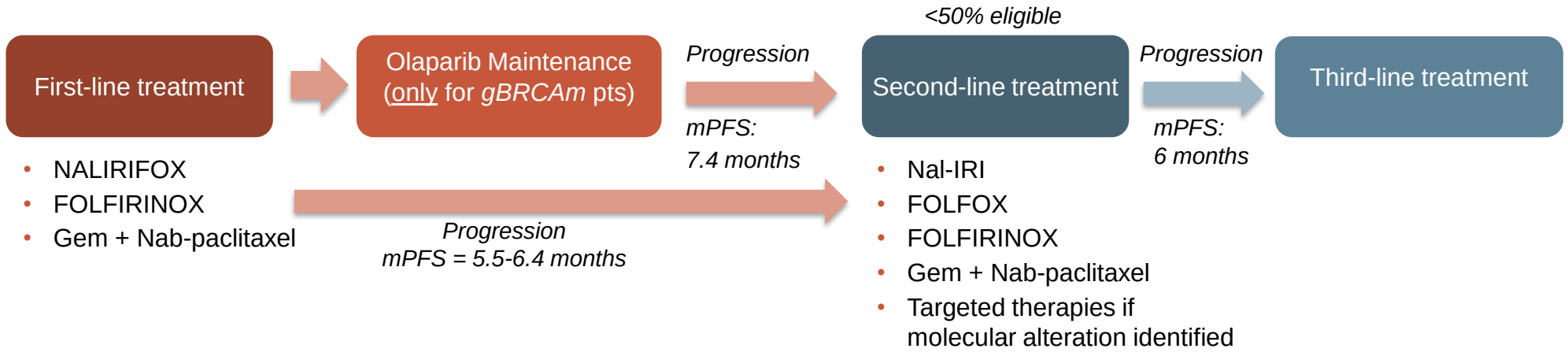


Figure adapted from Casolino 2022

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]	

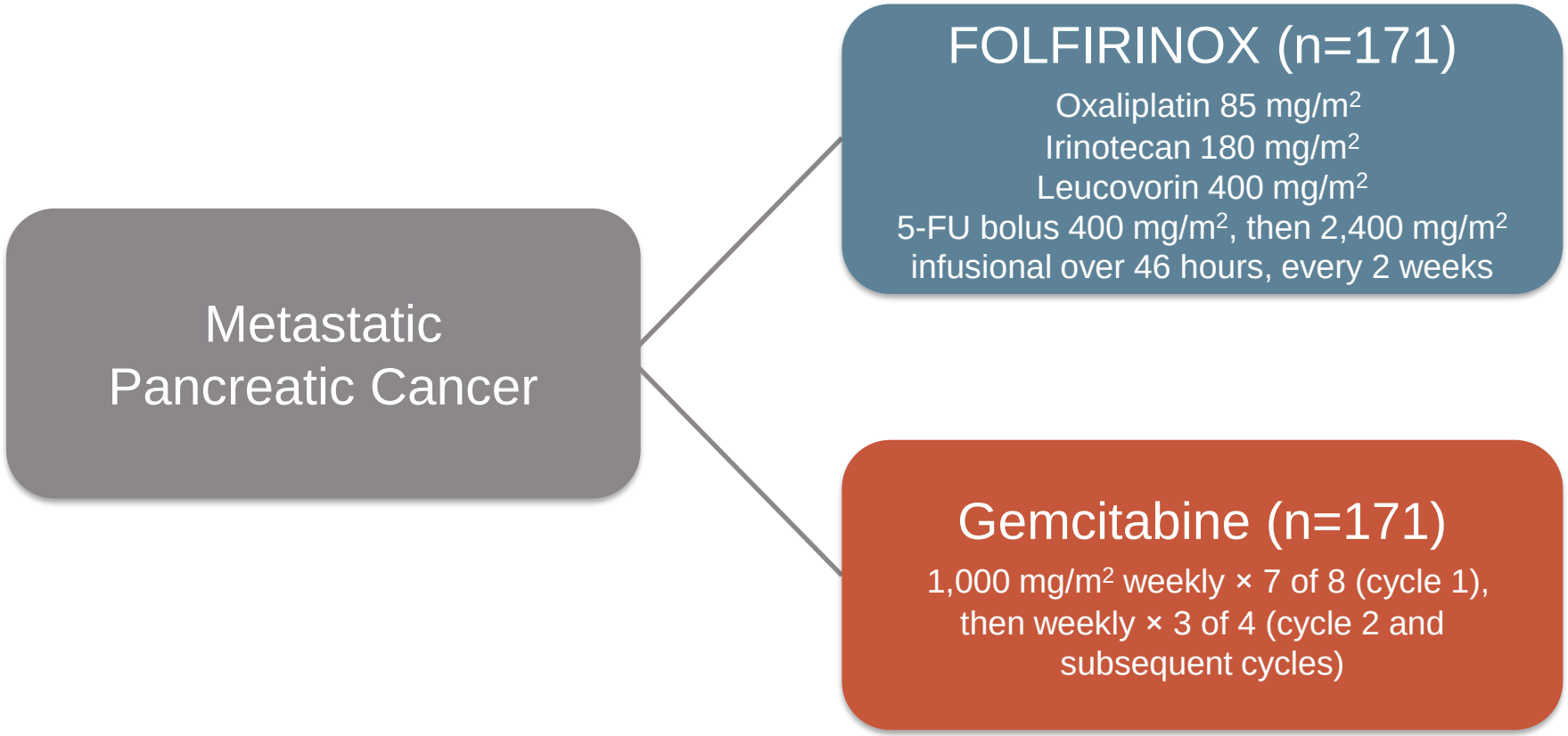
[a] Patients with germline mutations in *BRCA1* or *BRCA2*, who had received at least 16 weeks of continuous platinum-based chemotherapy as the first line treatment for metastatic pancreatic cancer, were enrolled; [b]At data cut-off 1

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

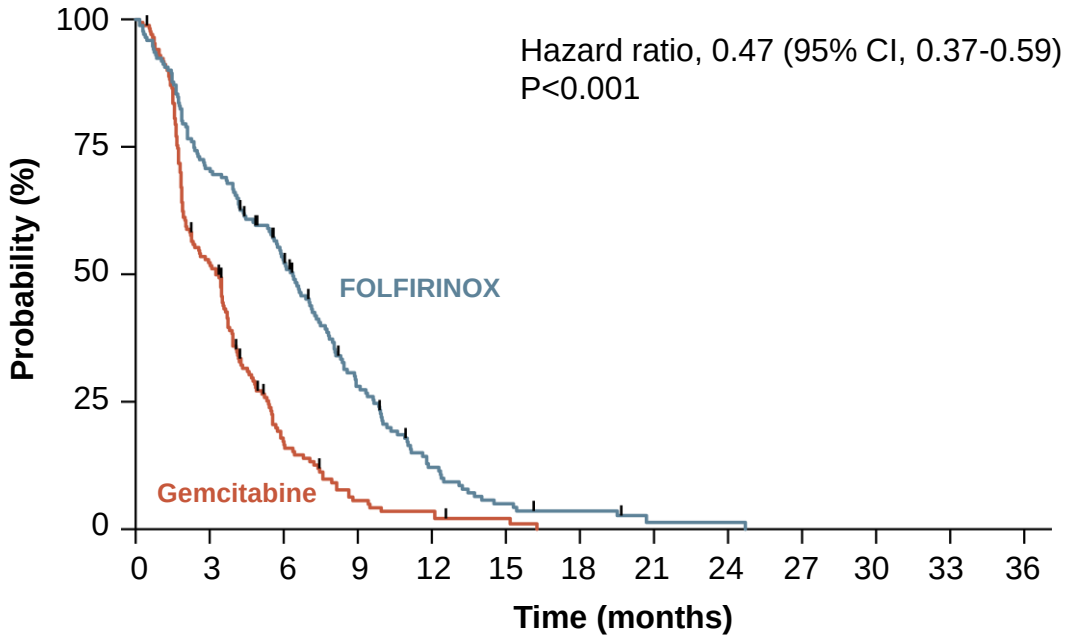


1L, first-line; 5-FU, fluorouracil; FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin

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

PRODIGE4/ACCORD11: FOLFIRINOX EMERGED AS A 1L OPTION

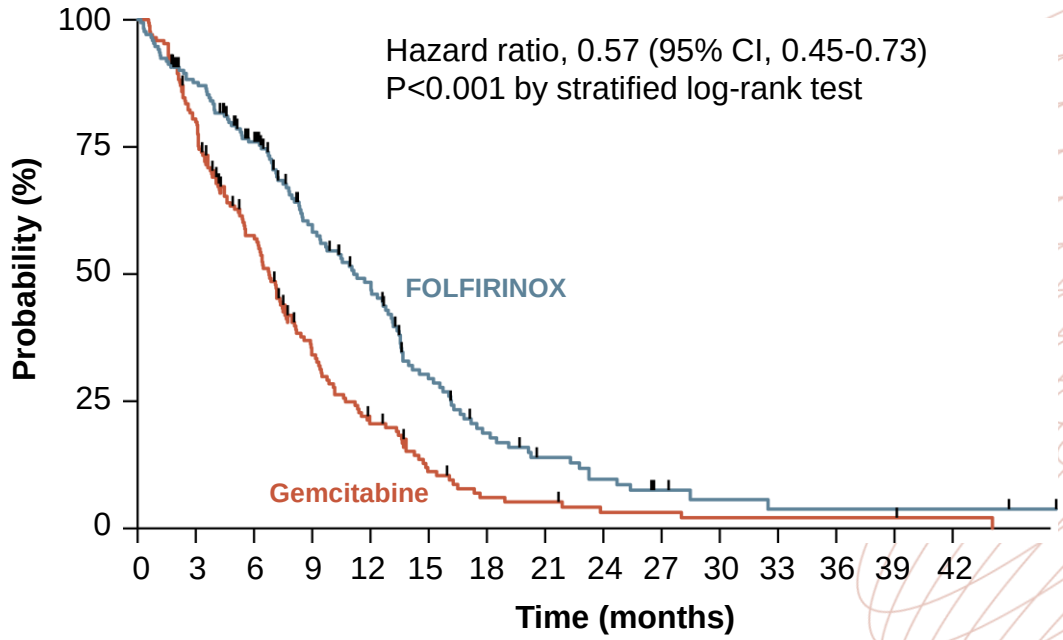
PROGRESSION-FREE SURVIVAL



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

Median PFS: 6.4 mo FOLFIRINOX vs 3.3 mo gemcitabine

OVERALL SURVIVAL



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

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

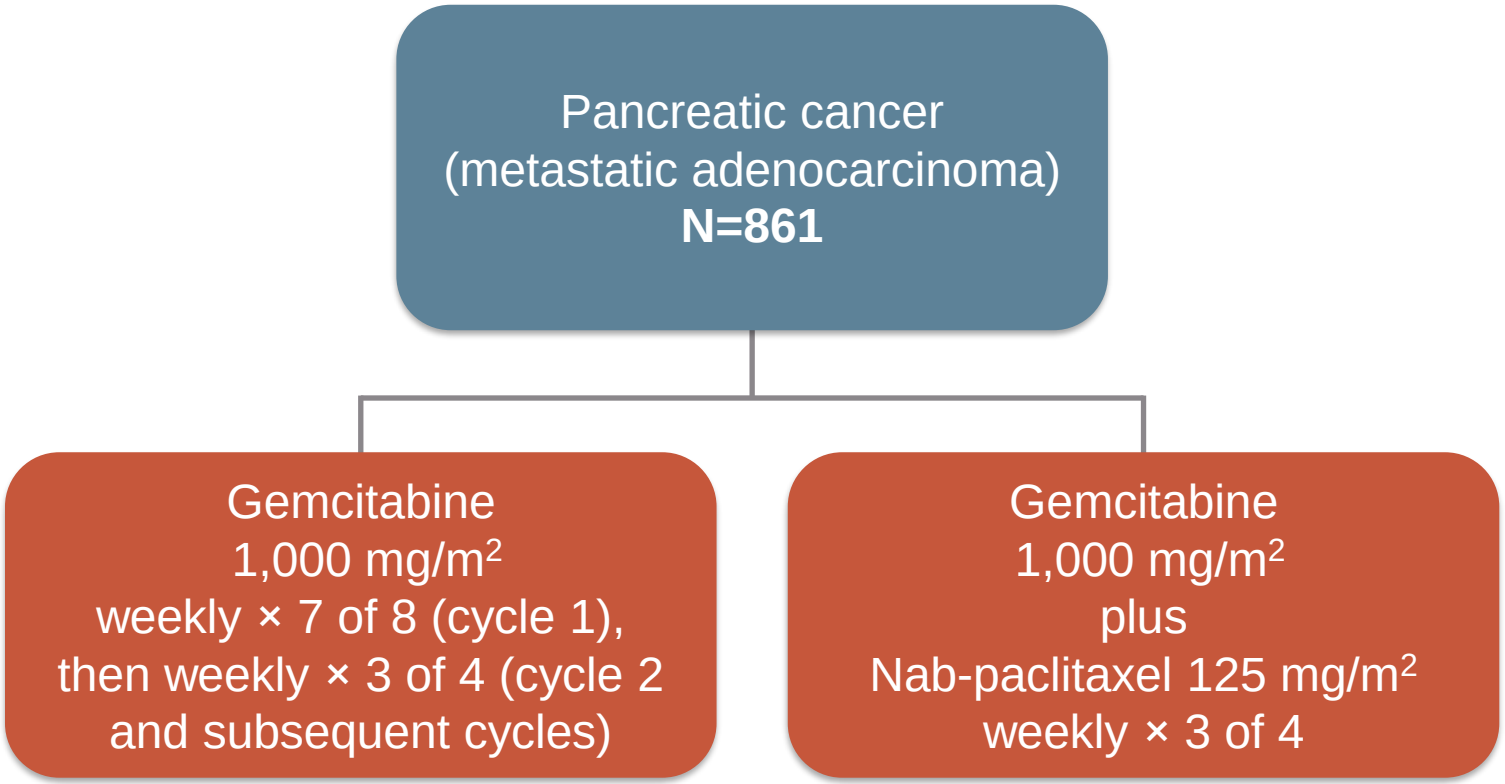
[a]Events listed are those that occurred in more than 5% of patients in either group. NS denotes not significant

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



1L, first-line; Nab, nanoparticle albumin-bound

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

MPACT: EFFICACY

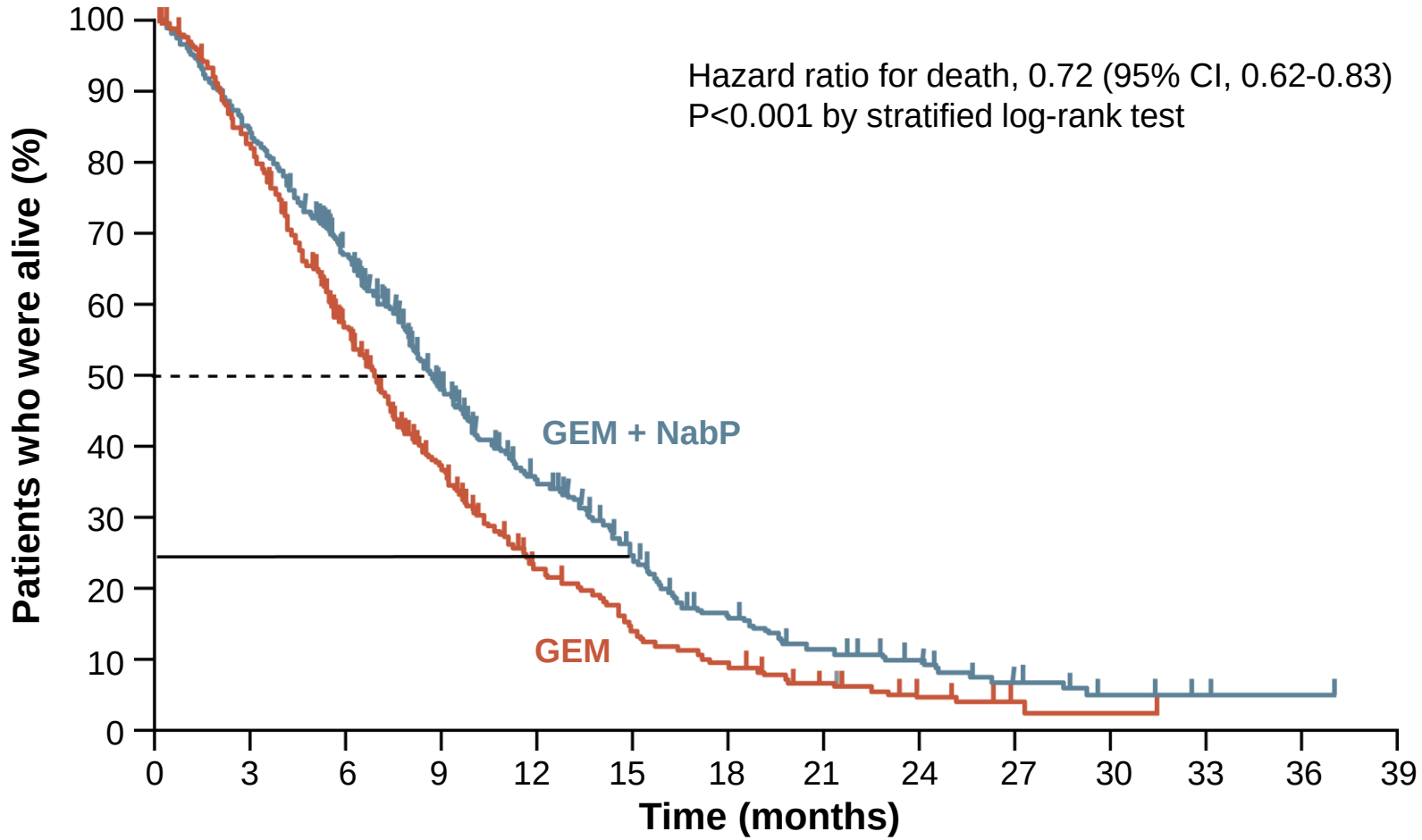
	GEM + NabP (n=431)	GEM (n=430)	Hazard ratio
Overall survival, months	8.5	6.7	0.72 (p<0.001)
One-year survival, %	35	22	
Progression-free survival, months	5.5	3.7	0.69 (p<0.001)
6-month PFS, %	44	25	
Response rate, %	23	7	p<0.001
Median treatment duration (range), months	3.9 (0.1-21.9)	2.8 (0.1-21.5)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

[a]Proportion 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



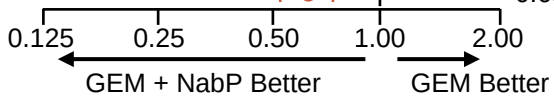
CI, confidence interval; GEM, gemcitabine; HR, hazard ratio; NabP, nanoparticle albumin-bound paclitaxel

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

MPACT: PRE-SPECIFIED SUBGROUP ANALYSIS

Overall Survival

Subgroup	GEM + NabP *No. of events/no. of patients*	GEM	Hazard Ratio for death (95% CI)
All patients	333/431	359/430	0.72 (0.62-0.83)
Age			
<65 yr	188/254	209/242	0.65 (0.53-0.79)
≥65 yr	145/177	150/188	0.81 (0.63-1.03)
Sex			
Female	138/186	141/173	0.72 (0.57-0.93)
Male	195/245	218/257	0.72 (0.59-0.88)
Karnofsky performance-status score			
70-80	142/179	146/161	0.61 (0.48-0.78)
90-100	187/248	212/268	0.75 (0.62-0.92)
Primary tumour location			
Head	142/191	155/180	0.59 (0.46-0.75)
Other	188/237	201/246	0.80 (0.65-0.98)
Liver metastases			
Yes	290/365	309/360	0.69 (0.59-0.81)
No	43/66	50/70	0.86 (0.56-1.33)
No. of metastatic sites			
1	21/33	16/21	0.41 (0.19-0.88)
2	159/202	163/206	0.75 (0.60-0.95)
3	104/136	121/140	0.79 (0.61-1.04)
>3	49/60	59/63	0.50 (0.33-0.76)
Level of CA19-9			
Normal	47/60	43/56	1.07 (0.69-1.66)
<59x ULN	96/122	95/120	0.83 (0.61-1.12)
≥59x ULN	151/197	171/195	0.61 (0.48-0.77)
Region			
Australia	50/61	53/59	0.67 (0.44-1.01)
Eastern Europe	62/64	59/62	0.84 (0.58-1.23)
Western Europe	14/38	17/38	0.72 (0.35-1.47)
North America	207/268	230/271	0.68 (0.56-0.82)



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 Gemcitabine	 20% 16%	 41% 47%

mGEM + NabP, modified regimen of gemcitabine and nanoparticle albumin-bound paclitaxel; OS, overall survival; PFS, progression-free survival

Ahn D, et al. Therapeutic Advances in Medical Oncology 2017; 9(2):75-8

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

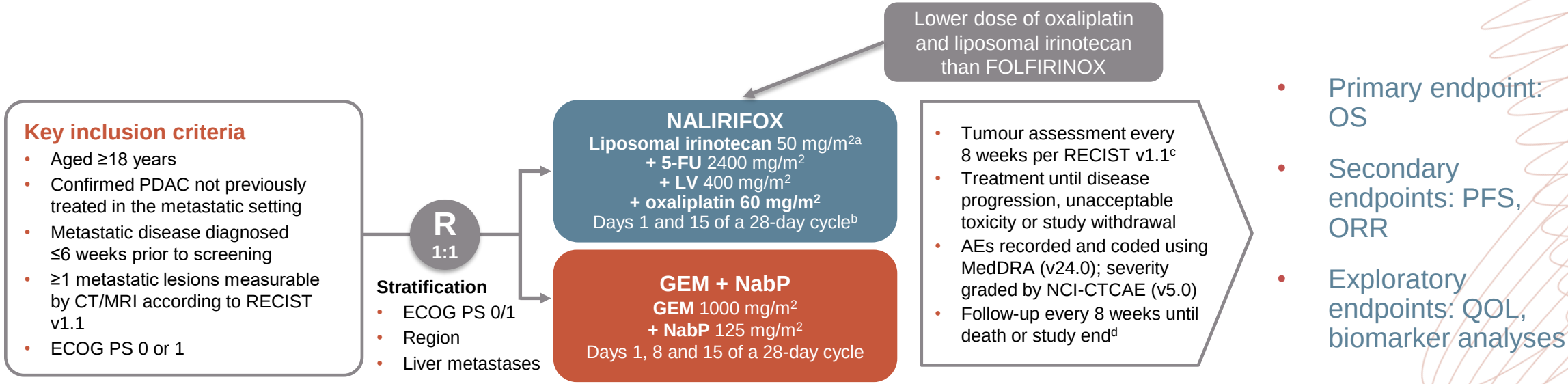
Median dosing was 600 mg/m^2 at fixed dose rate for GEM and 125 mg/m^2 for NabP given predominantly (~90%) every two weeks

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

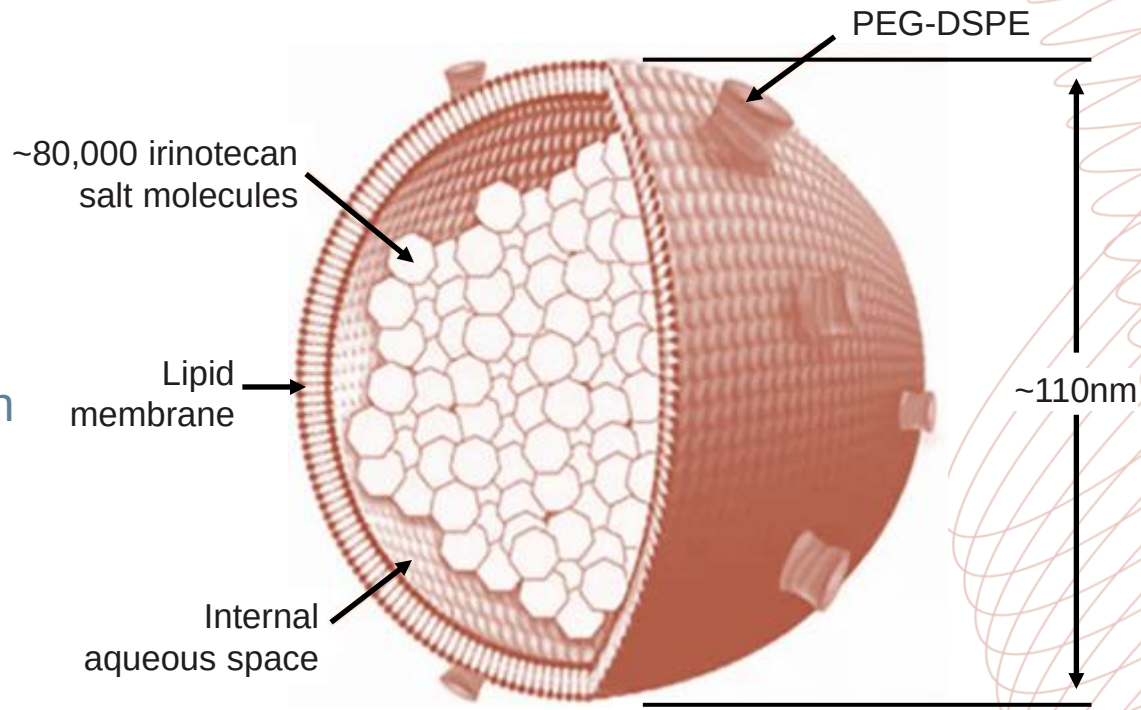
5-FU, fluorouracil; AE, adverse event; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; GEM, gemcitabine; LV, leucovorin calcium (folinic acid); MedDRA, Medical Dictionary 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

O'Reilly E, et al. J. Clin Oncol. 2023;41;16_suppl:4006 (ASCO 2023 oral presentation); Jung K, et al. Ther Adv Med Oncol 2023; 15: 1-15

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

- **Nanoliposomal irinotecan:** irinotecan encapsulated in liposome nanoparticles[1]
- Liposome shelters irinotecan from conversion to its active metabolite (SN-38) thereby remaining in the circulation for longer than free (unencapsulated) irinotecan[1-3]
- Leads to increases and prolonged intratumoural levels of both irinotecan and SN-38 compared with free irinotecan[1]
- Median OS of 5·2 months for Nal-IRI in a phase 2 study of gemcitabine-refractory metastatic pancreatic cancer[1,4]

Liposomal irinotecan[5]



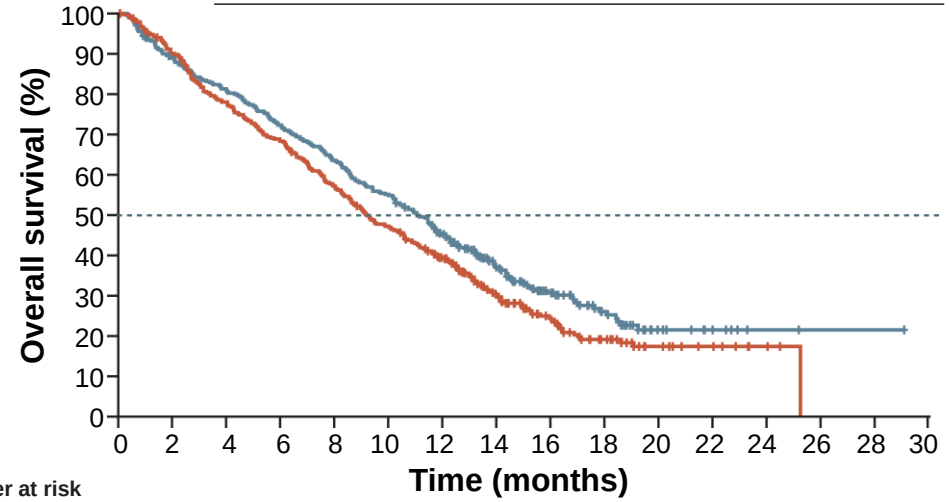
Nal-IRI, nanoliposomal irinotecan; OS, overall survival; PEG-DSPE, polyethylene glycol-distearoylphosphatidylethanolamine

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

	NALIRIFOX	GEM + NabP
Median (95% CI), mo	11.1 (10.0-12.1)	9.2 (8.3-10.6)
Hazard ratio (95% CI)	0.83 (0.70-0.99)	
P value	0.036	

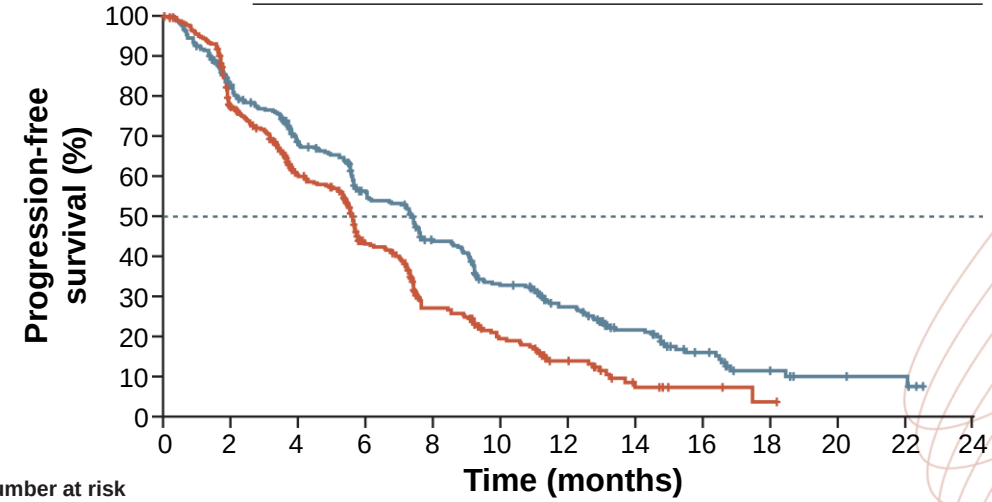


Number at risk (number censored)

NALIRIFOX	383	337	308	274	241	209	162	98	59	32	13	7	2	1	1	0
	(0)	(4)	(4)	(4)	(4)	(4)	(15)	(53)	(77)	(97)	(111)	(117)	(122)	(123)	(123)	(124)
GEM + NabP	387	345	298	261	218	179	140	80	50	28	15	10	3	0	0	0
	(0)	(4)	(5)	(5)	(6)	(7)	(17)	(48)	(65)	(77)	(88)	(93)	(100)	(102)	(102)	(102)

PROGRESSION-FREE SURVIVAL

	NALIRIFOX	GEM + NabP
Median (95% CI), mo	7.4 (6.0-7.7)	5.6 (5.3-5.8)
Hazard ratio (95% CI)	0.69 (0.58-0.83)	
P value	P<0.0001	



Number at risk (number censored)

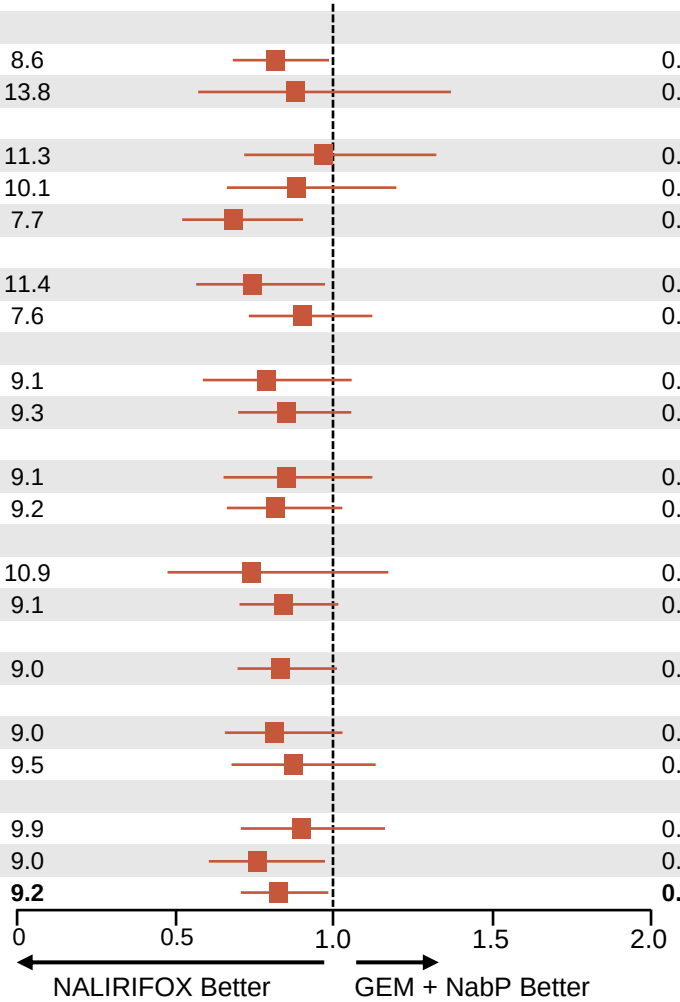
NALIRIFOX	383	271	210	164	122	87	61	39	20	9	5	4	0
	(0)	(52)	(68)	(77)	(84)	(88)	(101)	(111)	(121)	(127)	(130)	(131)	(134)
GEM + NabP	387	267	182	112	60	38	19	6	3	1	0	0	0
	(0)	(40)	(68)	(89)	(102)	(108)	(117)	(123)	(126)	(127)	(128)	(128)	(128)

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)

Age	Events/patients NALIRIFOX	Events/patients GEM + NabP	NALIRIFOX, median (months)	GEM + NabP, median (months)	Hazard ratio (95% CI)
Presence of liver metastases at baseline					
Yes	220/309	242/309	10.3	8.6	0.82 (0.68-0.98)
No	39/74	43/78	15.0	13.8	0.89 (0.57-1.37)
Number of metastatic sites					
1	75/114	92/138	11.5	11.3	0.98 (0.72-1.32)
2	87/120	83/108	11.5	10.1	0.89 (0.65-1.20)
≥3	97/149	110/141	10.9	7.7	0.69 (0.52-0.90)
Baseline ECOG performance status					
0	97/168	112/171	13.9	11.4	0.75 (0.57-0.98)
1	162/215	173/216	8.5	7.6	0.91 (0.73-1.13)
Region					
North America	85/120	94/122	11.2	9.1	0.79 (0.59-1.06)
Rest of the world	174/263	191/265	11.1	9.3	0.86 (0.70-1.05)
Main pancreatic tumour location					
Head	97/147	116/156	10.2	9.1	0.86 (0.65-1.12)
Other	162/236	169/231	11.7	9.2	0.83 (0.67-1.02)
Baseline CA 19-9					
<37 U/mL	34/60	45/71	13.2	10.9	0.75 (0.48-1.17)
≥37 U/mL	223/321	240/316	11.1	9.1	0.84 (0.70-1.01)
Race					
White	218/315	240/324	10.7	9.0	0.84 (0.70-1.01)
Sex					
Male	139/204	175/230	10.9	9.0	0.82 (0.66-1.02)
Female	120/179	110/157	11.6	9.5	0.88 (0.68-1.14)
Age, years					
<65	127/193	130/191	11.5	9.9	0.92 (0.72-1.17)
≥65	132/190	155/196	11.0	9.0	0.77 (0.61-0.97)
Overall	**259/383**	**285/387**	**11.1**	**9.2**	**0.83 (0.70-0.99)**



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

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

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 (%)

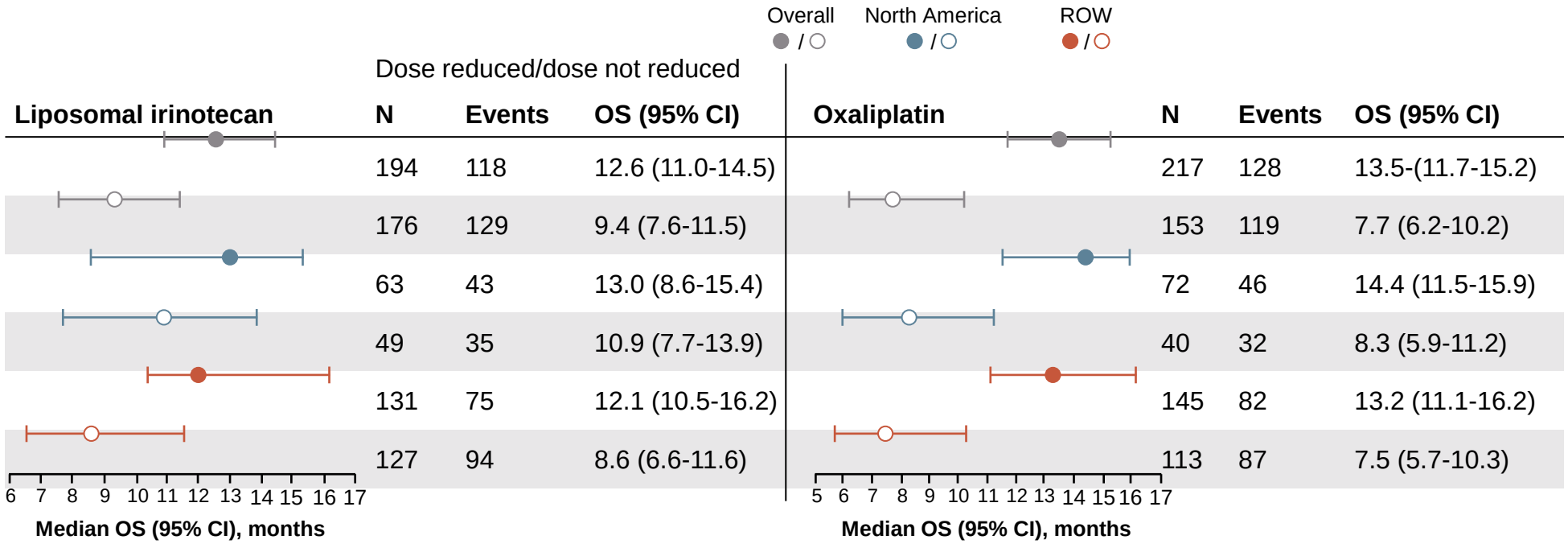
AEs, adverse events; GEM, gemcitabine; NabP, nanoparticle albumin-bound paclitaxel; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; TEAE, treatment-emergent adverse event

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

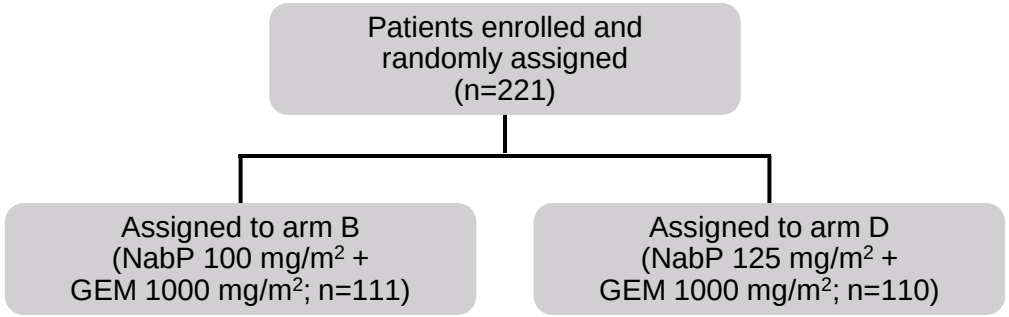
	NALIRIFOX[1] N=370	FOLFIRINOX[2] N=171
Efficacy Results		
Median OS, months	11.1	11.1
OS at 12 months, %	45.6	48.4
OS at 18 months, %	26.2	18.6
Median PFS, months	7.4	6.4
ORR, %	41.8	31.6
Safety Results		
Grade 3-4 diarrhoea, %	20.3	12.7
Grade 3-4 vomiting, %	7.0	14.5
Grade 3-4 neuropathy, %	3.2	9.0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

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

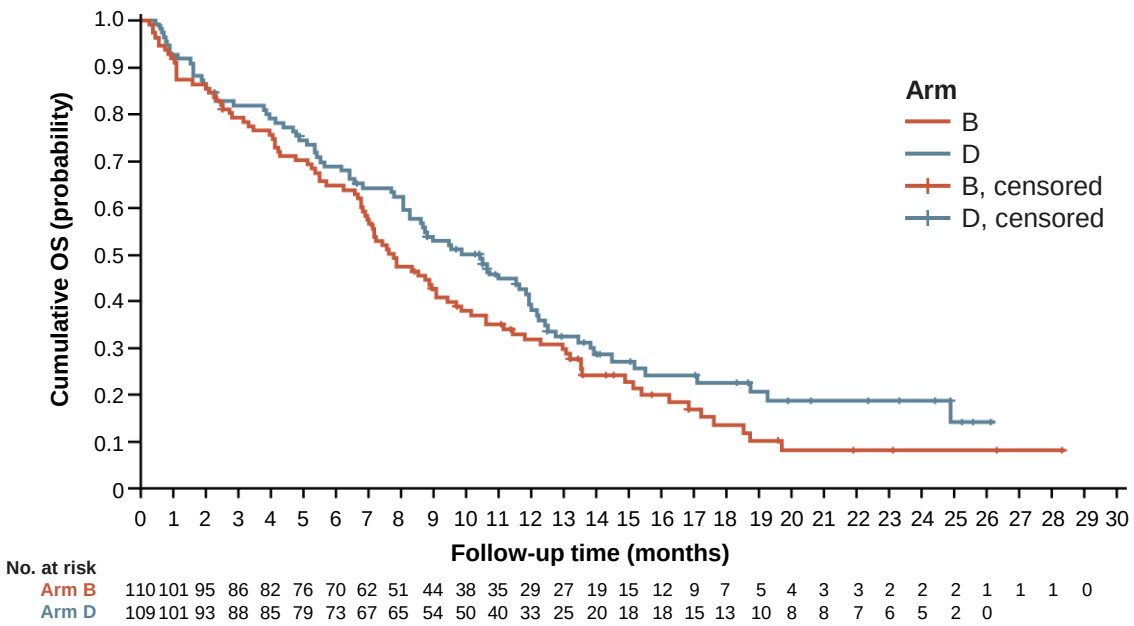
FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

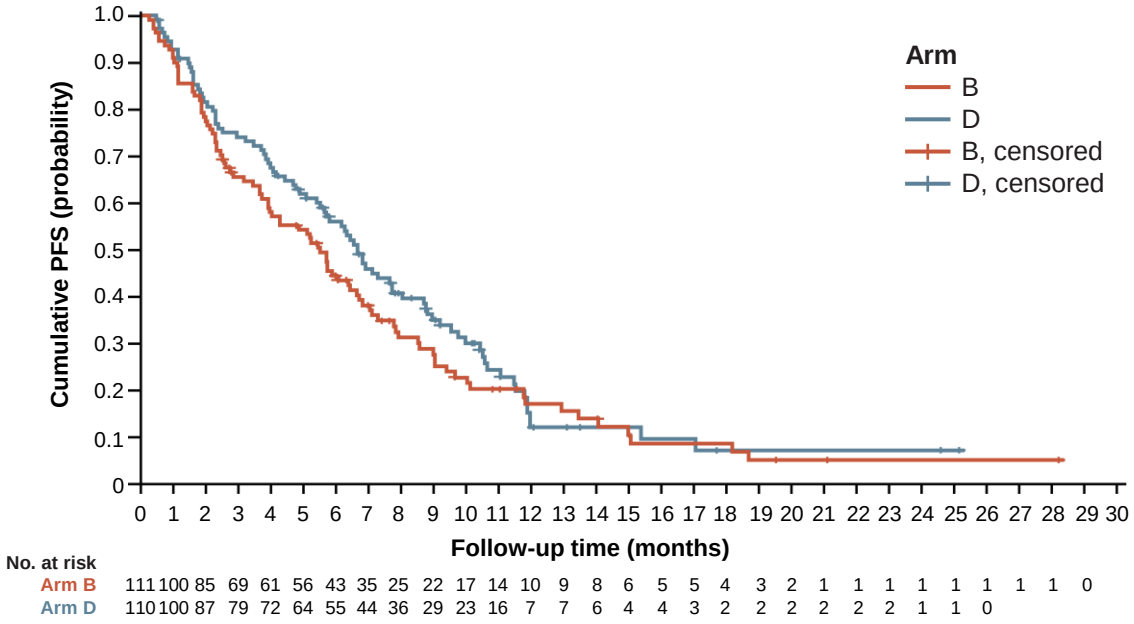
1. Wainberg Z, et al. Lancet 2023; 402:1272-81; 2. Conroy T, et al. N Engl J Med. 2011;364:1817-25

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



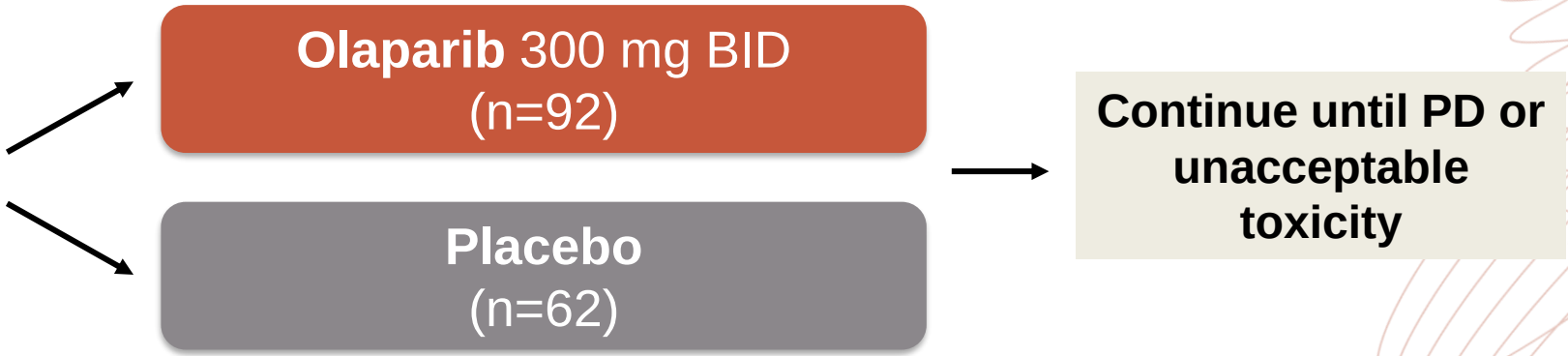


AEs, adverse events; GEM, gemcitabine; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; NabP, nanoparticle albumin-bound paclitaxel
Maccarulla T, et al. J Clin Oncol. 2019;37:230-238

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

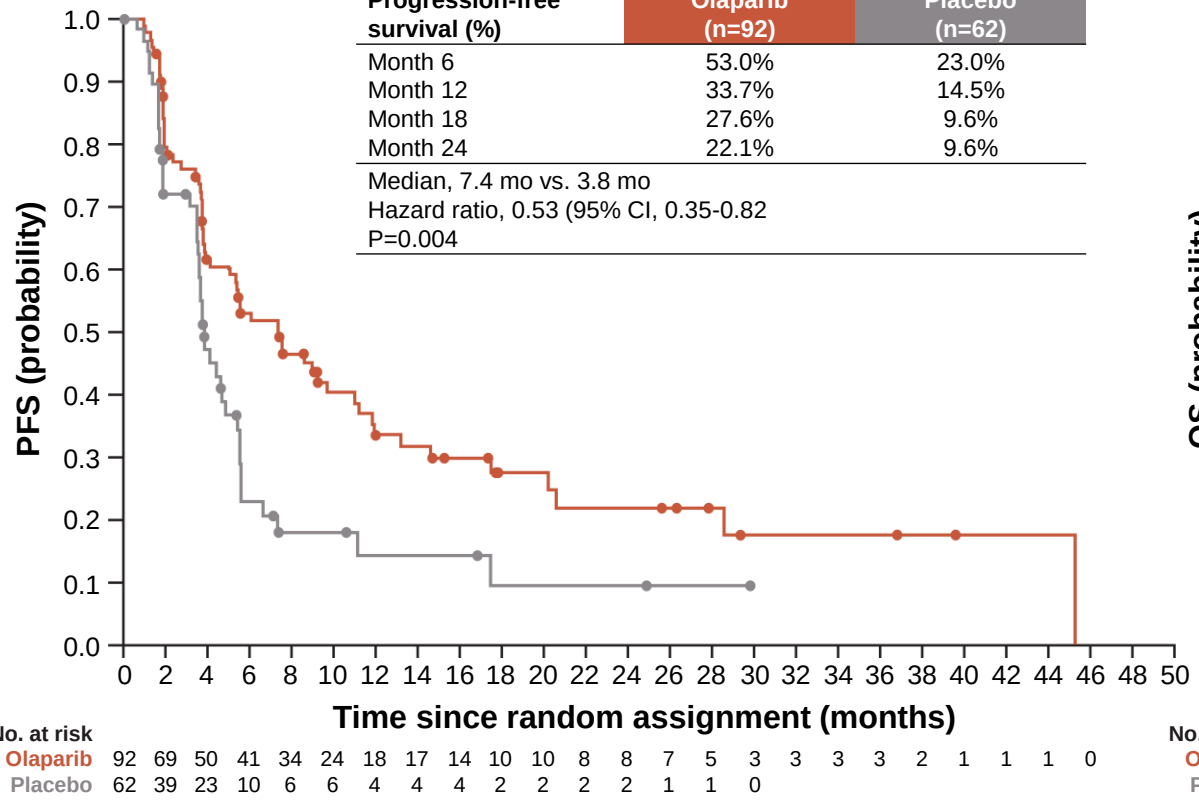
1L, first-line; BID, twice daily; BRCA, BReast CAncer 1/2 gene; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS(2), (second) progression-free survival; wks, weeks

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 SURVIVAL[1]

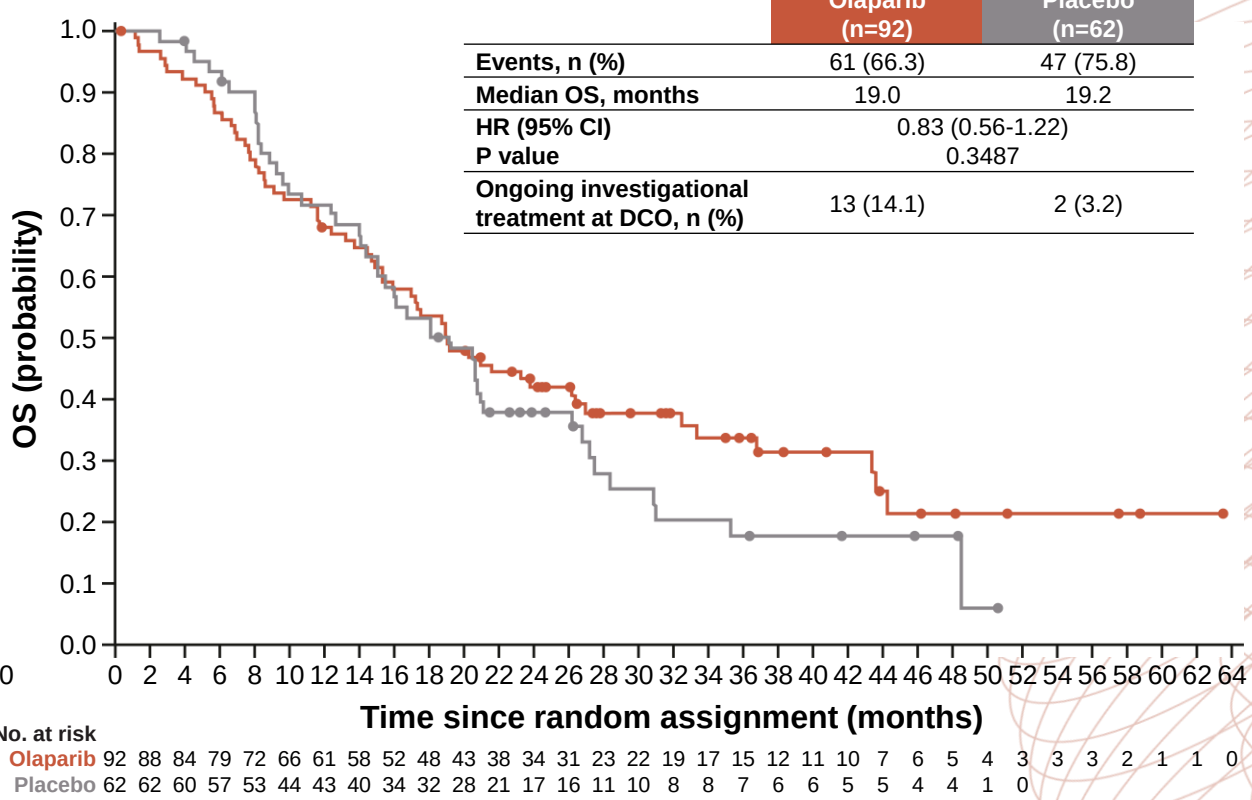
Progression-free survival (%)	Olaparib (n=92)	Placebo (n=62)
Month 6	53.0%	23.0%
Month 12	33.7%	14.5%
Month 18	27.6%	9.6%
Month 24	22.1%	9.6%
Median, 7.4 mo vs. 3.8 mo Hazard ratio, 0.53 (95% CI, 0.35-0.82 P=0.004		



No. at risk																									
Olaparib	92	69	50	41	34	24	18	17	14	10	10	8	8	7	5	3	3	3	3	2	1	1	1	0
Placebo	62	39	23	10	6	6	4	4	4	2	2	2	2	1	1	0								

OVERALL SURVIVAL[2]

	Olaparib (n=92)	Placebo (n=62)
Events, n (%)	61 (66.3)	47 (75.8)
Median OS, months	19.0	19.2
HR (95% CI)	0.83 (0.56-1.22)	
P value	0.3487	
Ongoing investigational treatment at DCO, n (%)	13 (14.1)	2 (3.2)



No. at risk																																	
Olaparib	92	88	84	79	72	66	61	58	52	48	43	38	34	31	23	22	19	17	15	12	11	10	7	6	5	4	3	3	3	2	1	1	0
Placebo	62	62	60	57	53	44	43	40	34	32	28	21	17	16	11	10	8	8	7	6	6	5	5	4	4	1	0						

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
NTRK gene fusions	Larotrectinib	1st line and subsequent treatment options for pts with *NTRK* gene fusion-positive locally advanced or metastatic pancreatic adenocarcinoma and for recurrent disease
	Entrectinib	
	Repotrectinib	Category 2B recommendation as 1st 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)
RET gene fusions	Selpercatinib	1st line: pts with locally advanced/metastatic disease (PS 0–2) and as subsequent therapy for pts with good PS (0–1)
NRG1 gene fusions	Zenocutuzumab-zbco	FDA approved for advanced, unresectable, or metastatic pancreatic adenocarcinoma harboring a NRG1 gene fusion with disease progression on or after prior systemic therapy. Awaiting incorporation into the NCCN guidelines
KRAS G12C mutations	Adagrasib	Subsequent therapy options for patients with any PS (category 2B for poor PS)
	Sotorasib	
BRAF V600E mutations	Dabrefenib/trametinib	1st line: metastatic disease (category 2B) and as subsequent line options (category 2A) for pts with good/poor PS and BRAF 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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