METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (mPDAC): FROM DIAGNOSIS TO TREATMENT

MICRO LEARNING MODULE TWO

CHEMOTHERAPY STRATEGIES FOR mPDAC

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DEVELOPED BY GI CONNECT

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THIS PROGRAMME HAS BEEN DEVELOPED BY EXPERTS

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EDUCATIONAL OBJECTIVES

Educational objectives

1. Understand the **different mechanisms of action (MoA)** of **chemotherapies** for mPDAC
2. Be able to **differentiate** the **efficacy and safety profiles** of **chemotherapies** for mPDAC
3. Recognise how to **optimise** chemotherapies for patients with mPDAC, and understand the optimal **combination** of treatments
4. 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 and has an extremely poor prognosis
- Systemic chemotherapy is the standard treatment for metastatic PDAC (mPDAC) 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

FIRST-LINE TREATMENT OPTIONS

OVERVIEW OF TREATMENT FOR mPDAC

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

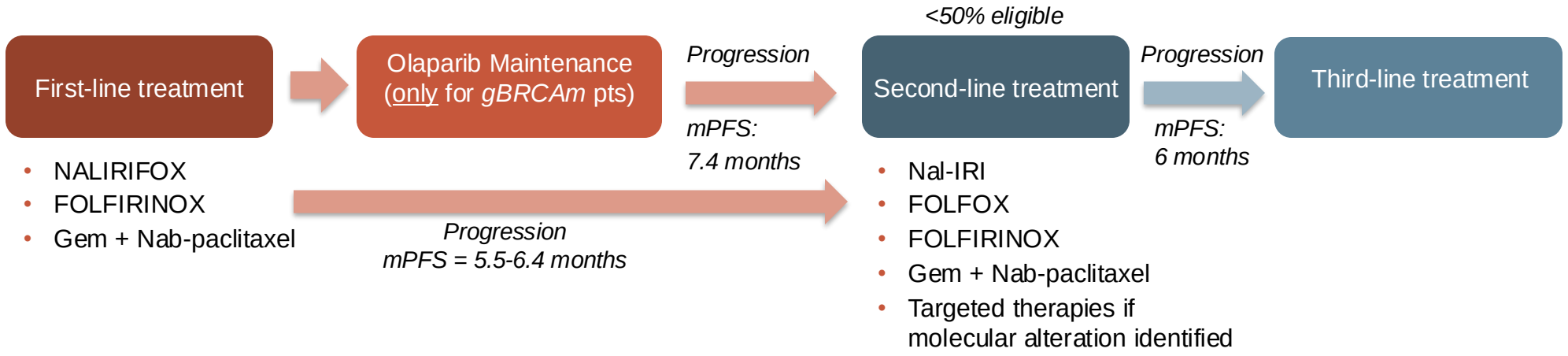


Figure adapted from Casolino 2022

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

CHEMOTHERAPY AGENTS USED IN THE TREATMENT OF mPDAC

MECHANISM OF ACTION

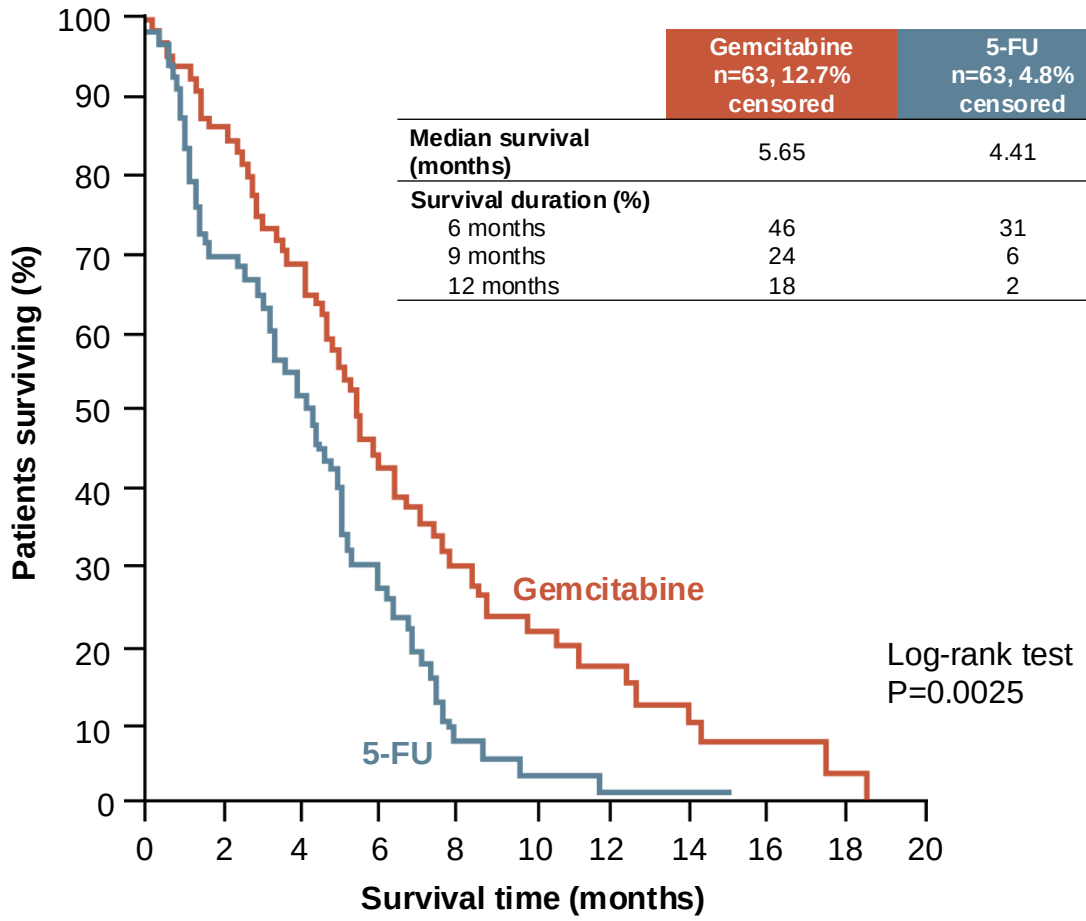
Drug class	Mechanism of action	mPDAC chemotherapy agents
Alkylating agents	Inducing DNA damage by transferring alkyl groups to DNA, generating covalent adducts that induce single or double stranded DNA breaks. Intercalating with DNA	Cisplatin Carboplatin Oxaliplatin
Antimetabolites	Incorporated into DNA instead of regular nucleotides or molecules, which inhibits of DNA synthesis and causes premature chain termination. Gemcitabine, cytarabine and fludarabine also inhibit DNA polymerase and ribonucleotide reductase to halt DNA replication, chain elongation and DNA repair	Fluorouracil (5-FU) Leucovorin Capecitabine Gemcitabine
Antimicrotubule agents	Binding to interior surface of microtubules, impeding movement and function	Cabazitaxel Nab-paclitaxel Paclitaxel
Topoisomerase inhibitors	Binding to topoisomerase by intercalating DNA to create a drug/enzyme complex. When the replication fork reaches this complex the collision causes double stranded DNA breaks	Irinotecan Nanoliposomal irinotecan

mPDAC, metatstatic pancreatic ductal adenocarcinoma; Nab-Paclitaxel, nanoparticle albumin-bound paclitaxel

Pavlidis N, et al. https://oncologypro.esmo.org/content/download/233711/3944768/file/2019-ESMO-ESO-Course-Valencia-Chemotherapy-Nicholas-Pavlidis.pdf. Accessed: November 2024; Tilsed C, et al. Frontiers in Oncology 2022; 12:960317

1L GEMCITABINE WAS STANDARD OF CARE FOR MANY YEARS

- Gemcitabine was approved in 1996 for first-line treatment of advanced pancreatic cancer



	Gemcitabine n=63, 12.7% censored	5-FU n=63, 4.8% censored
Median survival (months)	5.65	4.41
Survival duration (%)		
6 months	46	31
9 months	24	6
12 months	18	2

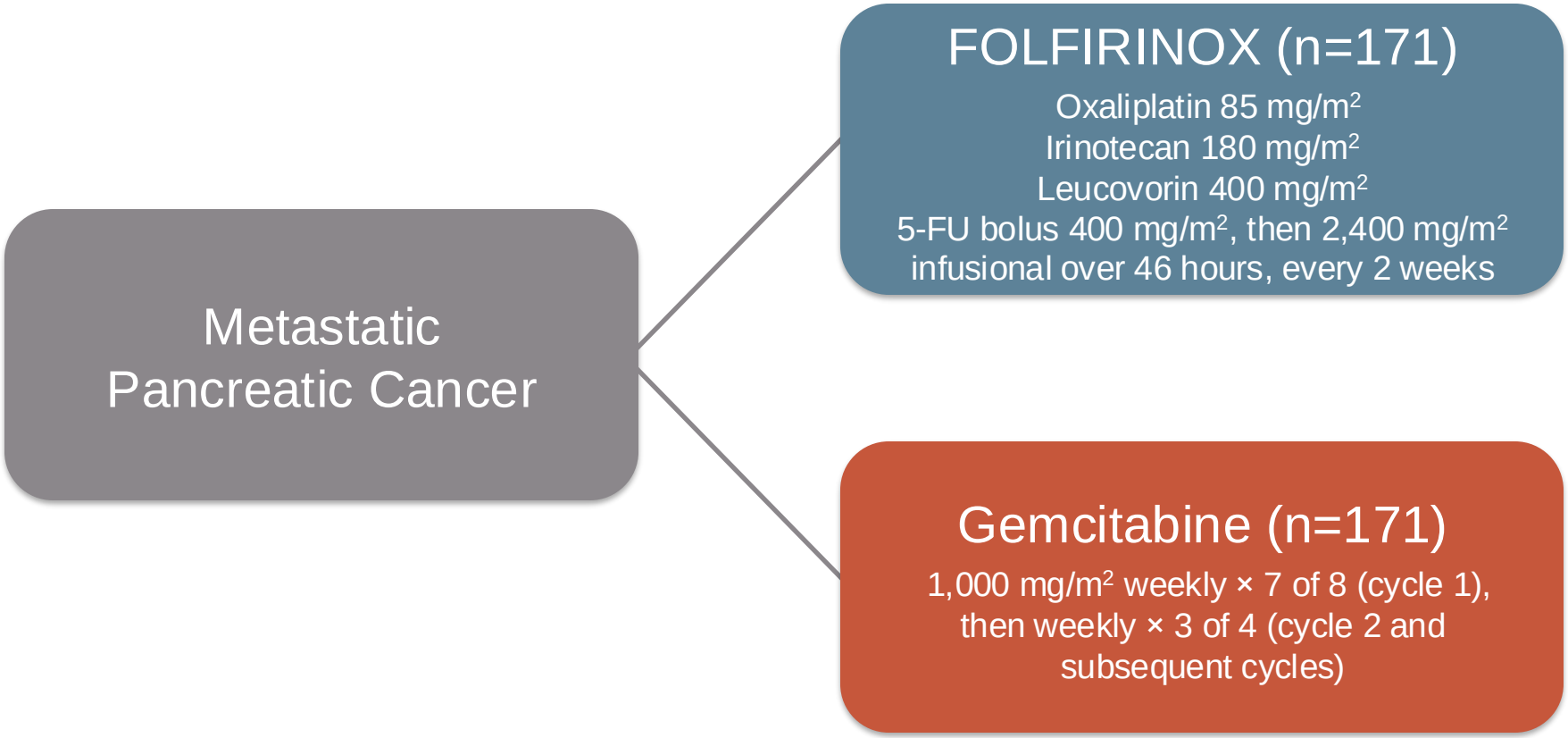
Clinical benefit:
23.8% gemcitabine
vs 4.8% 5-FU

1L, first-line; 5-FU, fluorouracil

Burris HA, et al. J Clin Oncol. 1997 Jun;15(6):2403-13; Barton-Burke M. Cancer Nurs. 1999; 22: 176-83

PRODIGE4/ACCORD11: STUDY DESIGN

FOLFIRINOX VS GEMCITABINE AS 1L THERAPY

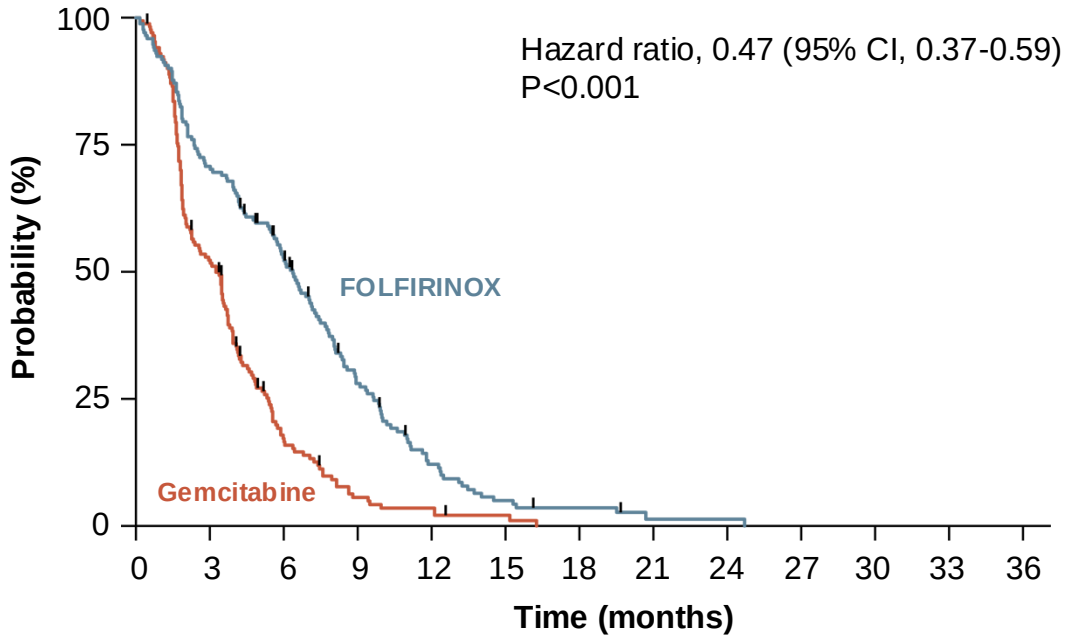


1L, first-line; 5-FU, fluorouracil; FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin

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

PRODIGE4/ACCORD11: FOLFIRINOX EMERGED AS A 1L OPTION

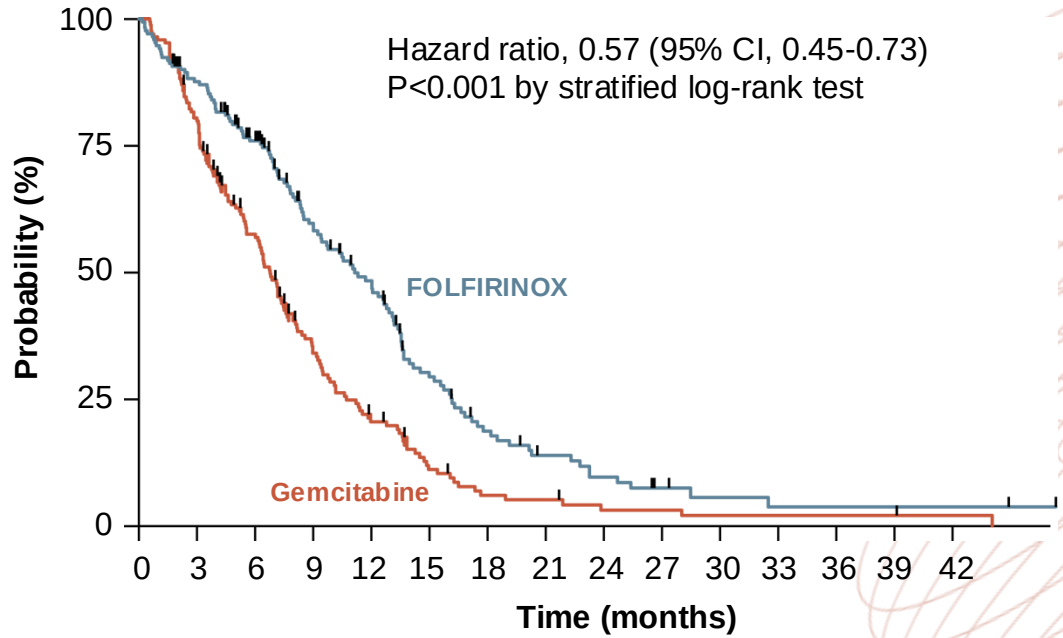
PROGRESSION-FREE SURVIVAL



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

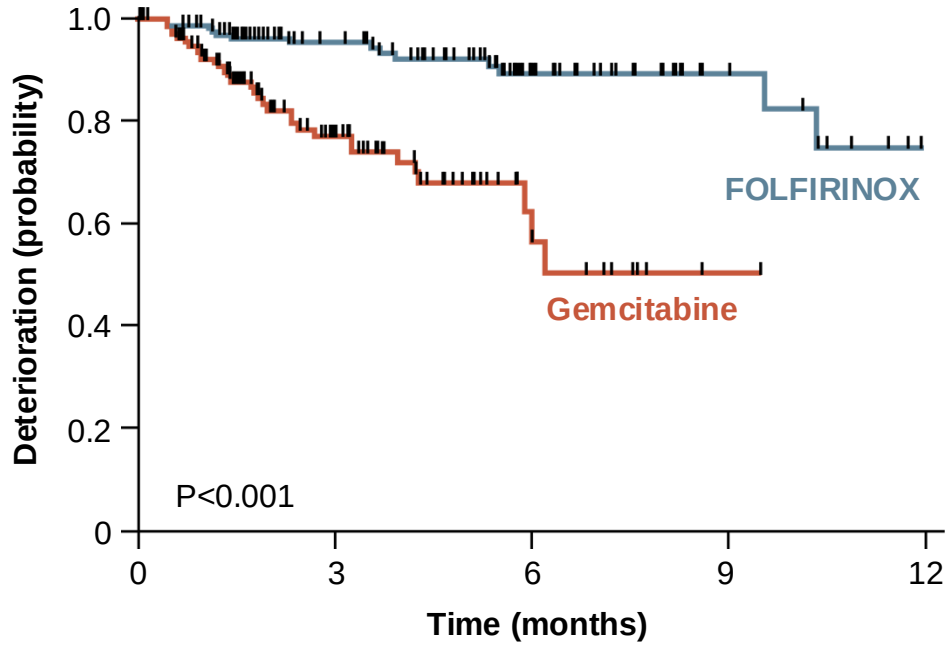
[a]Events listed are those that occurred in more than 5% of patients in either group. NS denotes not significant

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

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

PRODIGE4/ACCORD11 TRIAL: QOL PROLONGED WITH FOLFIRINOX

- Time until definitive deterioration >20 points, EORTC-C30 global health status/QoL questionnaire



No. at risk					
Gemcitabine	157	55	11	1	0
FOLFIRINOX	163	97	40	14	4

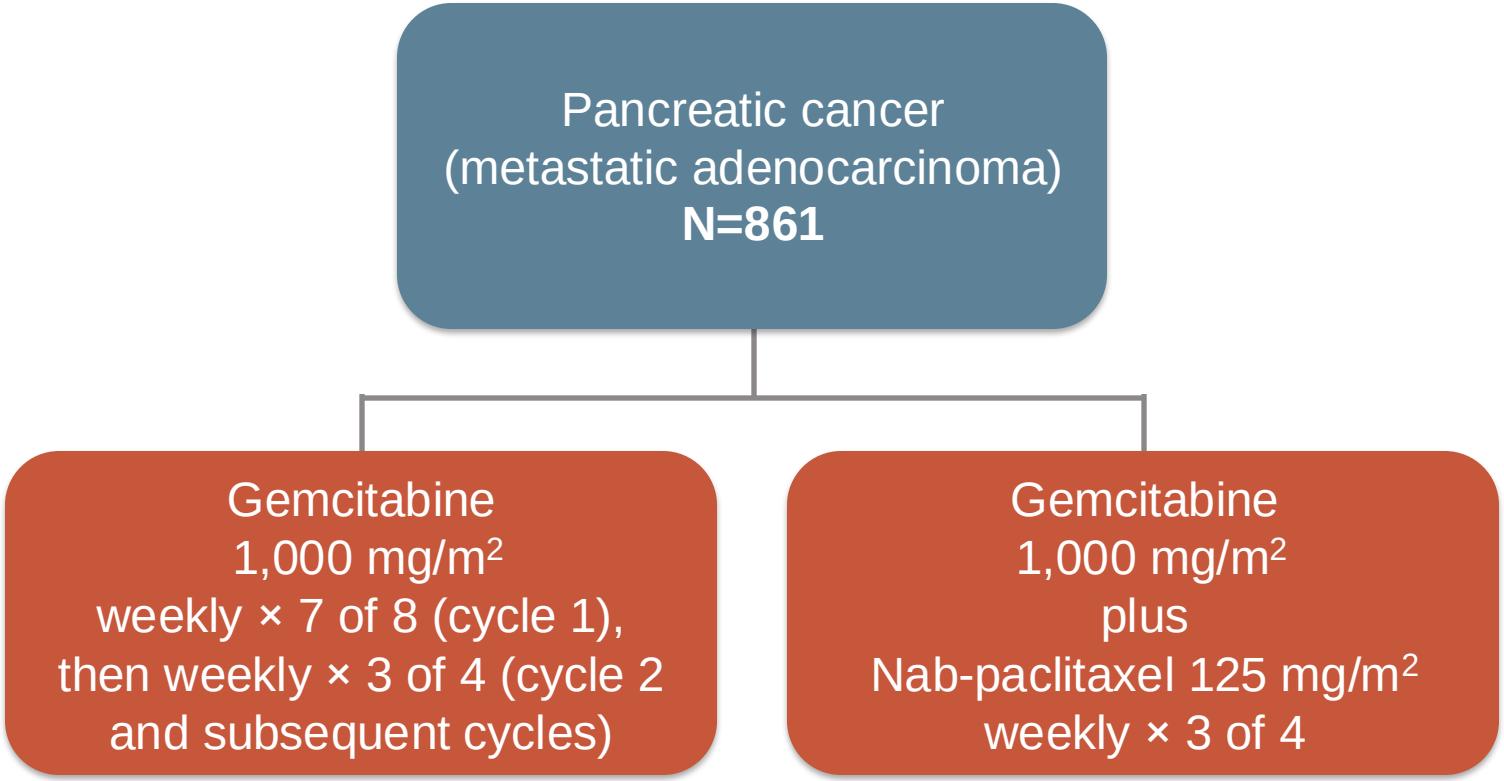
- Prolongation of QoL in patients treated with FOLFIRINOX compared to gemcitabine, despite greater toxicity – longer time to deterioration in:
  - Global health score
  - Physical, cognitive, and social functioning
  - Symptoms such as fatigue, nausea and vomiting, pain, and anorexia

EORTC, European Organisation for the Research and Treatment of Cancer Core 30; FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; QoL, quality of life

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

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

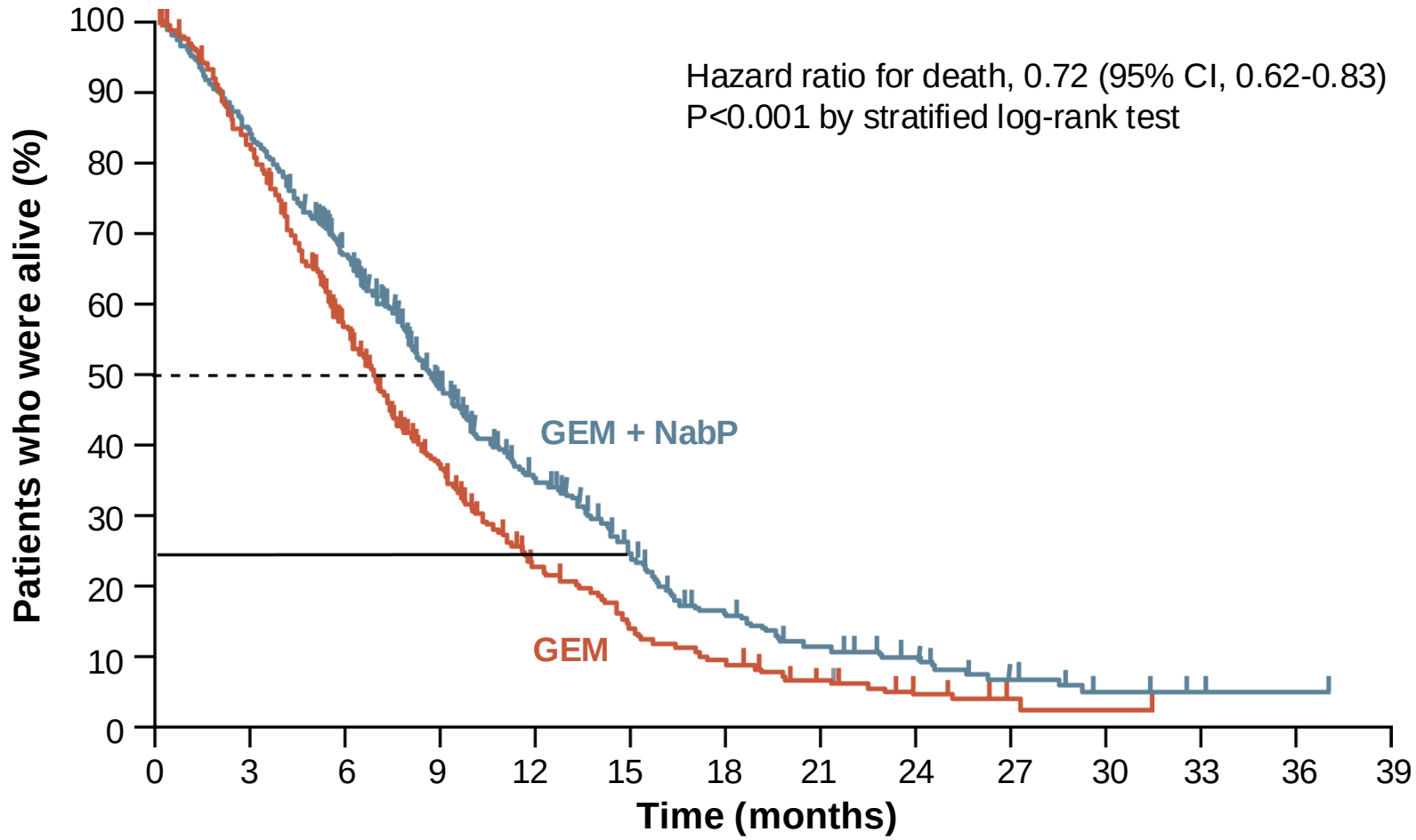
	GEM + NabP (n=431)	GEM (n=430)	Hazard ratio
Overall survival, months	8.5	6.7	0.72 (p<0.001)
One-year survival, %	35	22	
Progression-free survival, months	5.5	3.7	0.69 (p<0.001)
6-month PFS, %	44	25	
Response rate, %	23	7	p<0.001
Median treatment duration (range), months	3.9 (0.1-21.9)	2.8 (0.1-21.5)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



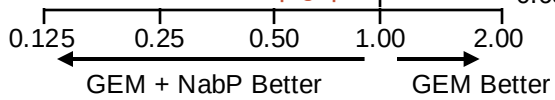
CI, confidence interval; GEM, gemcitabine; HR, hazard ratio; NabP, nanoparticle albumin-bound paclitaxel

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 *No. of events/no. of patients*	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

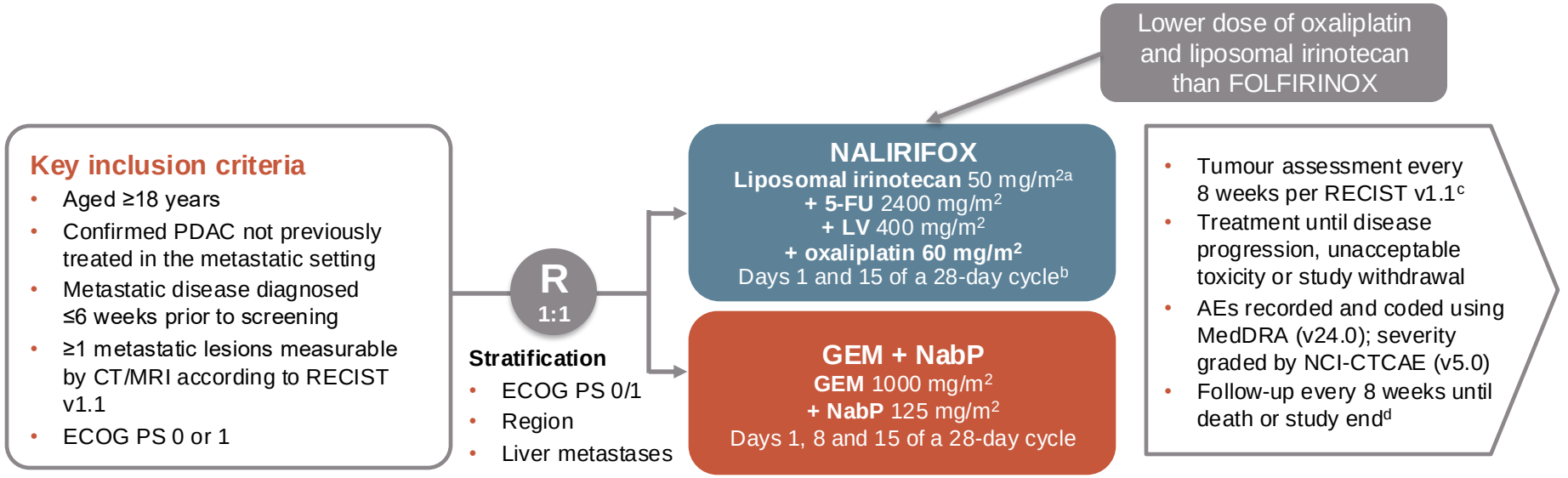
Median dosing was 600 mg/m^2 at fixed dose rate for GEM and 125 mg/m^2 for NabP given predominantly (~90%) every two weeks

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

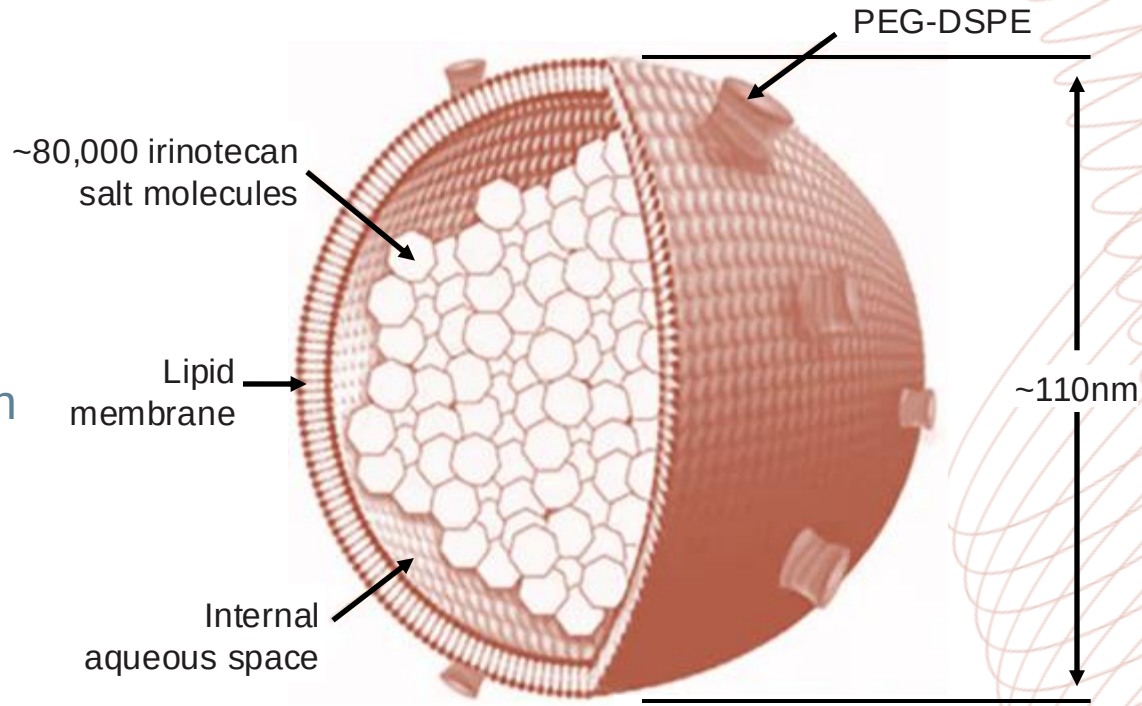
5-FU, fluorouracil; AE, adverse event; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; GEM, gemcitabine; LV, leucovorin calcium (folinic acid); MedDRA, Medical Dictionary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

	NALIRIFOX (n=383)	GEM + NabP (n=387)
Age, years		
Mean (SD)	62.8 (9.7)	64.0 (8.3)
Median (range; IQR)	64.0 (20-85; 57-70)	65.0 (36.82; 59-70)
Sex, n (%)		
Female	179 (47%)	157 (41%)
Male	204 (53%)	230 (59%)
Race, n (%)		
White	315 (82%)	324 (84%)
Asian	20 (5%)	18 (5%)
Black or African American	12 (3%)	7 (2%)
Other	7 (2%)	6 (2%)
Multiple	3 (1%)	0
American Indian or Alaska Native	0	2 (1%)
Native Hawaiian or other Pacific Islander	0	1 (<1%)
Not reported	26 (7%)	29 (7%)
ECOG performance status score, n (%)		
0	160 (42%)	168 (43%)
1	222 (58%)	219 (57%)
2	1 (<1%)[a]	0
Metastatic sites, n (%)		
1	114 (30%)	138 (36%)
2	120 (31%)	108 (28%)
≥3	149 (39%)	141 (36%)
Liver metastases, n (%)	307 (80%)	311 (80%)

	NALIRIFOX (n=383)	GEM + NabP (n=387)
Geographical region, n (%)		
North America	120 (31%)	122 (32%)
East Asia	11 (3%)	11 (3%)
Rest of world	252 (66%)	254 (66%)
Main pancreatic tumour location, n (%)		
Head	147 (38%)	156 940%)
Other[b]	236 (62%)	231 (60%)
Baseline CA 19-9[c]		
<37 U/mL, n (%)	60 (16%)	71 (18%)
≥37 U/mL, n (%)	321 (84%)	316 (82%)
Median (range; IQR), U/mL	1856.0 (0.6-8000.0; 178.0-8000.0)	1544.0 (0.6-8000.0; 93.7-8000.0)
Any previous anti-cancer therapy, n (%)	22 (6%)	27 (7%)
Chemotherapy	14 (4%)	16 (4%)
Radiotherapy	10 (3%)	6 (2%)
Surgical procedure	18 (5%)	25 (7%)
Time from diagnosis of metastatic disease at study entry to randomisation, weeks		
Mean (SD)	3.6 (2%)	3.9 (2%)
Median (range; IQR)	3.0 (0.6-9.1; 2.1-4.7)	3.6 (0.4-10.9; 2.4-5.1)

Data are based on the intention-to-treat population.

[a] One patient was considered to have an ECOG performance status score of 2 after randomisation and continued to receive treatment.
[b] Body, tail, or unknown location.
[c] Baseline values were missing for two patients (1%) in the NALIRIFOX arm. The upper limit of detection was 8000 U/mL.

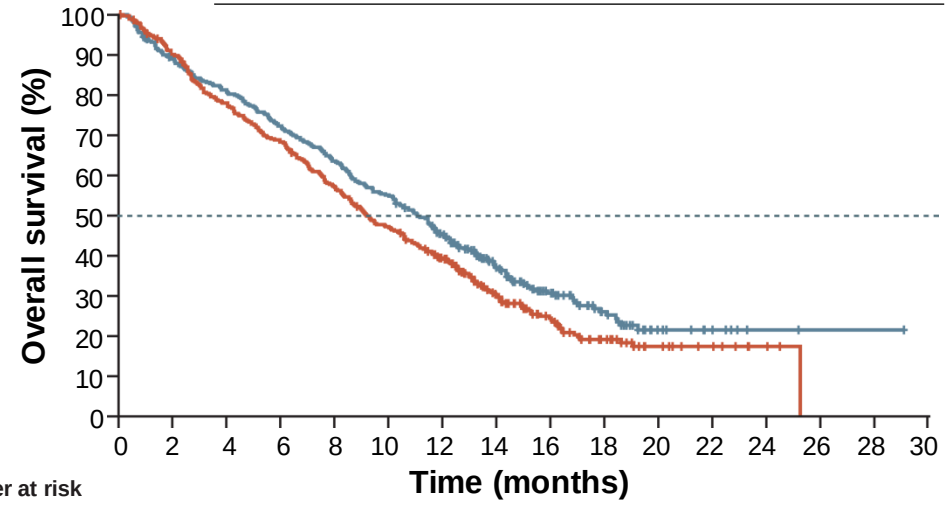
CA 19-9, carbohydrate antigen 19-9; ECOG, Eastern Cooperative Oncology Group; GEM, gemcitabine; IQR, inter-quartile range; NabP, nanoparticle albumin-bound paclitaxel; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; SD, standard deviation

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

NAPOLI-3: NALIRIFOX MORE EFFECTIVE THAN NabP/GEM

OVERALL SURVIVAL

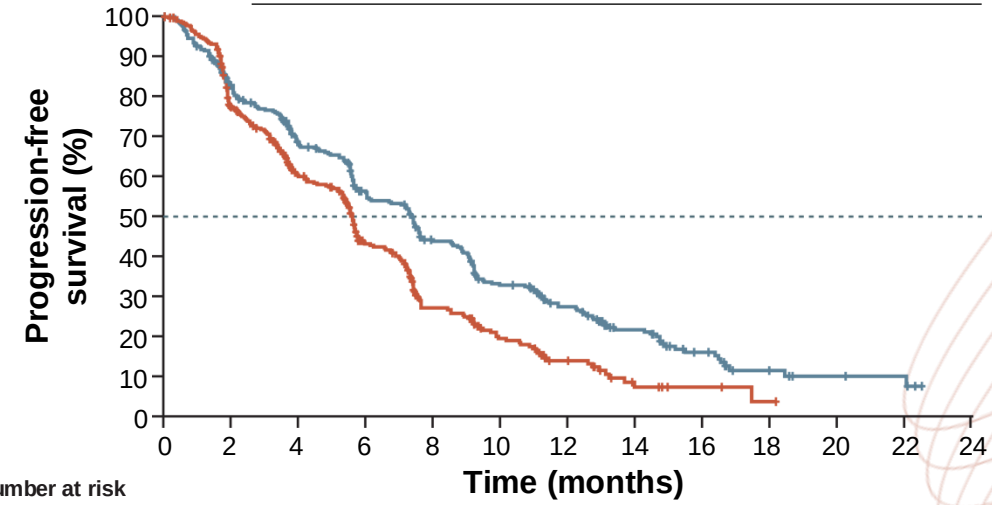
	NALIRIFOX	GEM + NabP
Median (95% CI), mo	11.1 (10.0-12.1)	9.2 (8.3-10.6)
Hazard ratio (95% CI)	0.83 (0.70-0.99)	
P value	0.036	



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



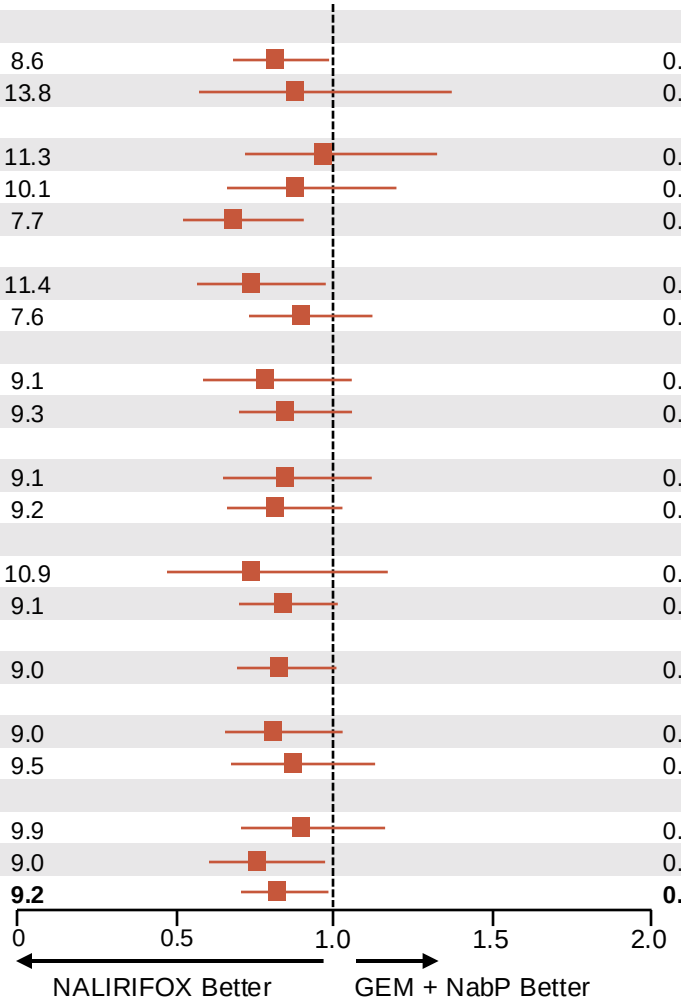
Number at risk (number censored)													
NALIRIFOX	383 (0)	271 (52)	210 (68)	164 (77)	122 (84)	87 (88)	61 (101)	39 (111)	20 (121)	9 (127)	5 (130)	4 (131)	0 (134)
GEM + NabP	387 (0)	267 (40)	182 (68)	112 (89)	60 (102)	38 (108)	19 (117)	6 (123)	3 (126)	1 (127)	0 (128)	0 (128)	0 (128)

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: RESULTS

TUMOUR RESPONSE

	NALIRIFOX (N=383)	GEM + NabP (N=387)
Objective response rate (95% CI), %	41.8 (36.8-46.9)	36.2 (31.4-41.2)
Best overall response, %		
Complete response	0.3	0.3
Partial response	41.5	35.9
Stable disease	25.8	26.1
Progressive disease	9.9	14.5
Not evaluable	22.5	23.3
Disease control rate, %	67.6	62.3
Median duration of response (95% CI), months	7.3 (5.8-7.6)	5.0 (3.8-5.6)

SUBSEQUENT ANTI-CANCER TREATMENT

	NALIRIFOX (N=370)	GEM + NabP (N=379)
Any further subsequent anti-cancer therapy, %	50.5	54.4
Systemic anti-neoplastic therapy	50.5	54.1
Surgery	0.3	0.5
Radiotherapy	0.5	1.1

CI, confidence interval; GEM, gemcitabine; 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 (appendix); O'Reilly E, et al. J. Clin Oncol. 2023;41;16_suppl:4006 (ASCO 2023 oral presentation)

NAPOLI-3: OVERALL SUMMARY OF ADVERSE EVENTS

	NALIRIFOX (N=370)	GEM + NabP (N=379)
Median duration of treatment (range; IQR), weeks	24.3 (0.4-100.9; 8.4-42.1)	17.6 90.7-81.7; 8.1-30.1)
Median number of treatment cycles (range; IQR)	5.0 (1-24; 2-10)	4.0 (1-20; 2-7)
Any dose reductions, n (%)	220 (60%)	204 (54%)
TEAEs, n (%)		
Any TEAE	369 (≥99%)	376 (99%)
Any treatment-related TEAE	352 (95%)	352 (93%)
Grade ≥3 TEAE	322 (87%)	326 (86%)
Grade ≥3 treatment-related TEAE	262 (71%)	258 (68%)
Any TEAE leading to discontinuation	118 (32%)	112 (30%)
Any treatment-related TEAE leading to discontinuation	94 (25%)	88 (23%)
Any TEAE leading to dose reduction	208 (56%)	190 (50%)
Any treatment-related TEAE leading to dose reduction	198 (54%)	184 (49%)
Any serious TEAEs	201 (54%)	195 (52%)
Any treatment-related serious TEAEs	98 (27%)	72 (19%)
TEAEs leading to death	22 (6%)	23 (6%)
Treatment-related TEAEs leading to death	6 (2%)	8 (2%)

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 events

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%)

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

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

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

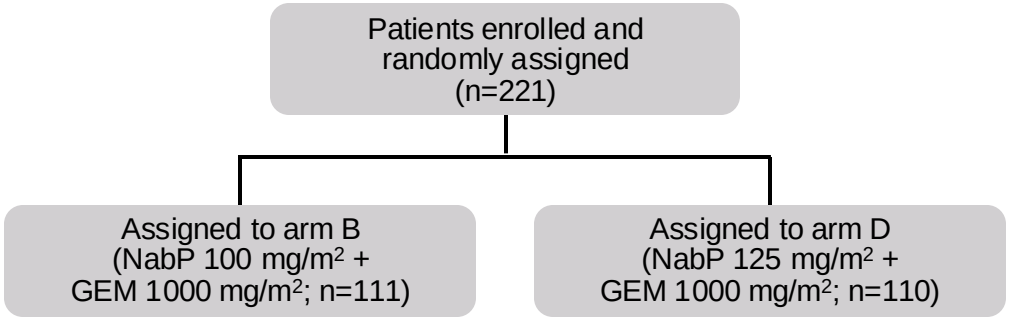
Data presented for information purposes. Cross-trial comparison is not intended

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

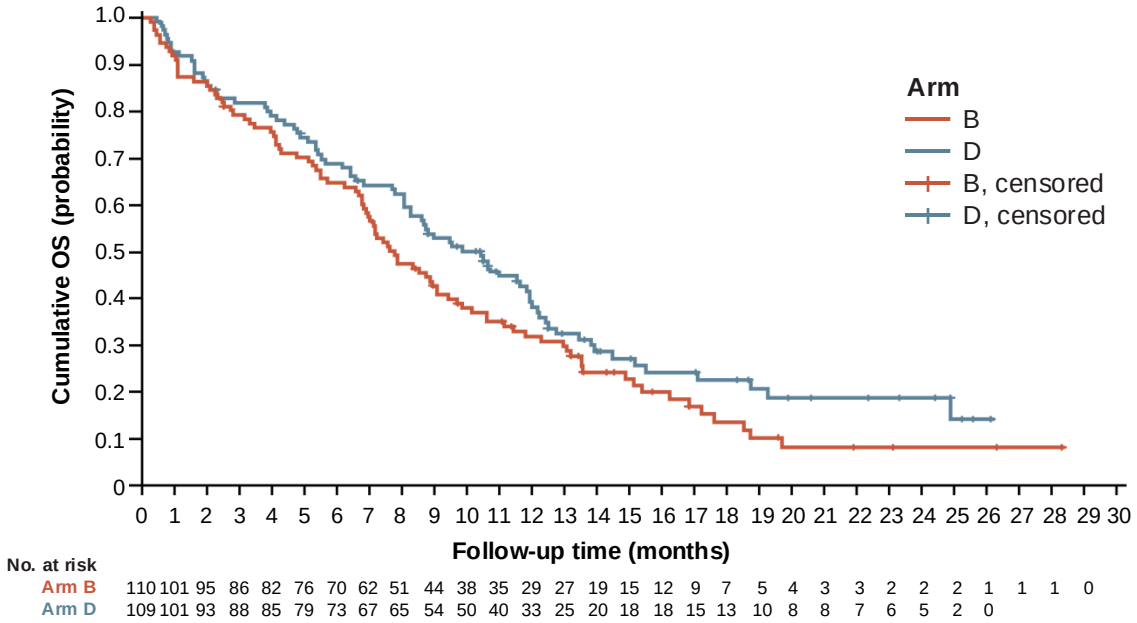
1. Wainberg Z, et al. Lancet 2023; 402:1272-81; 2. Conroy T, et al. N Engl J Med. 2011;364:1817-25

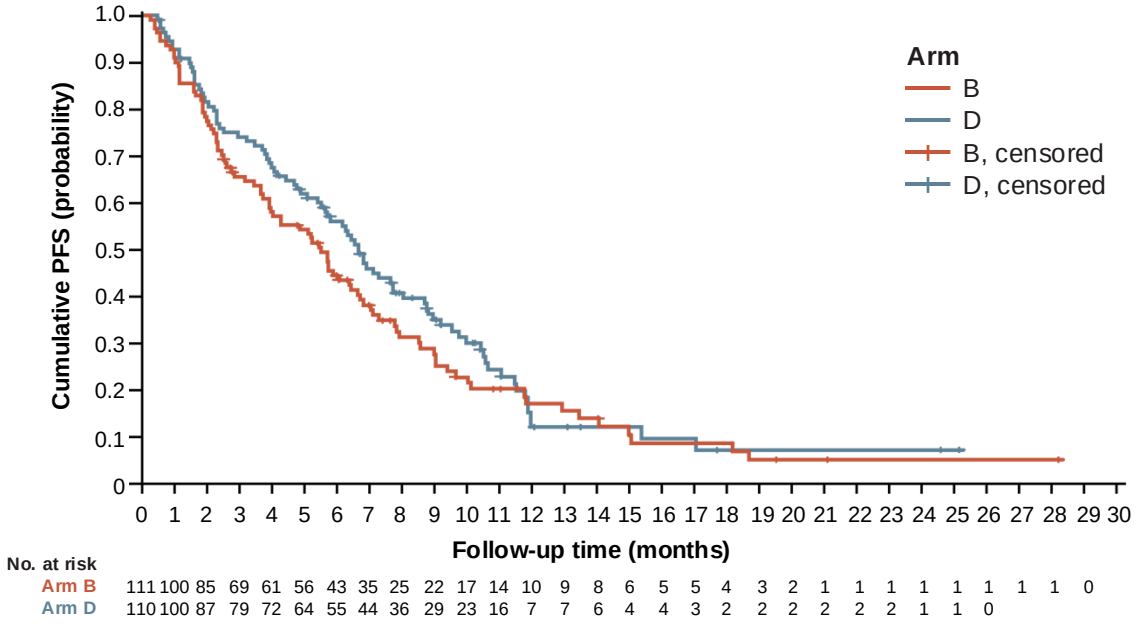
MANAGING VULNERABLE PATIENTS DURING FIRST-LINE TREATMENT

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

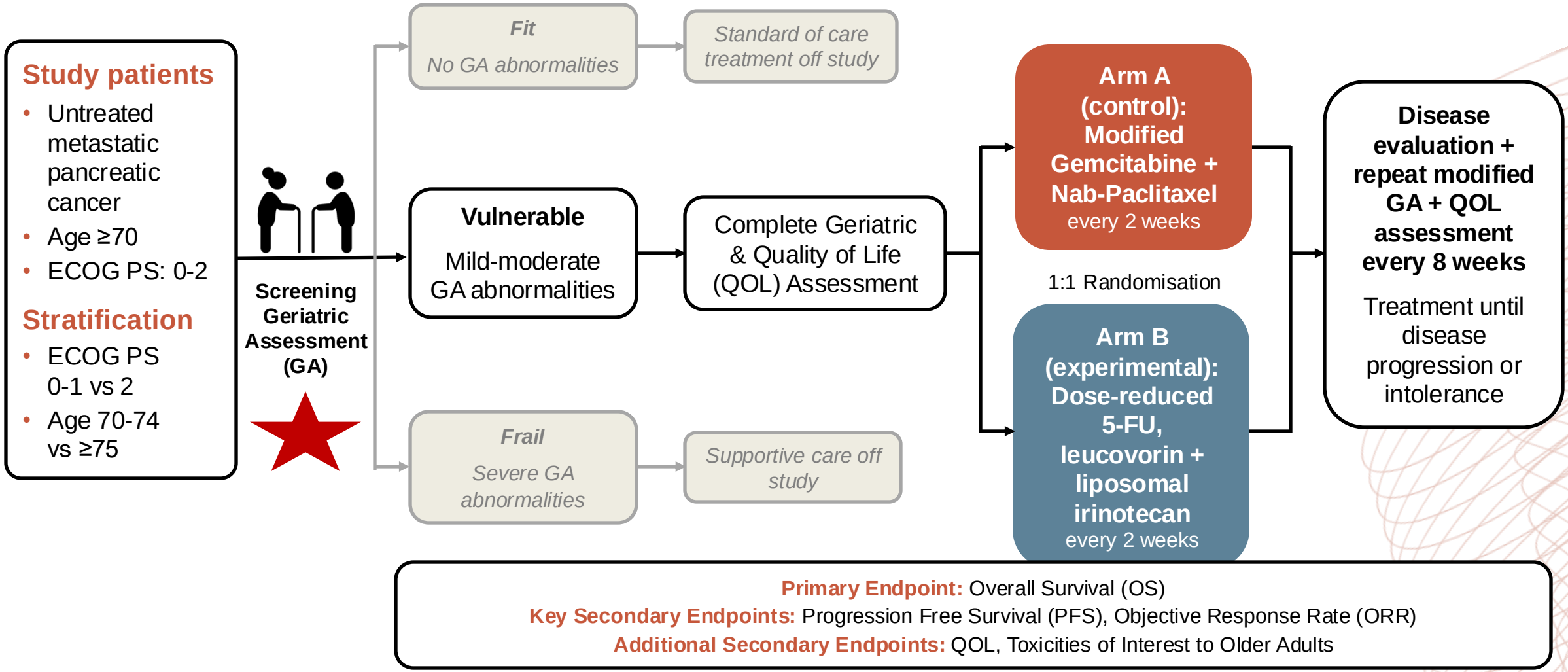




AEs, adverse events; GEM, gemcitabine; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; NabP, nanoparticle albumin-bound paclitaxel
Maccarulla T, et al. J Clin Oncol. 2019;37:230-238

EA2186 (GIANT) – STUDY DESIGN

- Study designed to determine whether elderly patients gain benefit from chemotherapy

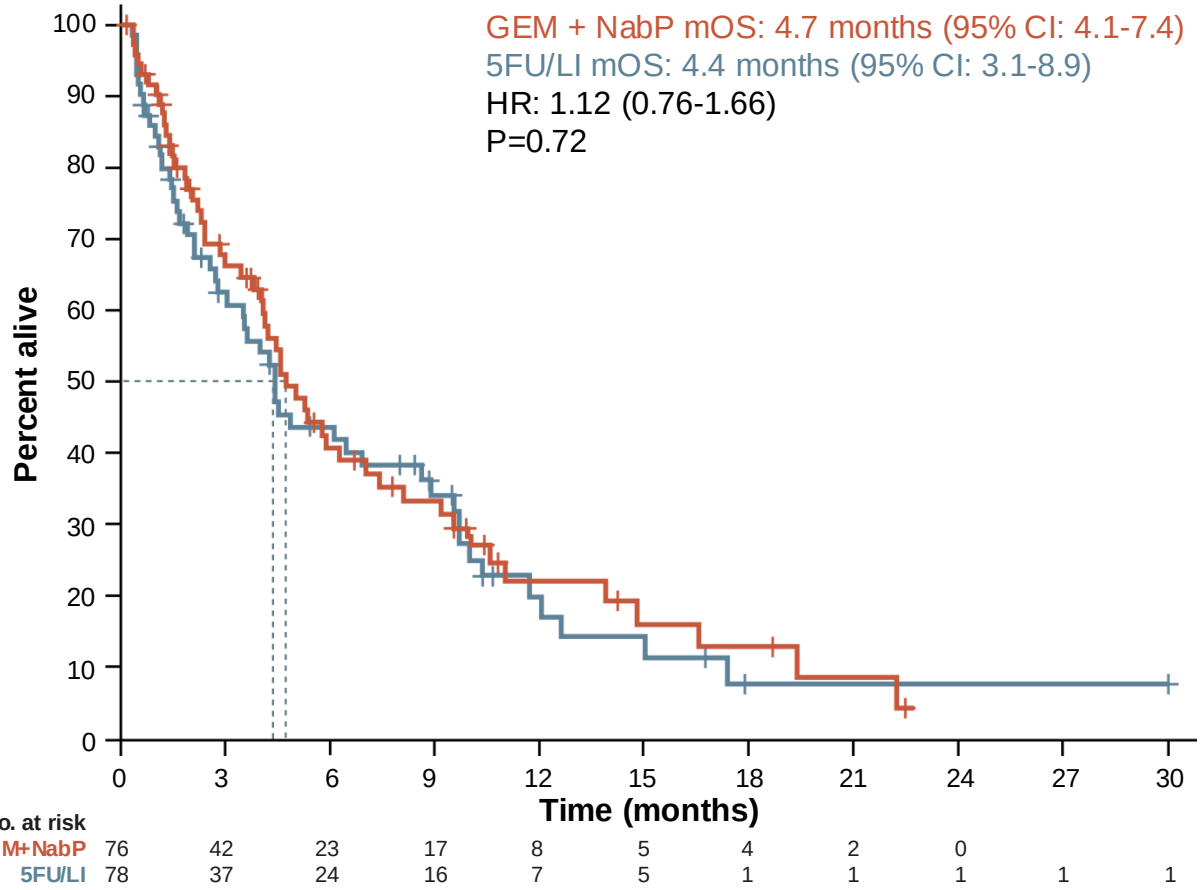


5-FU, fluorouracil; ECOG PS, Eastern Cooperative Oncology Group performance status; Nab, nanoparticle albumin-bound; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

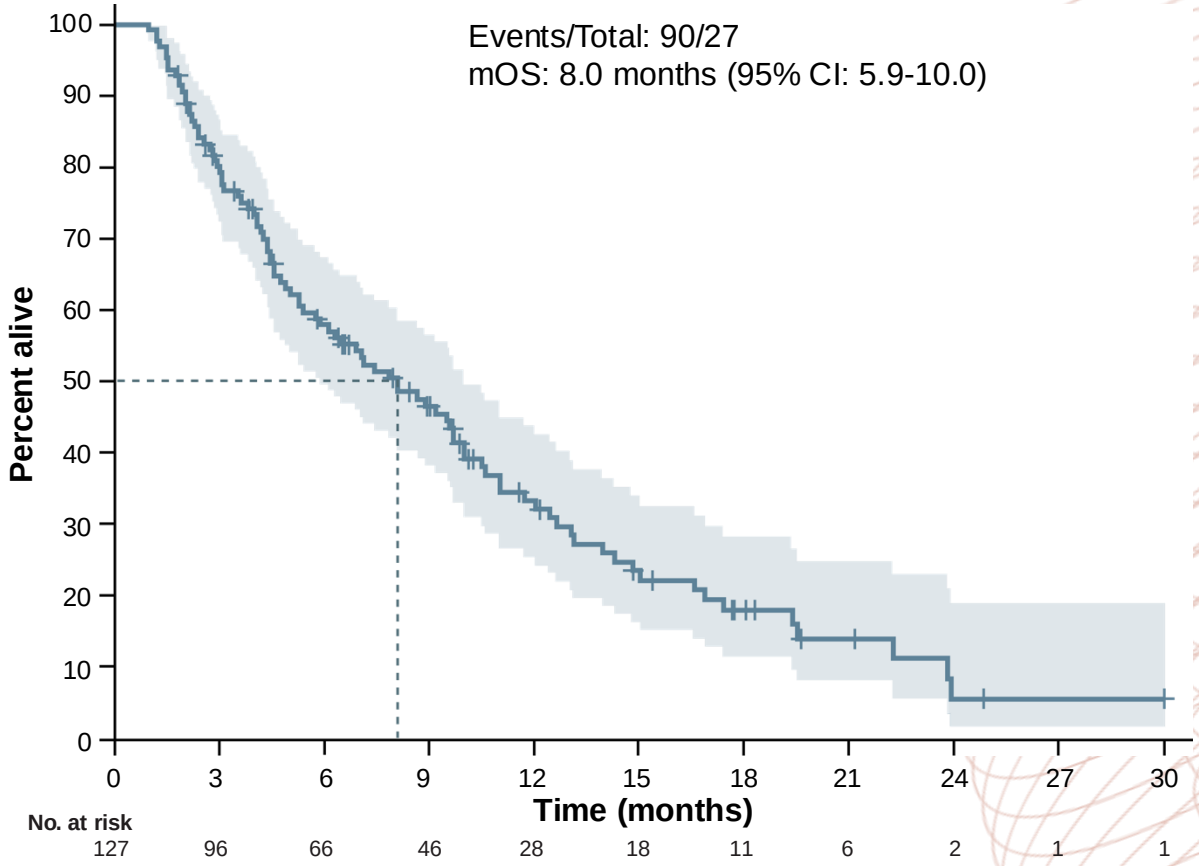
Dotan E, et al. J Clin Oncol. 2024;42(16_suppl):4003 (oral presentation)

ELDERLY PATIENTS BENEFIT FROM DOSE REDUCED CHEMOTHERAPY

PRIMARY ENDPOINT OS – ITT



OS ANALYSIS OF PATIENTS WHO RECEIVED ≥ 4 WEEKS OF TREATMENT

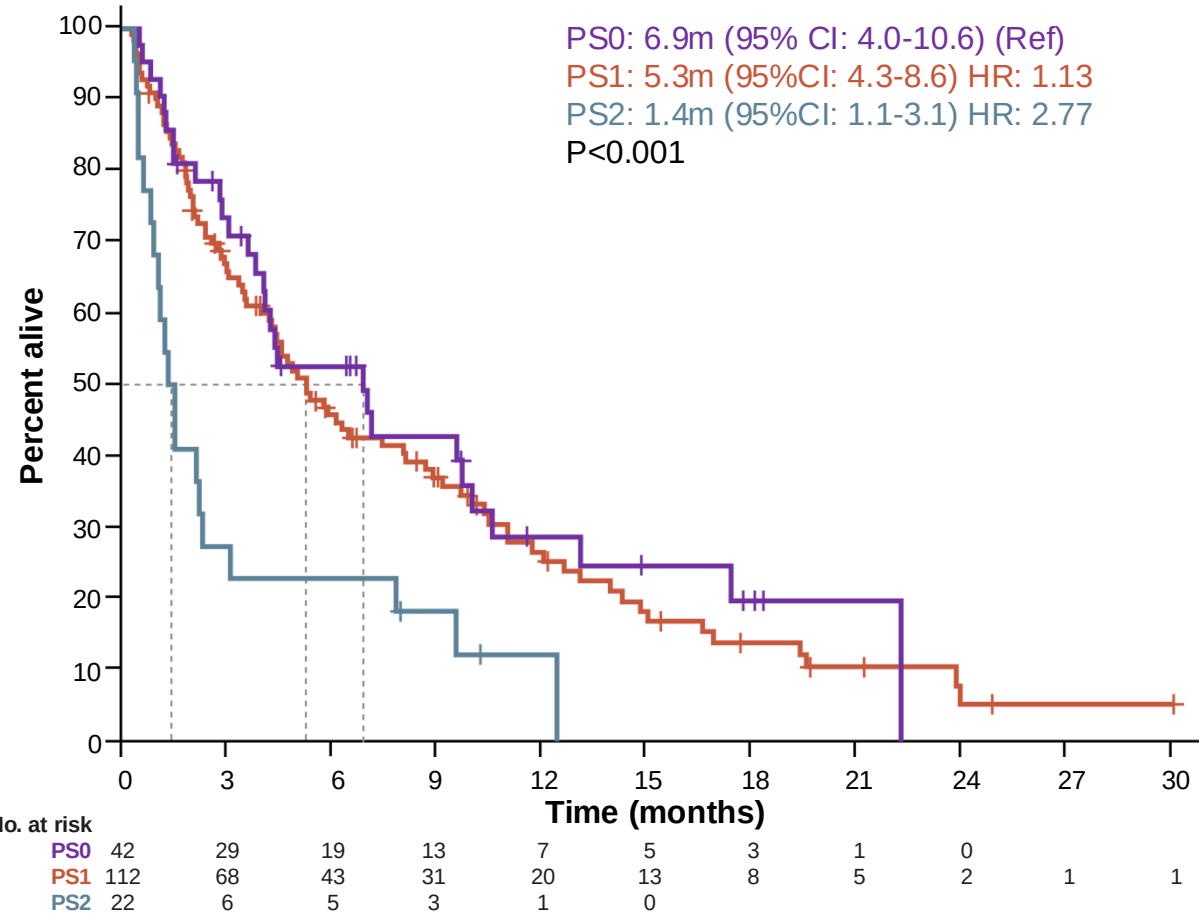


5-FU, fluorouracil; CI, confidence interval; GEM, gemcitabine; HR, hazard ratio; ITT, intention-to-treat; LI, liposomal irinotecan; (m)OS, (median) overall survival; NabP, nanoparticle albumin-bound paclitaxel

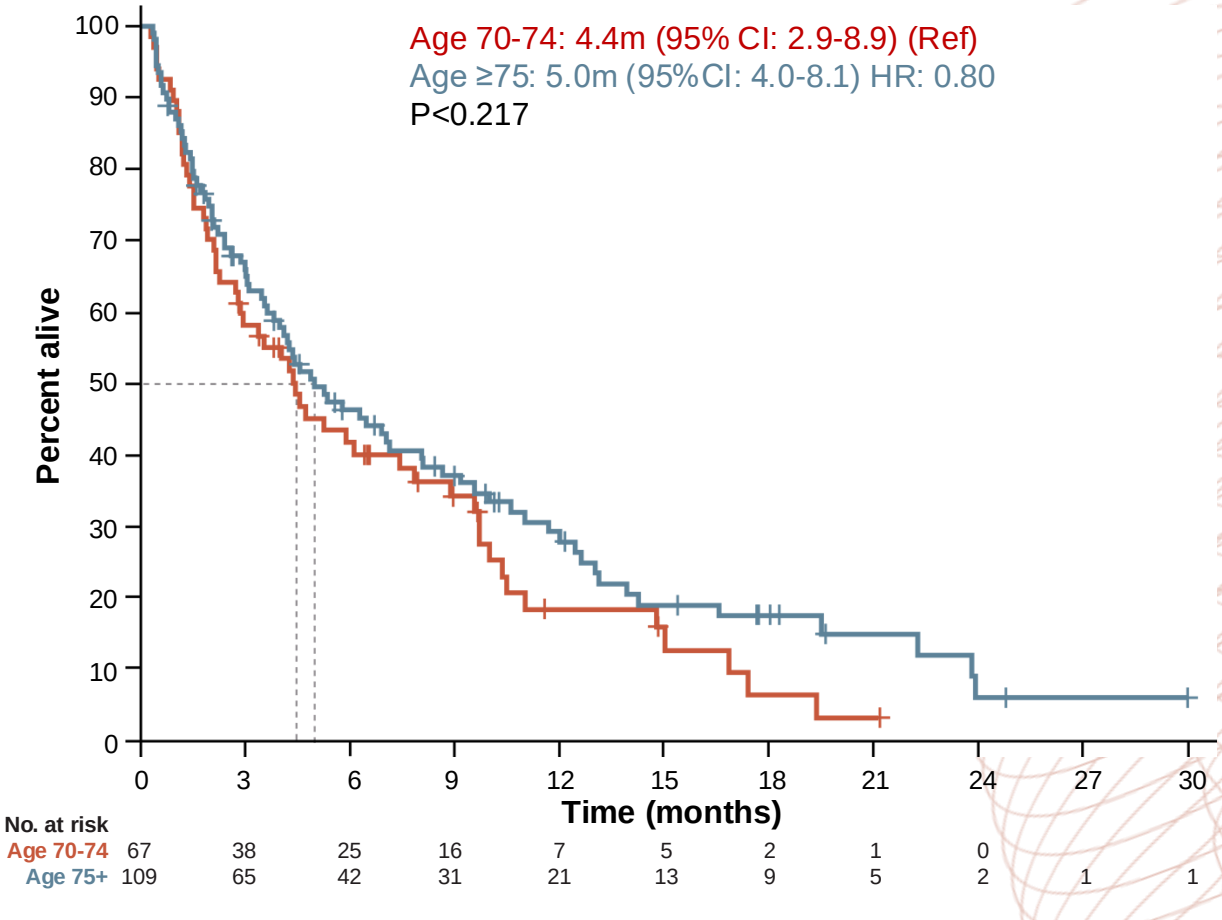
Dotan E, et al. J Clin Oncol. 2024;42(16_suppl):4003 (oral presentation)

ELDERLY PATIENTS WITH A POOR PERFORMANCE STATUS DO NOT BENEFIT FROM CHEMOTHERAPY

MEDIAN OS STRATIFIED BY ECOG PS



MEDIAN OS STRATIFIED BY AGE



CI, confidence interval; HR, hazard ratio; m, months; PS, performance status; Ref, reference

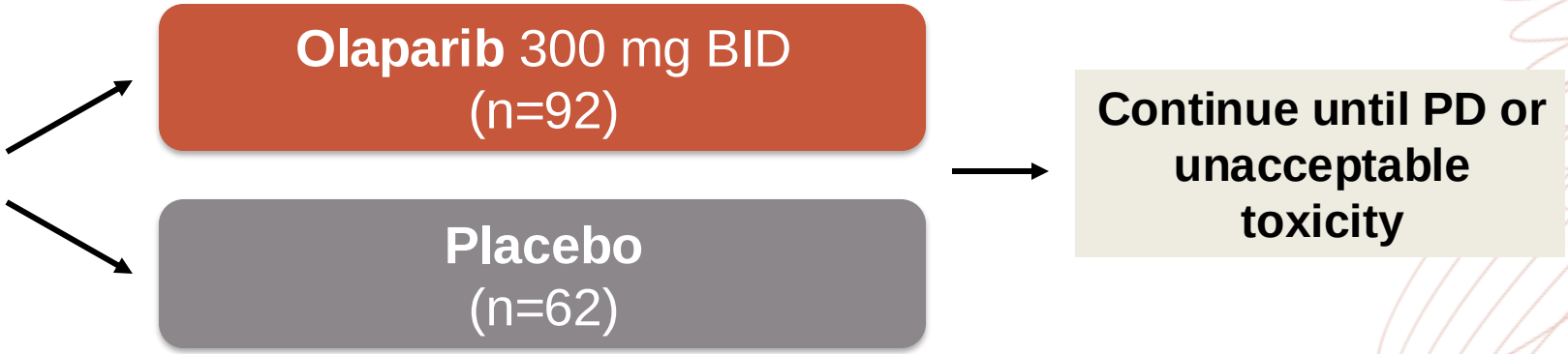
Dotan E, et al. J Clin Oncol. 2024;42(16_suppl):4003 (oral presentation)

MAINTENANCE THERAPY

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)



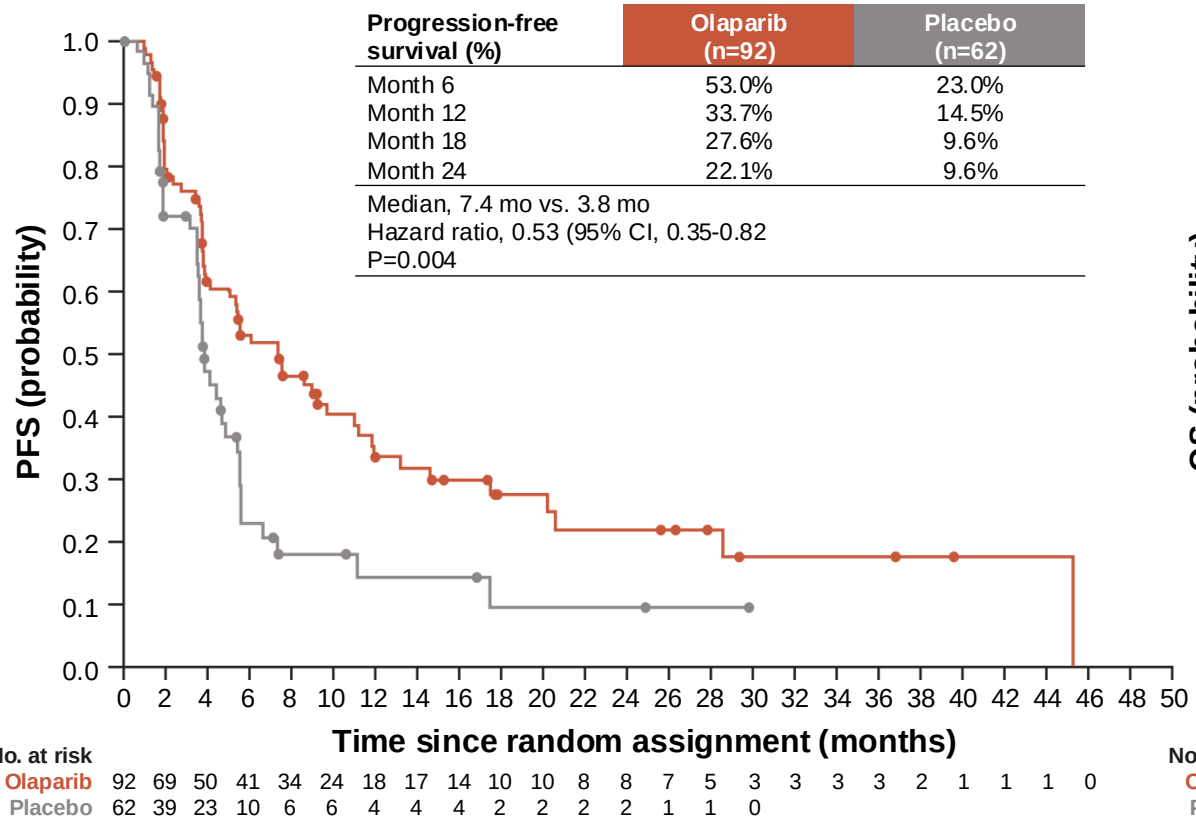
- **Primary endpoint:** PFS by blinded independent central review
- **Key secondary endpoints:** safety/tolerability, PFS2, ORR, OS, HRQoL

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

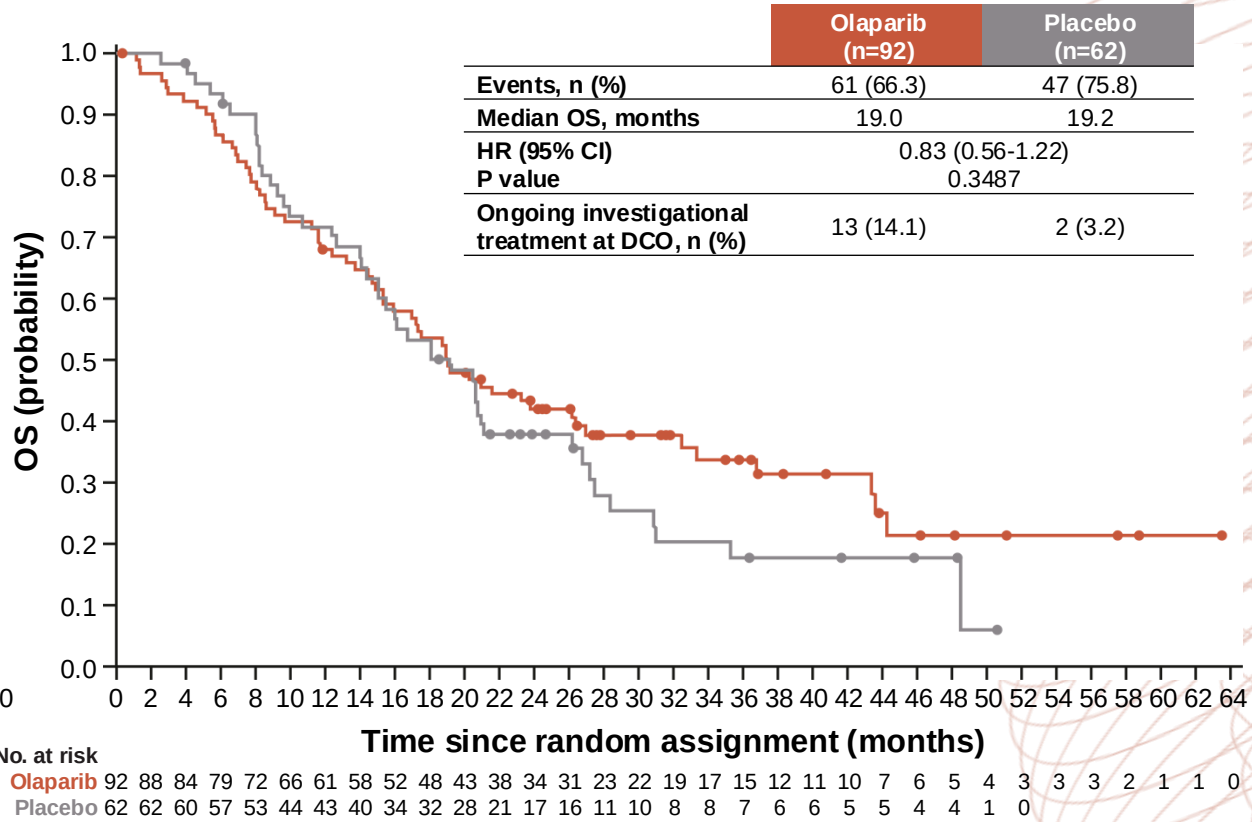
PROGRESSION-FREE SURVIVAL[1]



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) P value	0.83 (0.56-1.22) 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

POLO: SAFETY SUMMARY

AES IN ≥ 15% OF STUDY POPULATION

Event, n (%)	Olaparib (N=90)		Placebo (N=61)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	89 (98.9)	44 (48.9)	56 (91.8)	15 (24.6)
Nausea	44 (48.9)	1 (1.1)	15 (24.6)	1 (1.6)
Fatigue	42 (46.7)	5 (5.6)	16 (26.2)	0 (0.0)
Diarrhoea	34 (37.8)	1 (1.1)	10 (16.4)	0 (0.0)
Abdominal pain	29 (32.2)	3 (3.3)	16 (26.2)	1 (1.6)
Anaemia	29 (32.2)	11 (12.2)	10 (16.4)	2 (3.3)
Constipation	25 (27.8)	0 (0.0)	7 (11.5)	0 (0.0)
Decreased appetite	25 (27.8)	3 (3.3)	4 (6.6)	0 (0.0)
Vomiting	23 (25.6)	2 (2.2)	10 (16.4)	1 (1.6)
Back pain	22 (24.4)	0 (0.0)	13 (21.3)	1 (1.6)
Arthralgia	16 (17.8)	1 (1.1)	7 (11.5)	0 (0.0)
Asthenia	16 (17.8)	1 (1.1)	6 (9.8)	1 (1.6)
Pyrexia	16 (17.8)	0 (0.0)	6 (9.8)	0 (0.0)
Causally related to study treatment[a]	75 (83.3)	22 (24.4)	37 (60.7)	2 (3.3)
Serious AE	28 (31.1)	NA	10 (16.4)	NA
Death	1 (1.1)	NA	0 (0.0)	NA
Interruption of intervention because of AE	37 (41.1)	NA	4 (6.6)	NA
Dose reduction because of AE	16 (17.8)	NA	3 (4.9)	NA
Discontinuation of intervention because of AE	8 (8.9)	NA	1 (1.6)	NA

[a] As assessed by the investigator

AE, adverse event; NA, not applicable

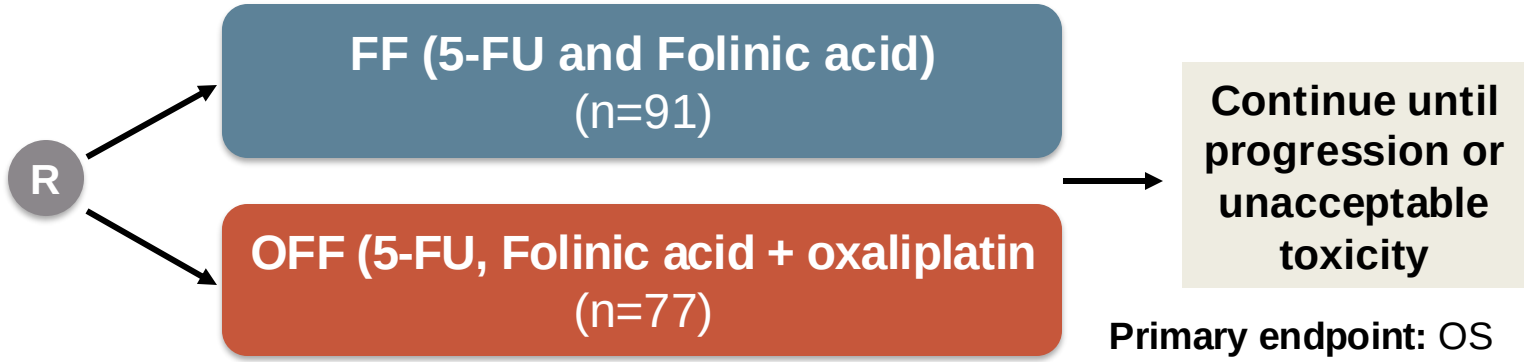
Kindler H, et al. J Clin Oncol. 2022;40:3929-39

SECOND-LINE TREATMENT OPTIONS

OXALIPLATIN PHASE 3 SECOND-LINE STUDIES

CONKO-003[1]

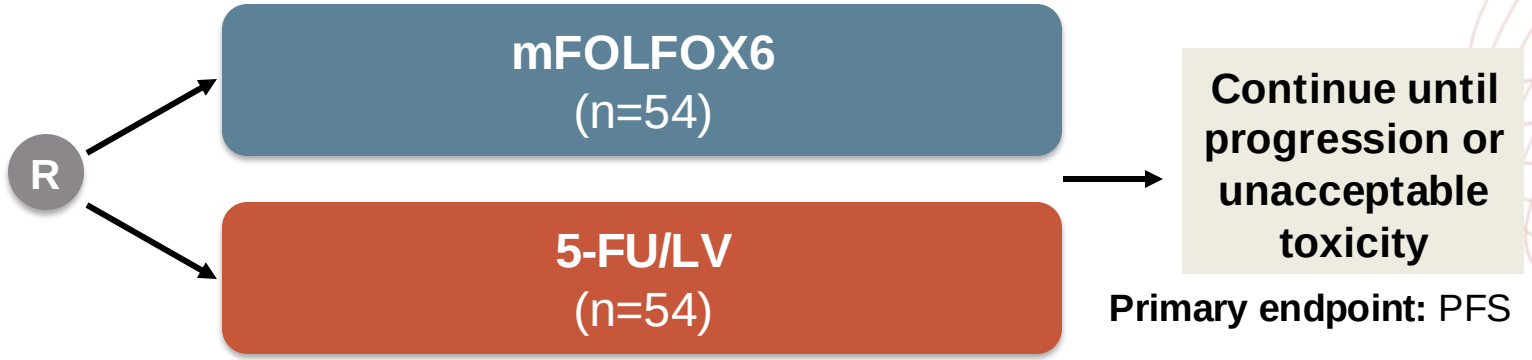
Patients with advanced pancreatic cancer previously treated with gemcitabine, with a
KPS ≥ 70%
N=168



Primary endpoint: OS

PANCREOX[2]

Patients with advanced pancreatic cancer previously treated with gemcitabine, with an ECOG PS 0-2
N=108



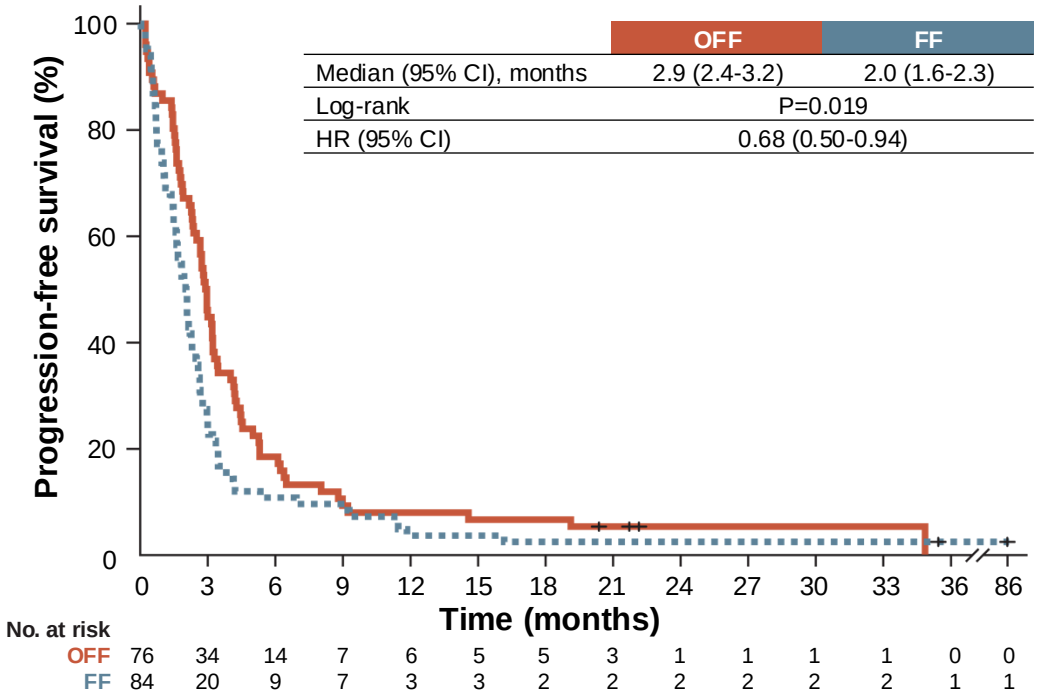
Primary endpoint: PFS

5-FU, fluorouracil; ECOG PS, Eastern Cooperative Oncology Group performance status; FF, folinic acid (leucovorin calcium) and fluorouracil; KPS, Karnofsky performance status; LV, leucovorin calcium (folinic acid); mFOLFOX6, modified FOLFOX6: folinic acid (leucovorin calcium), fluorouracil, and oxaliplatin; OFF, oxaliplatin and FF; OS, overall survival; PFS, progression-free survival

1. Oettle H, et al. J Clin Oncol. 2014 Aug 10;32:2423-9; 2. Gill S, et al. J Clin Oncol. 2016;10;3914-20

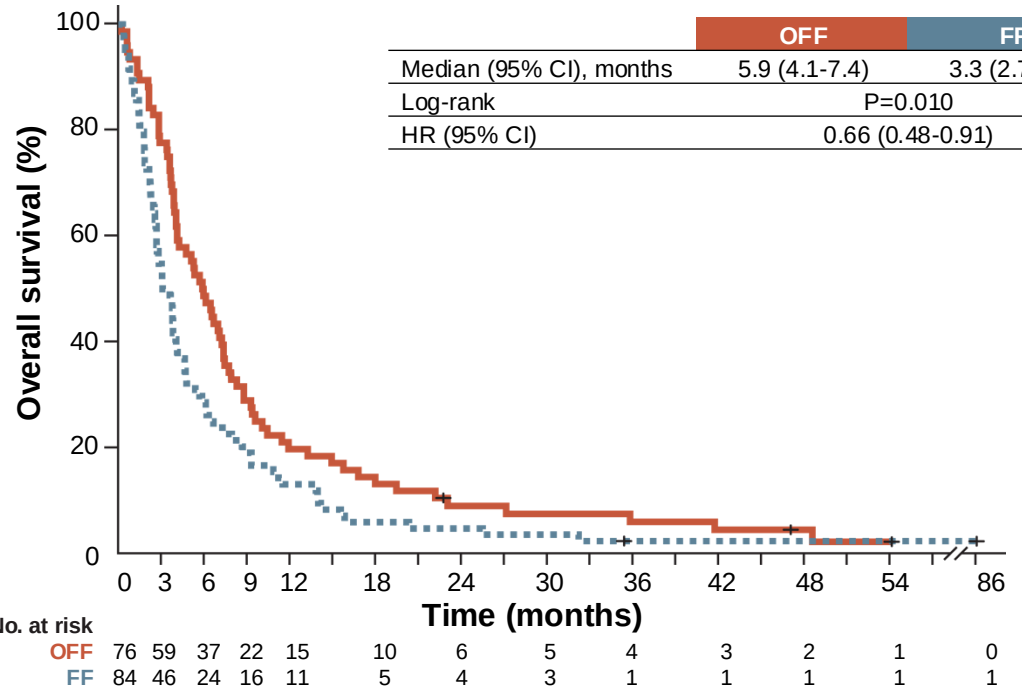
CONKO-003: 5FU+ FOLINIC ACID +/- OXALIPLATIN (OFF) EFFICACY

PROGRESSION-FREE SURVIVAL



	OFF	FF
Median (95% CI), months	2.9 (2.4-3.2)	2.0 (1.6-2.3)
Log-rank	P=0.019	
HR (95% CI)	0.68 (0.50-0.94)	

OVERALL SURVIVAL



	OFF	FF
Median (95% CI), months	5.9 (4.1-7.4)	3.3 (2.7-4.0)
Log-rank	P=0.010	
HR (95% CI)	0.66 (0.48-0.91)	

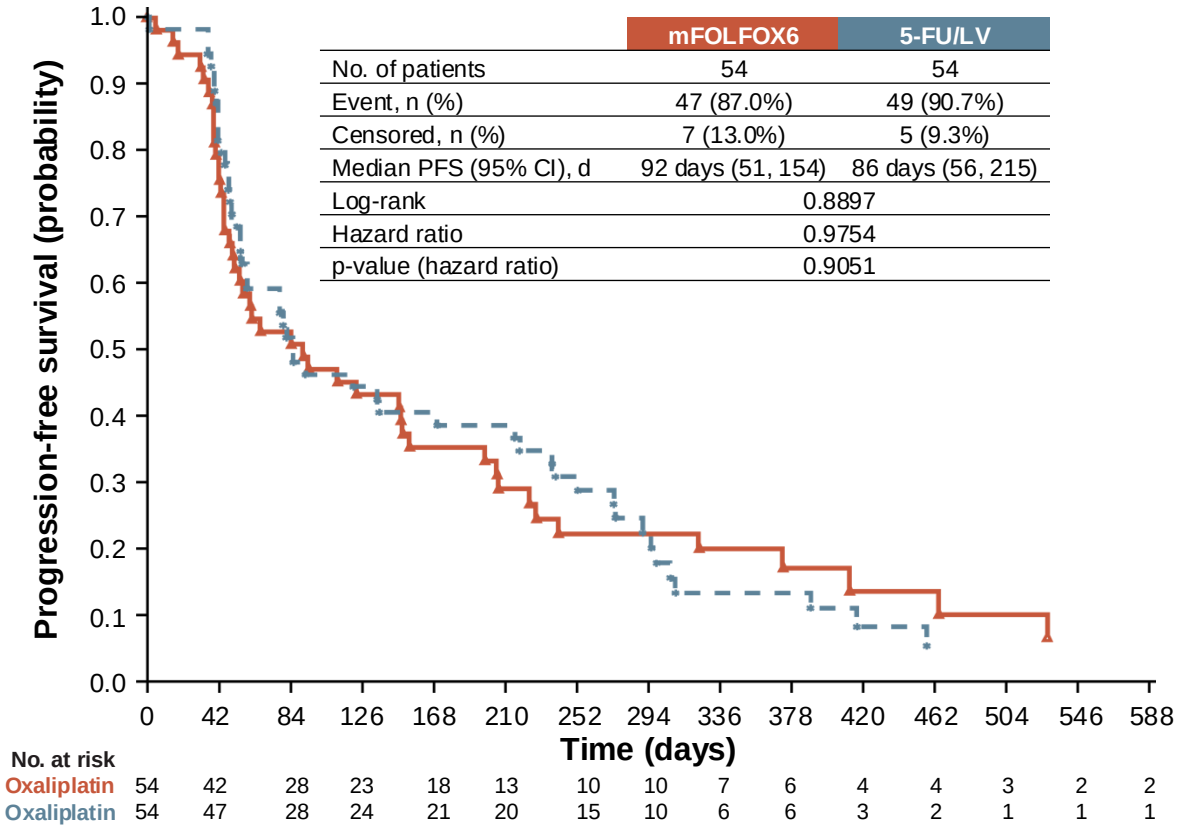
- Rates of **adverse events were similar between treatment arms, except for grades 1 to 2 neurotoxicity**, which were reported in 29 patients (38.2%) and six patients (7.1%) in the OFF and FF groups, respectively (P<0.001)

1L, first-line; 5-FU, fluorouracil; CI, confidence interval; FF, folinic acid (leucovorin calcium) and fluorouracil; HR, hazard ratio; OFF oxaliplatin and FF

Oettle H, et al. J Clin Oncol. 2014 Aug 10;32:2423-9

PANCREOX: ADDITION OF OXALIPLATIN TO 5-FU IN 2L WAS DETRIMENTAL

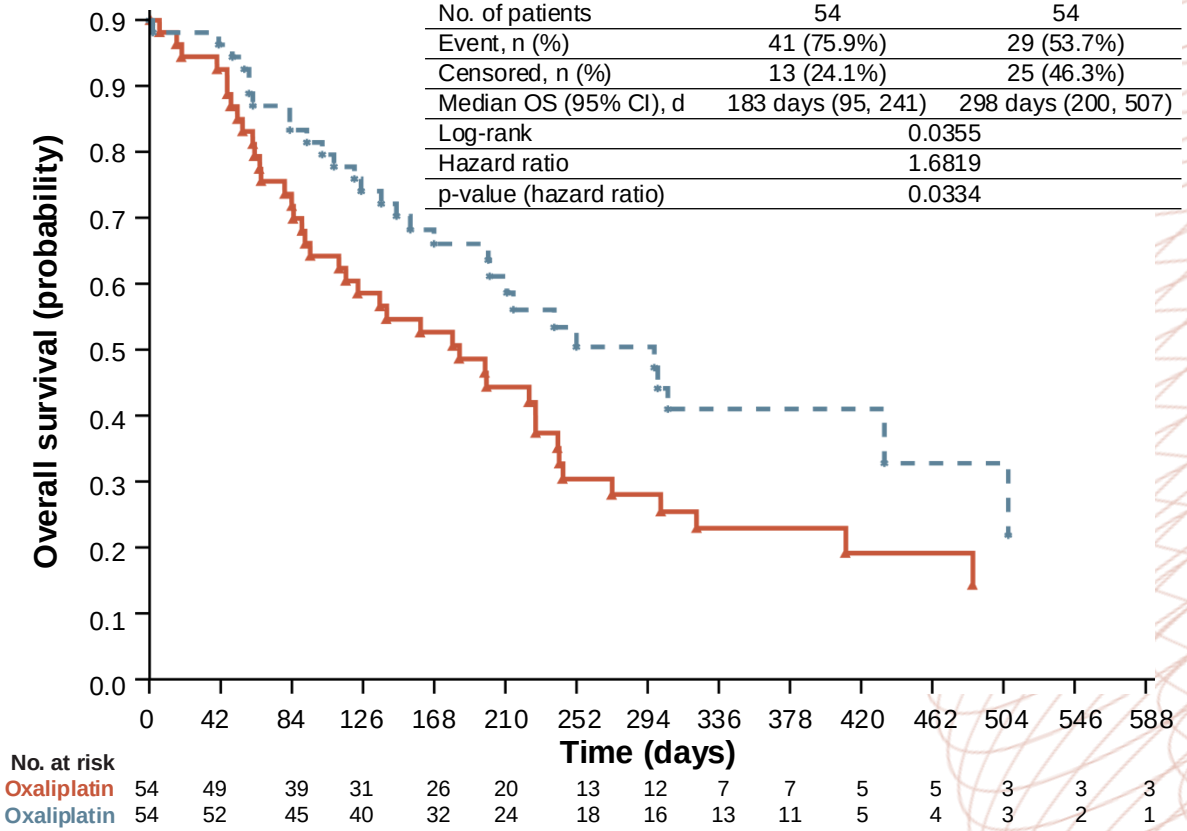
PROGRESSION-FREE SURVIVAL



	mFOLFOX6	5-FU/LV
No. of patients	54	54
Event, n (%)	47 (87.0%)	49 (90.7%)
Censored, n (%)	7 (13.0%)	5 (9.3%)
Median PFS (95% CI), d	92 days (51, 154)	86 days (56, 215)
Log-rank	0.8897	
Hazard ratio	0.9754	
p-value (hazard ratio)	0.9051	

No. at risk															
Oxaliplatin	54	42	28	23	18	13	10	10	7	6	4	4	3	2	2
No Oxaliplatin	54	47	28	24	21	20	15	10	6	6	3	2	1	1	1

OVERALL SURVIVAL



	mFOLFOX6	5-FU/LV
No. of patients	54	54
Event, n (%)	41 (75.9%)	29 (53.7%)
Censored, n (%)	13 (24.1%)	25 (46.3%)
Median OS (95% CI), d	183 days (95, 241)	298 days (200, 507)
Log-rank	0.0355	
Hazard ratio	1.6819	
p-value (hazard ratio)	0.0334	

No. at risk															
Oxaliplatin	54	49	39	31	26	20	13	12	7	7	5	5	3	3	3
No Oxaliplatin	54	52	45	40	32	24	18	16	13	11	5	4	3	2	1

- **Grade 3 or 4 toxicity:** 63% on mFOLFOX6; 11% on 5-FU/LV

2L, second-line; 5-FU, fluorouracil; CI, confidence interval; d, days; LV, leucovorin calcium (folinic acid); mFOLFOX6, modified infusional fluorouracil, leucovorin (folinic acid), and oxaliplatin; PFS, progression-free survival

Gill S, et al. J Clin Oncol. 2016;10;3914-20

PHASE 3 EXPERIENCE IN 2L WITH OXALIPLATIN

CONTRADICTING RESULTS OBSERVED WITH SECOND-LINE OXALIPLATIN REGIMENS IN THE CONKO-003 AND PANCREOX TRIALS

	CONKO-003[1] N=160		PANCREOX[2] N=108	
Treatment	**OFF**	**5-FU/LV**	**mFOLFOX6**	**5-FU/LV**
Median OS, mo	5.9	3.3	6.1	9.9
HR	0.66, P=0.01		1.78, P=0.02	
Median PFS, mo	2.9	2.0	3.0	2.8
HR	0.68, P=0.02		0.98, P=0.91	

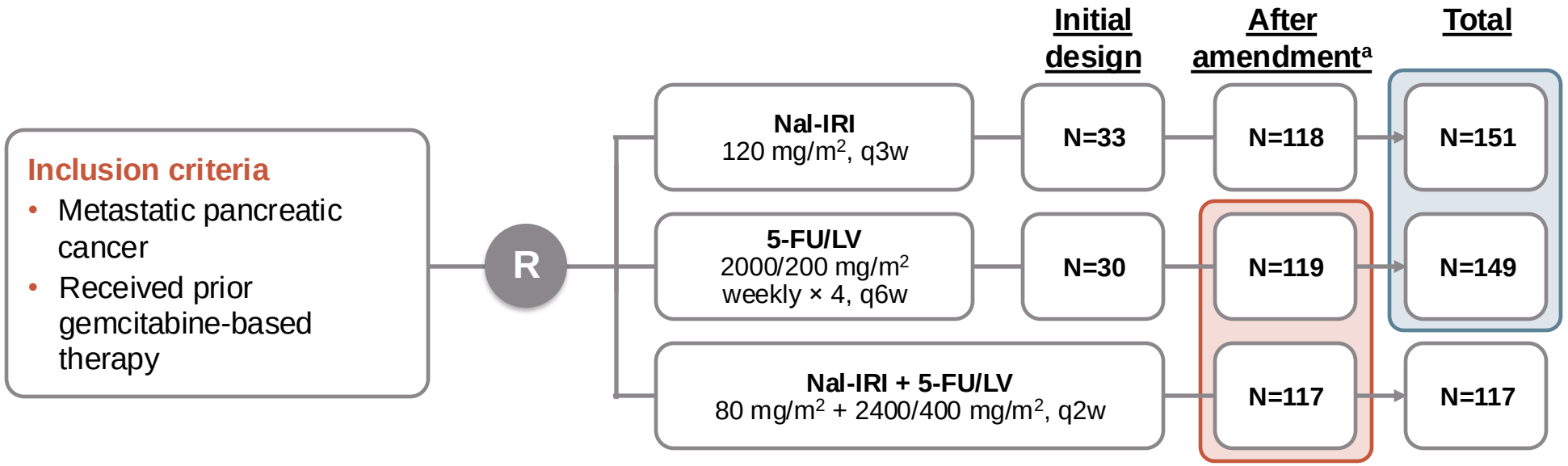
Data presented for information purposes. Cross-trial comparison is not intended

2L, second-line; 5-FU, fluorouracil; HR, hazard ratio; LV, leucovorin calcium (folinic acid); mFOLFOX6, modified infusional fluorouracil, leucovorin, and oxaliplatin; mo, months; OS, overall survival; PFS, progression-free survival; OFF, folinic acid (leucovorin calcium), fluorouracil and oxaliplatin

1. Oettle H, et al. J Clin Oncol. 2014;32: doi.org/10.1200/JCO.2013.53.6995; 2. Gill S, et al. J Clin Oncol. 2016;10; 3914-20

NAPOLI-1: STUDY DESIGN

NAL-IRI ALONE AND IN COMBINATION WITH 5-FU/LV AS 2L THERAPY



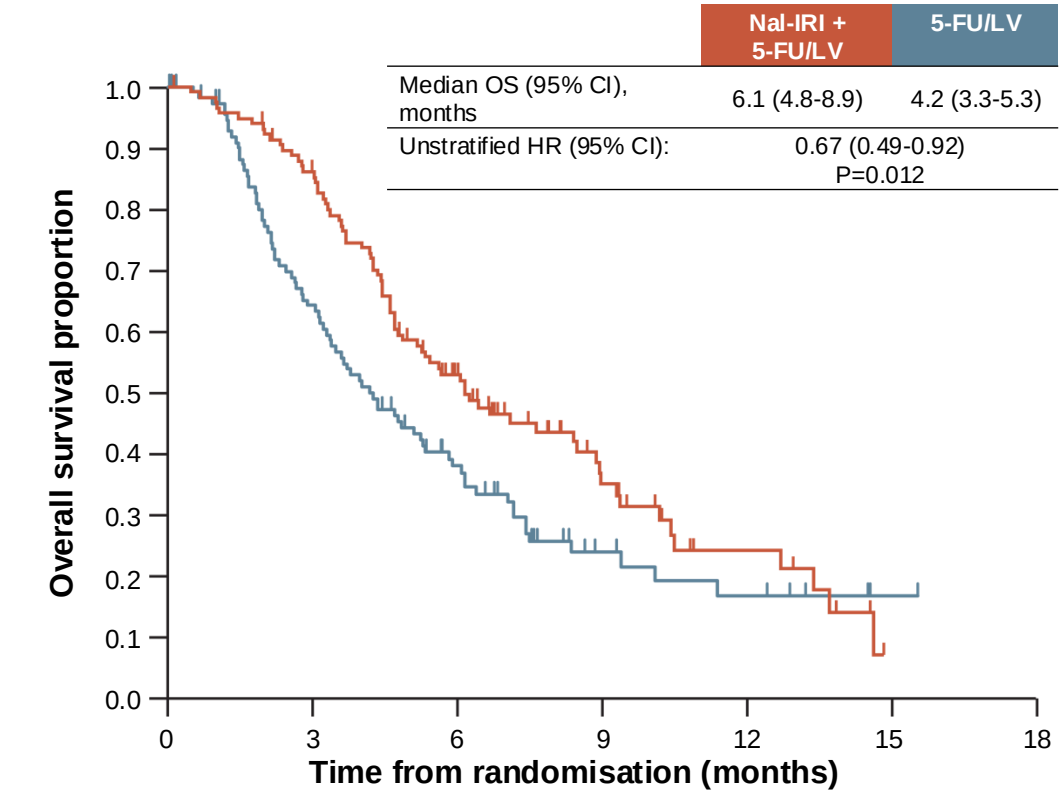
Stratification factors: Albumin, KPS and ethnicity
Primary endpoint: Overall survival
Secondary endpoints: PFS, ORR, TTTF, CA19-9 response safety

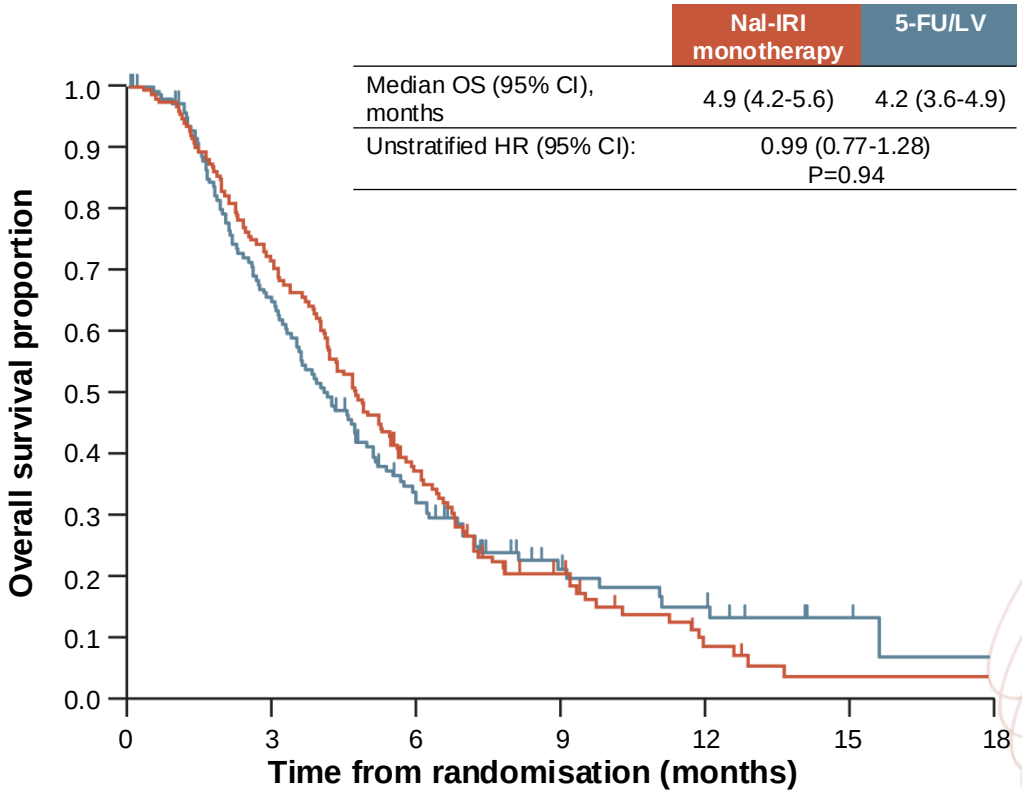
[a] Study was amended to add the Nal-IRI + 5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5FU/LV arm after the amendment (N=119), were used as the control for the combination arm

2L, second-line; 5-FU, fluorouracil; CA19-9; carbohydrate antigen 19-9; KPS, Karnofsky performance status; LV, leucovorin calcium (folinic acid); Nal-IRI, nanoliposomal irinotecan; ORR, overall response rate; PFS, progression-free survival; q2w/q3w/q6/w, every 2/3/6 weeks; R, randomised; TTTF, time to treatment failure

Wang-Gillam A, et al. Lancet. 2016;387:545-57

NAPOLI-1: OVERALL SURVIVAL (ITT)





Protocol-defined primary analysis data cut (14 February 2014, after 305 events)

5-FU, fluorouracil; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; LV, leucovorin calcium (folinic acid); Nal-IRI, nanoliposomal irinotecan; OS, overall survival

Wang-Gillam A, et al. Lancet. 2016;387:545-57

NAPOLI-1: SAFETY

Adverse event, n (%)	Nal-IRI + 5-FU/LV (N=117)		Nal-IRI monotherapy (N=147)		5-FU/LV (N=134)	
	Any grade	Grades 3-4	Any grade	Grades 3-4	Any grade	Grades 3-4
Diarrhoea	69 (59%)	15 (13%)	103 (70%)	31 (21%)	35 (26%)	6 (4%)
Vomiting	61 (52%)	13 (11%)	80 (54%)	20 (14%)	25 (26%)	4 (3%)
Nausea	60 (51%)	9 (8%)	89 (61%)	8 (5%)	46 (34%)	4 (3%)
Decreased appetite	52 (44%)	5 (4%)	72 (49%)	13 (19%)	43 (32%)	3 (2%)
Fatigue	47 (40%)	16 (14%)	54 (37%)	9 (6%)	37 (28%)	5 (4%)
Neutropenia[a]	46 (39%)	32 (27%)	37 (25%)	22 (15%)	7 (5%)	2 (1%)
Anaemia	44 (38%)	11 (9%)	48 (33%)	16 (11%)	31 (23%)	9 (7%)
Hypokalaemia	14 (12%)	4 (3%)	32 (22%)	17 (12%)	12 (9%)	3 (2%)

Data are number of patients (%). The table shows grade 3 and 4 adverse events reported in ≥5% of patients whose treatment included nanoliposomal irinotecan with ≥2% incidence versus fluorouracil and folinic acid. [a] includes agranulocytosis, febrile neutropenia, granulocytopenia, neutropenia, neutropenic sepsis, decreased neutrophil count, and pancytopenia

5-FU, fluorouracil; LV, leucovorin calcium (folinic acid); Nal-IRI, nanoliposomal irinotecan

Wang-Gillam A, et al. Lancet 2016;387:545-57

NAPOLI-1: DOSE MODIFICATIONS OF NAL-IRI + 5-FU/LV

POST HOC ANALYSIS: IMPACT OF DOSE MODIFICATIONS OR DELAYS ON EFFICACY

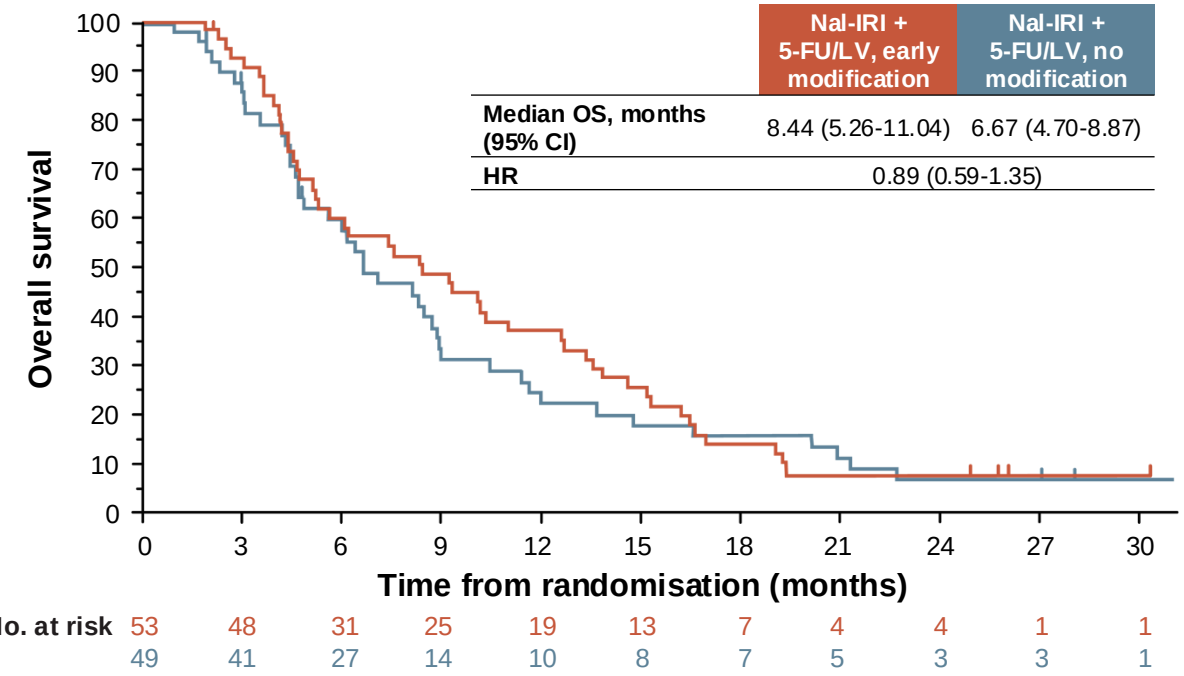
	Nal-IRI + 5-FU/LV	5-FU/LV
	Nal-IRI dose delay	
Median overall survival, mos	8.4 (N=49)	4.2 (N=105)
Hazard ratio (95% CI)	0.66 (0.46, 0.94)	
	Nal-IRI dose reduction	
Median overall survival, mos	9.4 (N=34)	4.2 (N=105)
Hazard ratio (95% CI)	0.58 (0.38, 0.88)	

5-FU, fluorouracil; CI, confidence interval; LV, leucovorin calcium (folinic acid); mos, months; Nal-IRI, nanoliposomal irinotecan; OS, overall survival

Wang-Gillam A, et al. J. Clin. Oncol. 2018; 36(4_suppl):388

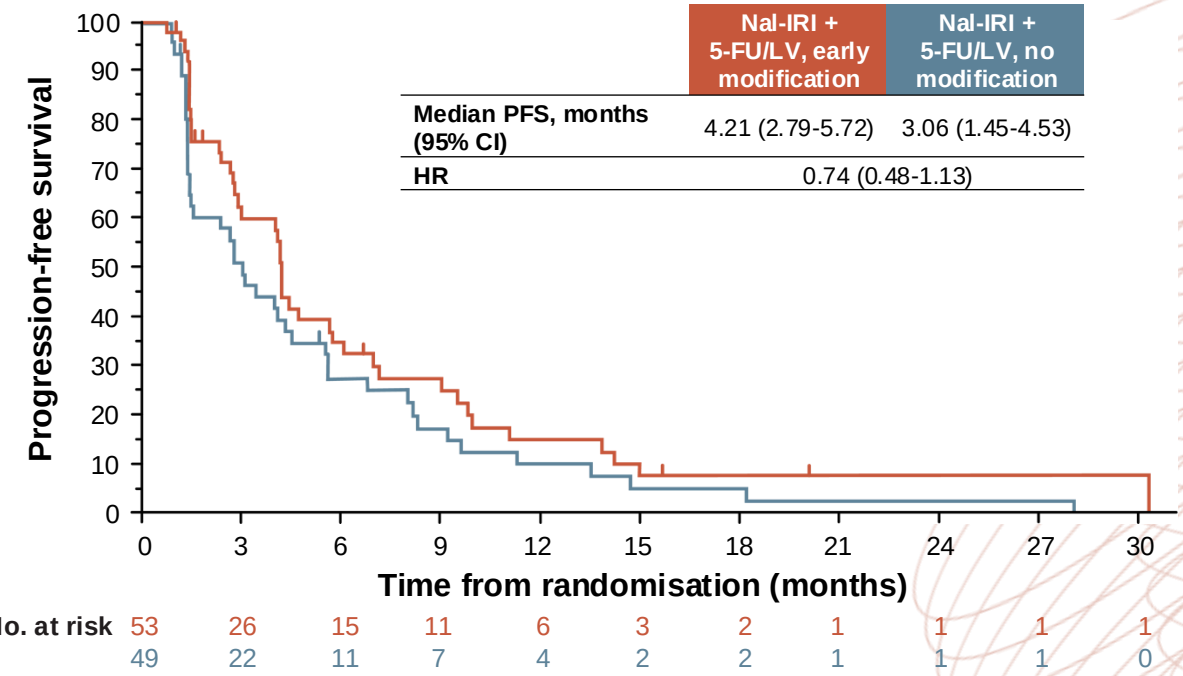
NAPOLI-1: DOSE MODIFICATIONS OF NAL-IRI + 5-FU/LV

POST HOC ANALYSIS: IMPACT ON EFFICACY



	Nal-IRI + 5-FU/LV, early modification	Nal-IRI + 5-FU/LV, no modification
Median OS, months (95% CI)	8.44 (5.26-11.04)	6.67 (4.70-8.87)
HR	0.89 (0.59-1.35)	

No. at risk											
Nal-IRI + 5-FU/LV, early modification	53	48	31	25	19	13	7	4	4	1	1
Nal-IRI + 5-FU/LV, no modification	49	41	27	14	10	8	7	5	3	3	1



	Nal-IRI + 5-FU/LV, early modification	Nal-IRI + 5-FU/LV, no modification
Median PFS, months (95% CI)	4.21 (2.79-5.72)	3.06 (1.45-4.53)
HR	0.74 (0.48-1.13)	

No. at risk											
Nal-IRI + 5-FU/LV, early modification	53	26	15	11	6	3	2	1	1	1	1
Nal-IRI + 5-FU/LV, no modification	49	22	11	7	4	2	2	1	1	1	0

- Tolerability-guided dose modification of liposomal irinotecan does not adversely affect efficacy outcomes

5-FU, fluorouracil; CI, confidence interval; HR, hazard ratio; LV, leucovorin calcium (folinic acid); Nal-IRI, nanoliposomal irinotecan; OS, overall survival; PFS, progression-free survival

Chen L-T, et al. Pancreatology. 2021;21:192-199

SUMMARY

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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