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

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mPDAC, metastatic pancreatic ductal adenocarcinoma

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

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

OVERVIEW OF TREATMENT FOR mPDAC

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

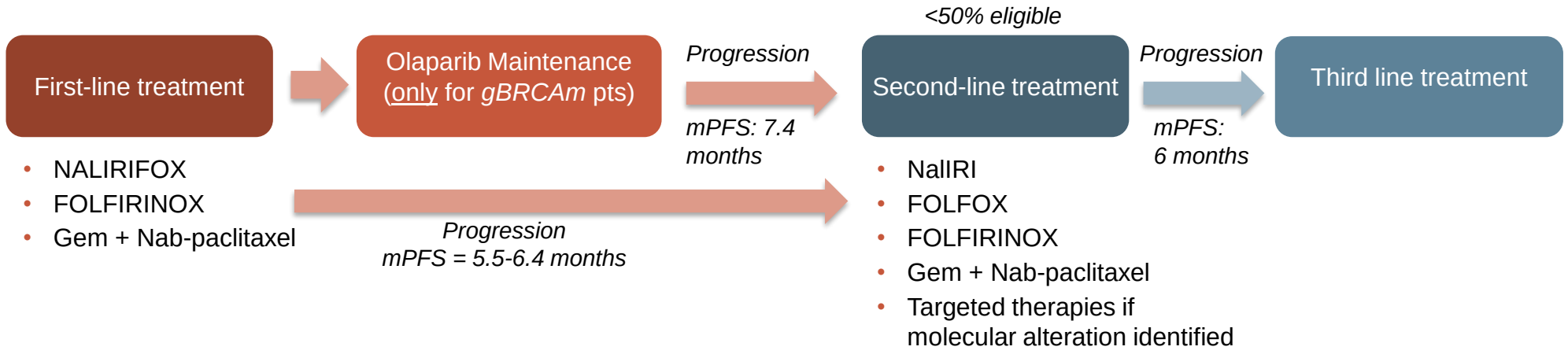


Figure adapted from Casolino 2022

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

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

KEY STUDIES OF 2L SYSTEMIC THERAPY FOR MPDAC

Study setting	Study	Study type	Arm (N)	Primary endpoint	Primary endpoint		Secondary endpoint	Secondary endpoint		ORR (%)	Notable adverse events
					Months	HR (95% CI)		Months	HR (95% CI)		
Second-line	CONKO-003[1] (2014)	RCT, phase 3	OFF (77)	OS	5.9	0.66 (0.48-0.91)	PFS	2.9	0.68 (0.50-0.94)	–	Rates of adverse events were similar between treatment arms, with the exception of grades 1 to 2 neurotoxicity 38.2% and 7.1% in the OFF and FF groups
			FF (91)		3.3			2.0		–	
Second-line	PANCREOX[2] (2016)	RCT, phase 3	mFOLFOX (54)	PFS	3.0	1.00 (0.66-1.53)	OS	6.1	1.78 (1.08-2.93)	13.2	Increased toxicity was observed with the addition of oxaliplatin, with grade 3/4 adverse events occurring in 63.0% of patients who received mFOLFOX6 and 11.0% of those who received FU/LV.
			5FU/LV (54)		2.8			9.9		8.5	
Second-line	NAPOLI-1[3] (2016)	RCT, phase 3	Nal-IRI + 5-FU/LV (117)	OS	6.1	0.67 (0.49 to 0.92)	PFS	3.1	0.56 (0.41 to 0.75)	16.2	Most frequent grade 3 or 4 AEs for Nal-IRI + 5-FU/LV vs 5-FU/LV: neutropenia 27.0 vs 1.0%, diarrhoea 13.0 vs 4.0%, vomiting 11.0 vs 3.0%, and fatigue 14.0 vs 4.0%
			5-FU/LV (119)		4.2			1.5		0.8	

5-FU, fluorouracil; AE, adverse event; CI, confidence interval; FF, folinic acid (leucovorin calcium) and fluorouracil; HR, hazard ratio; LV, leucovorin calcium (folinic acid); mFOLFOX, modified FOLFOX: folinic acid (leucovorin calcium), fluorouracil, and oxaliplatin; mPDAC, metastatic pancreatic ductal adenocarcinoma; Nal-IRI, nanoliposomal irinotecan; OFF, oxaliplatin and FF; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial

1. Oettle H, et al. J Clin Oncol. 2014; 32: 2423-9; 2. Gill S, et al. J Clin Oncol. 2016;10;3914-20; 3. Wang-Gillam A, et al. Lancet 2016;387:545-57

CONSIDERATIONS FOR TREATMENT SELECTION

- Prior treatments
- Patient performance status
- Age and frailty
- Co-morbidities
- Residual side effects from prior treatments
- Molecular profile
- Patient preference
- Supportive system

Jiang Y, et al. JCO Oncol Pract. 2023;19(1):19-32

SYSTEMIC THERAPIES FOR GOOD PS 0-1

BASED ON NCCN GUIDELINES

First-line

- FOLFIRINOX / mFOLFIRINOX
- NALIRIFOX

Gemcitabine-based therapy:
- Gemcitabine + Nab-paclitaxel
- Gemcitabine + cisplatin for known *BRCA1/2* or *PALB2* mutations)

Maintenance

Olaparib maintenance, only for patients with germline *BRCA1/2* mutations

Subsequent therapy

- Liposomal irinotecan (Nal-IRI) +FU/LV *(if no prior irinotecan)*
- Gemcitabine
- Gemcitabine-based therapy

- Liposomal irinotecan (Nal-IRI) +FU/LV
- Fluoropyrimidine-based therapy

Targeted therapies
Useful in certain circumstances

- Entrectinib, Larotrectinib, Repotrectinib (*NTRK* fusion)
- Dabrafenib + trametinib (*BRAF* V600E mutation)
- Selpercatinib (*RET* fusion)
- Pembrolizumab (MSI-H, dMMR, or TMB-H)

Chemotherapy is recommended as front-line therapy for mPDAC patients, but targeted therapies may be useful in certain circumstances (e.g. if a patient can no longer tolerate chemotherapy)

- Entrectinib, Larotrectinib, Repotrectinib (*NTRK* fusion)
- Dabrafenib + trametinib (*BRAF* V600E mutation)
- Selpercatinib (*RET* fusion)
- Adagrasib, sotorasib (*KRAS* G12C)
- Trastuzumab deruxtecan (*HER2*)

If no prior immunotherapy:

- Pembrolizumab (MSI-H, dMMR, or TMB-H)
- Dostarlimab (MSI-H or dMMR)
- Nivolumab + ipilimumab (TMB-H)

5-FU, fluorouracil; BRAF, B-Raf proto-oncogene serine/threonine kinase; BRCA1/2, BReast CAncer 1/2 gene; dMMR, deficient DNA mismatch repair; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene homolog; LV, leucovorin calcium (folinic acid); (m)FOLFIRINOX, (modified) FOLFIRINOX, folinic acid (leucovorin calcium), fluorouracil, irinotecan, and oxaliplatin; MSI-H, microsatellite instability-high; Nab, nanoparticle albumin-bound; Nal-IRI, nanoliposomal irinotecan; NALIRIFOX; Nal-IRI, fluorouracil/folinic acid (leucovorin calcium), and oxaliplatin; NCCN, National Comprehensive Cancer Network; NRG1, neuregulin-1; NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localiser of BRCA2; PS, performance status; 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)

SYSTEMIC THERAPIES FOR INTERMEDIATE PS 2 OR HIGHER

BASED ON NCCN GUIDELINES

First-line

- Capecitabine
  FOLFOX, FOLFIRI, CapeOx
  5-FU
- Gemcitabine + Nab-paclitaxel
  Gemcitabine

Maintenance

Olaparib maintenance, only for patients with germline *BRCA1/2* mutations

Subsequent therapy

- Liposomal irinotecan (Nal-IRI) +FU/LV *(if no prior irinotecan)*
- Gemcitabine + Nab-paclitaxel
- Gemcitabine

- Liposomal irinotecan +FU/LV
- Capecitabine
- 5-FU/LV

Targeted therapies
Useful in certain circumstances

- Entrectinib, Larotrectinib, Repotrectinib (*NTRK* fusion)
- Dabrafenib + trametinib (*BRAF* V600E mutation)
- Selpercatinib (*RET* fusion) [ECOG PS 2 only for first-line]
- Pembrolizumab (MSI-H, dMMR, or TMB-H)

Chemotherapy is recommended as front-line therapy for mPDAC patients, but targeted therapies may be useful in certain circumstances (e.g. if a patient can no longer tolerate chemotherapy)

- Entrectinib, Larotrectinib, Repotrectinib (*NTRK* fusion)
- Dabrafenib + trametinib (*BRAF* V600E mutation)
- Selpercatinib (*RET* fusion) [ECOG PS 2 only for first-line]
- Adagrasib, sotorasib (*KRAS* G12C)

If no prior immunotherapy:

- Pembrolizumab (MSI-H, dMMR, or TMB-H)
- Dostarlimab (MSI-H or dMMR)
- Nivolumab + ipilimumab (TMB-H)

5-FU, fluorouracil; BRAF, B-Raf proto-oncogene serine/threonine kinase; BRCA1/2, BReast CAncer 1/2 gene; CapeOX, capecitabine and oxaliplatin; dMMR, deficient DNA mismatch repair; FOLFOX, folinic acid (leucovorin calcium), fluorouracil, and oxaliplatin; FOLFIRI, folinic acid (leucovorin calcium), fluorouracil and irinotecan; KRAS, Kirsten rat sarcoma viral oncogene homolog; LV, leucovorin calcium (folinic acid); MSI-H, microsatellite instability-high; Nab, nanoparticle albumin-bound; NCCN, National Comprehensive Cancer Network; NRG1, neuregulin-1; NTRK, neurotrophic tyrosine receptor kinase; PALB2, partner and localiser of BRCA2; PS, performance status; 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;

PATIENTS WITH POOR PERFORMANCE STATUS AND PROGRESSIVE DISEASE

PALLIATIVE CARE

- **Single agent chemotherapy** *(gemcitabine)*
- **Targeted therapy** *(based on molecular profiling and as clinically indicated)*
- **Palliative radiotherapy**
  - To relieve pain, bleeding and/or local obstructive symptoms

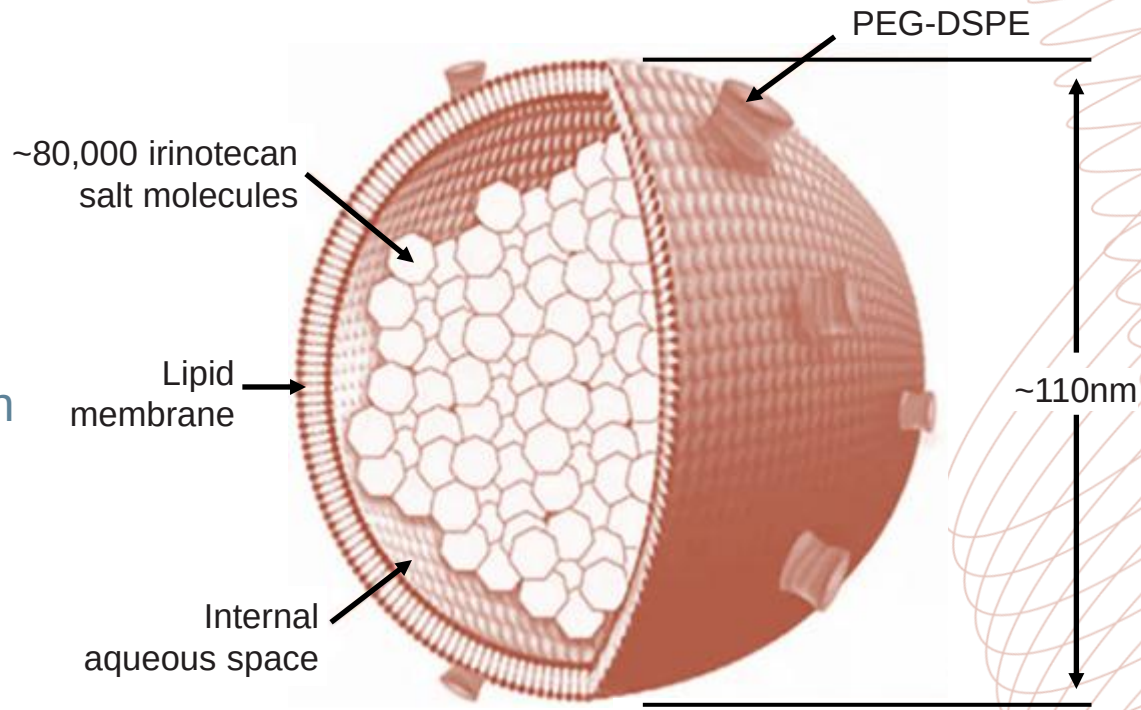
NCCN, National Comprehensive Cancer Network

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

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]



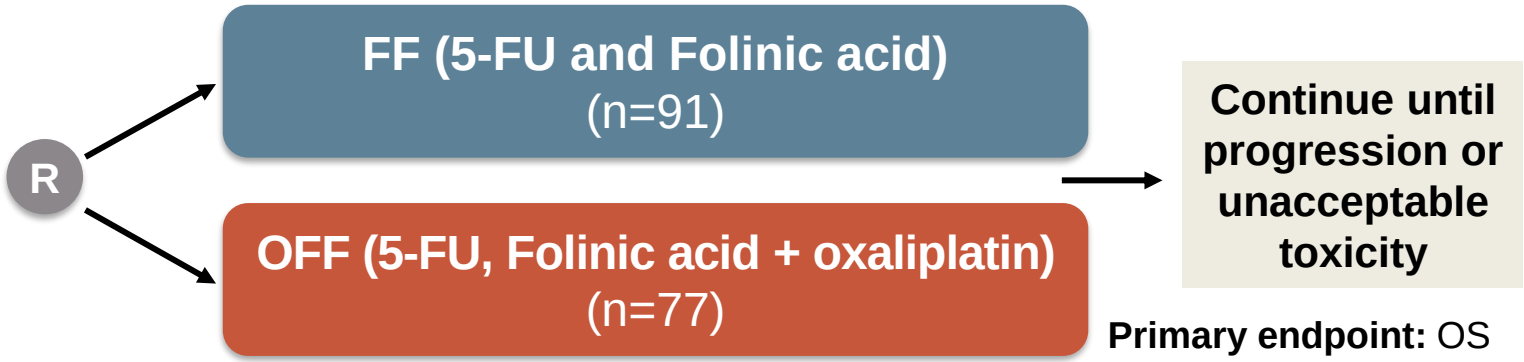
Nal-IRI, nanoliposomal irinotecan; OS, overall survival; PEG-DSPE, polyethylene glycol-distearoylphosphatidylethanolamine

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

OXALIPLATIN PHASE 3 SECOND-LINE STUDIES

CONKO-003[1]

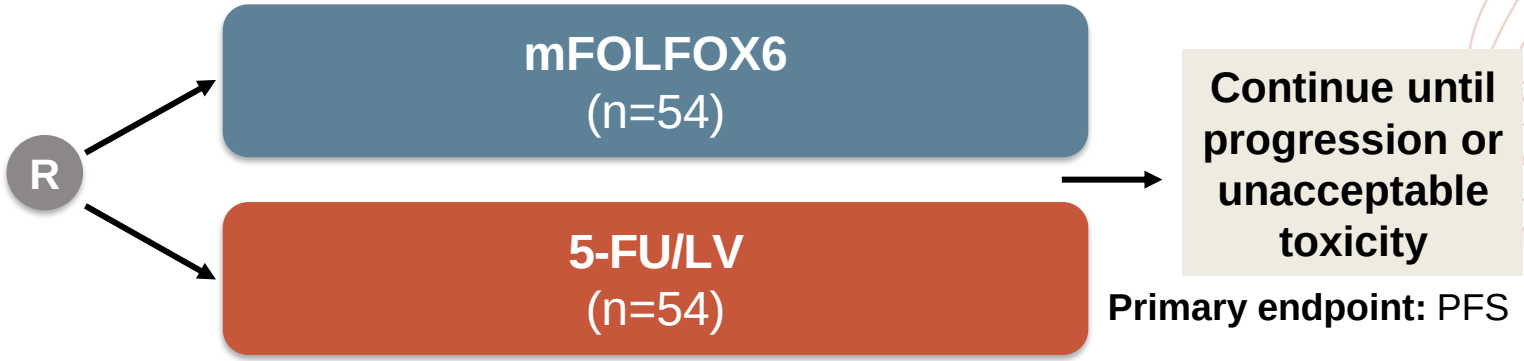
Patients with advanced pancreatic cancer previously treated with gemcitabine, with a KPS ≥ 70%
N=168



Primary endpoint: OS

PANCREOX[2]

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



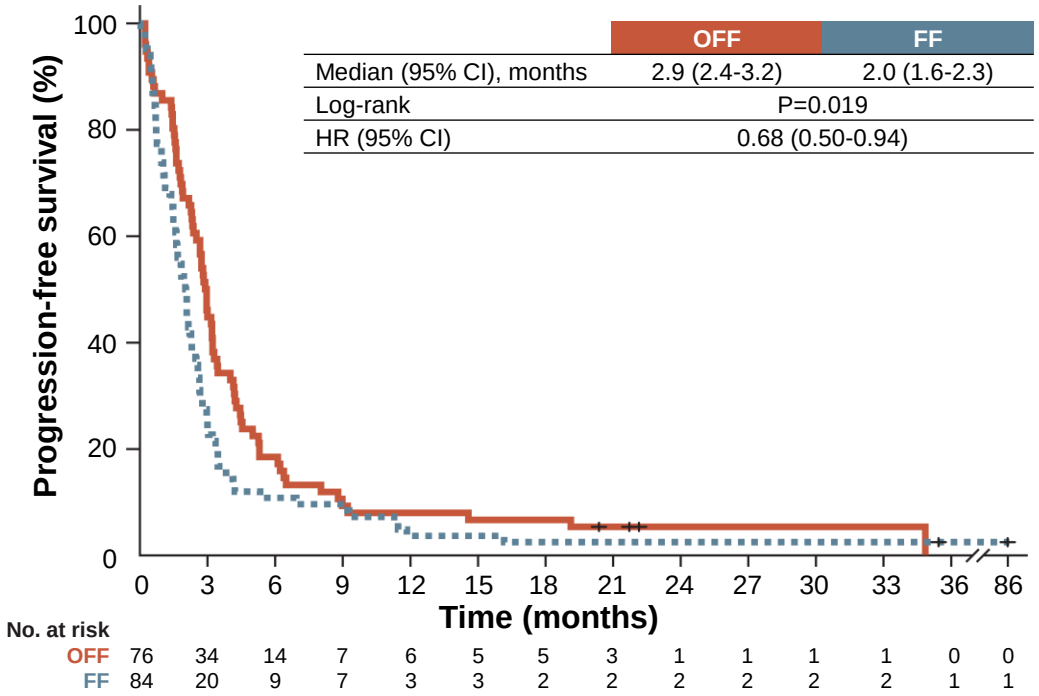
Primary endpoint: PFS

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

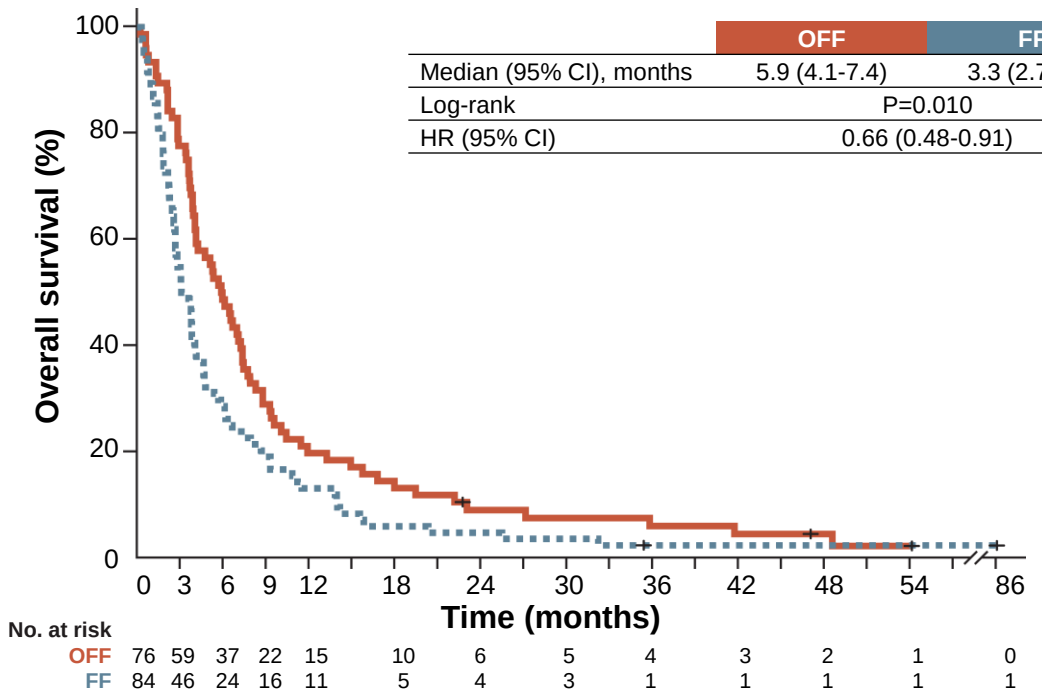
CONKO-003: 5FU+ FOLINIC ACID +/- OXALIPLATIN (OFF) EFFICACY

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)	

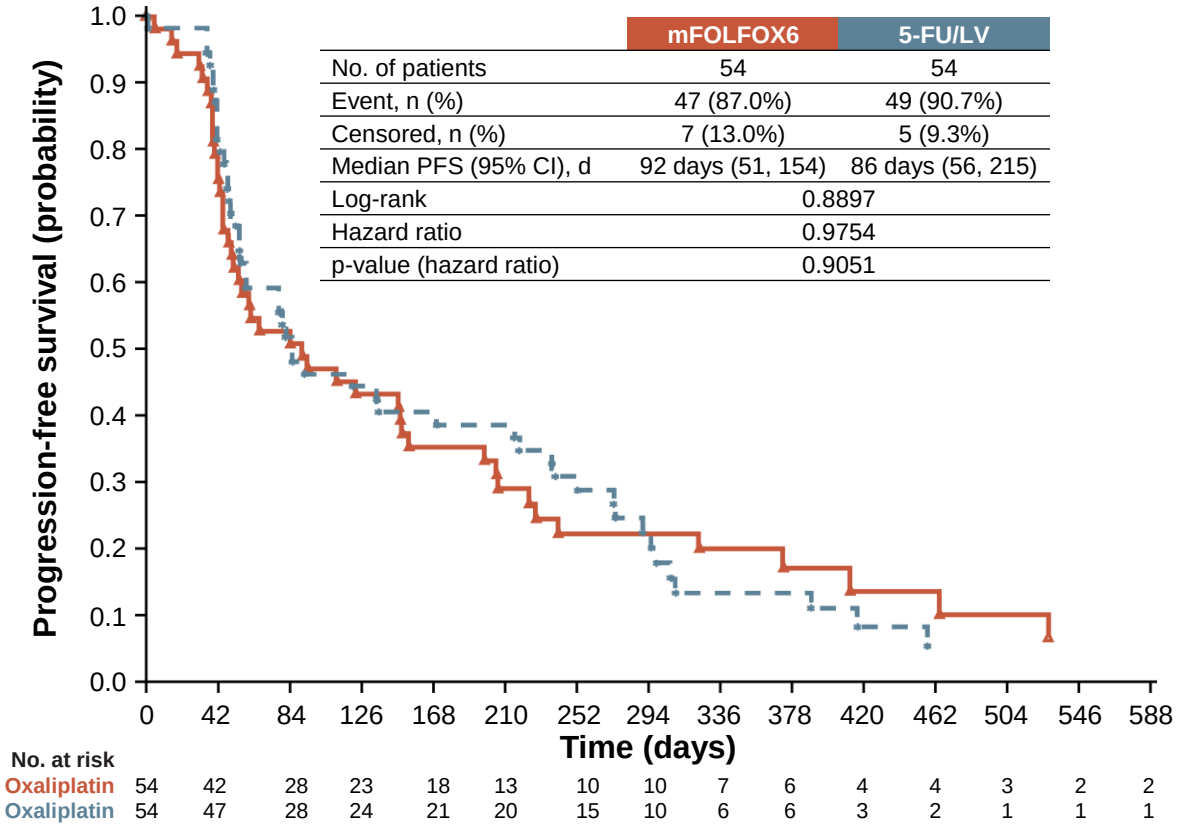
- Rates of **adverse events were similar between treatment arms, except for grades 1 to 2 neurotoxicity**, which were reported in 29 patients (38.2%) and six patients (7.1%) in the OFF and FF groups, respectively (P<0.001)

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

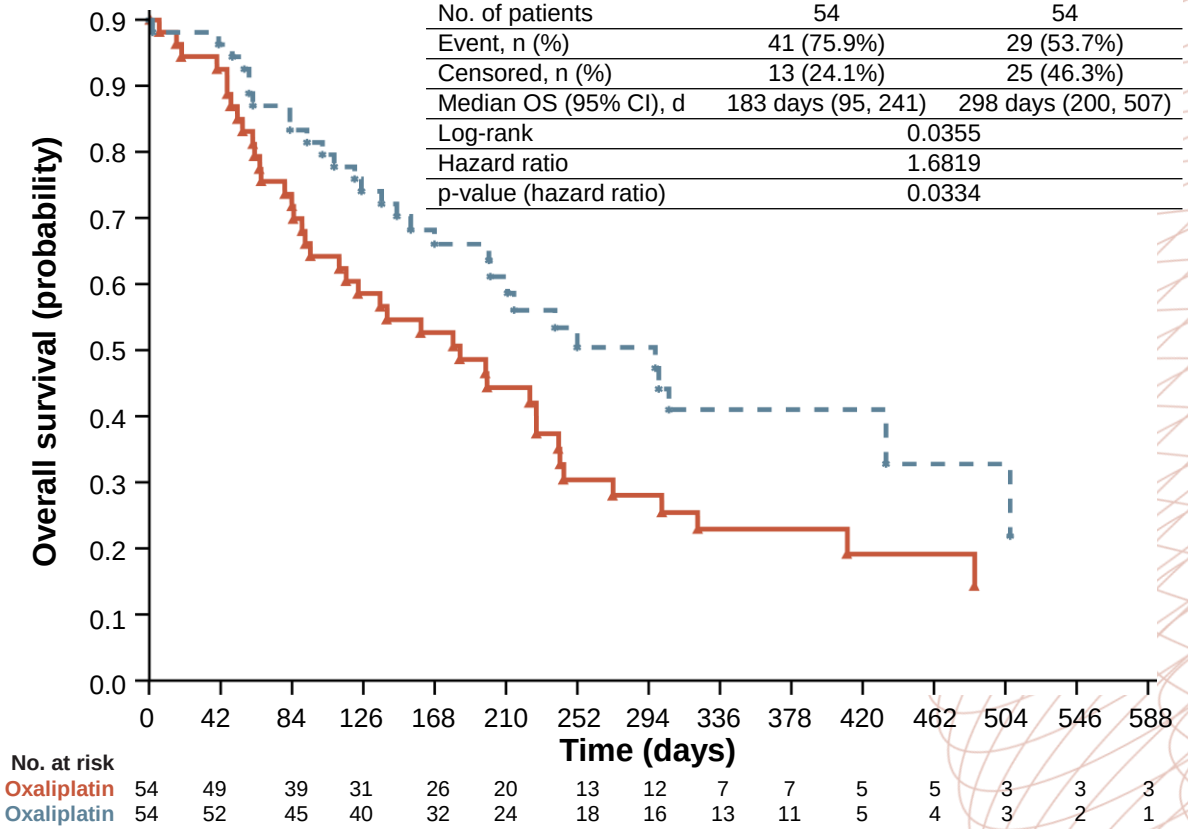
PROGRESSION-FREE SURVIVAL



	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[a]		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

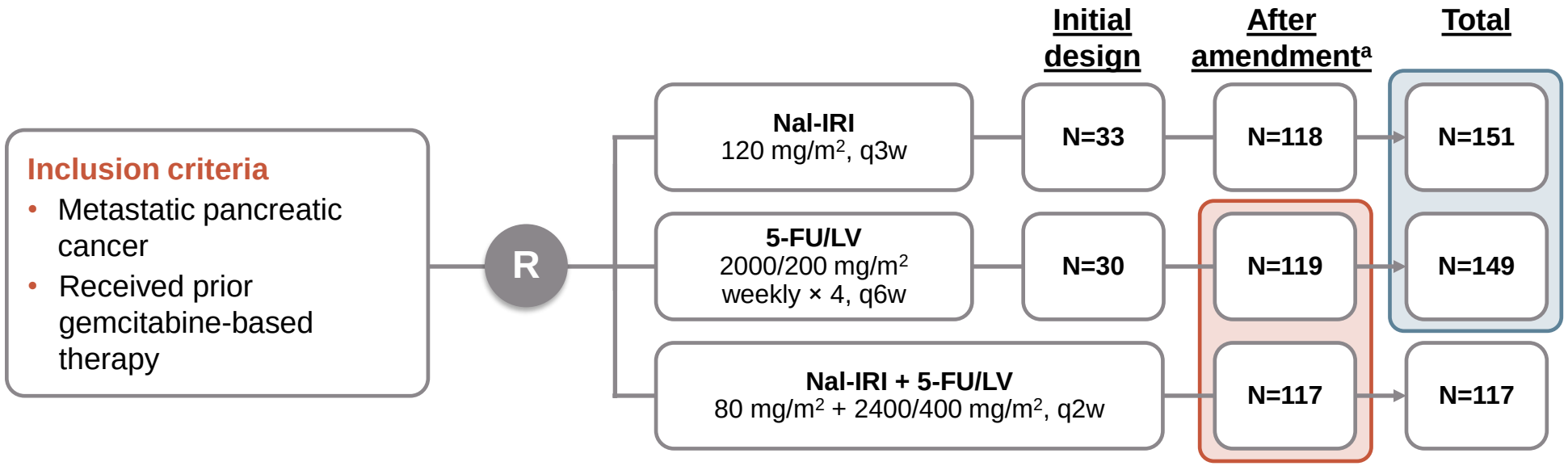
[a]Patients eligible for primary analysis

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

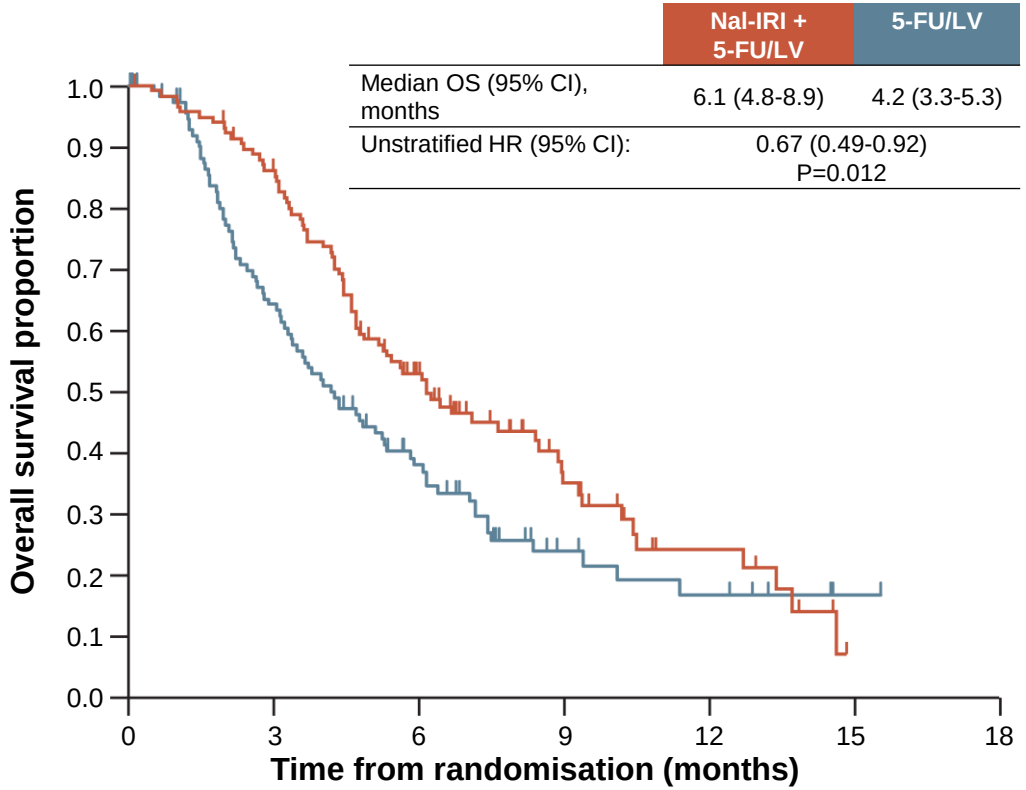
Secondary endpoints: PFS, ORR, TTTF, CA19-9 response, safety

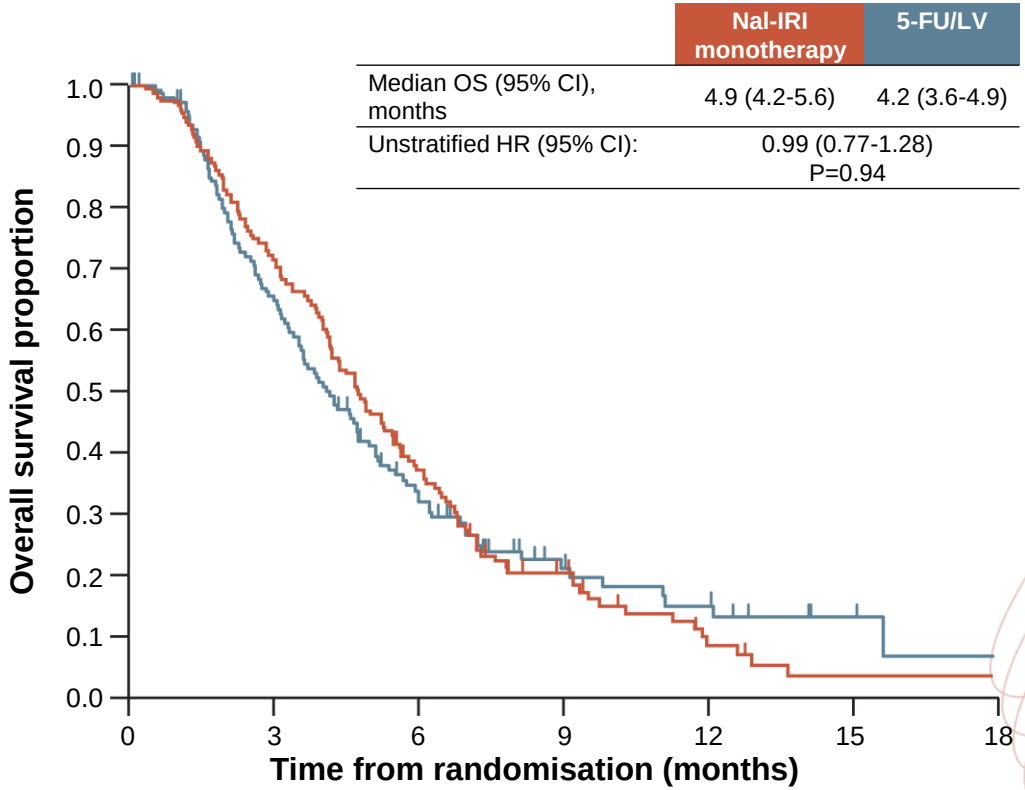
[a] Study was amended to add the Nal-IRI + 5-FU/LV arm once safety data on the combination became available. Only those patients enrolled in the 5FU/LV arm after the amendment (N=119), were used as the control for the combination arm

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

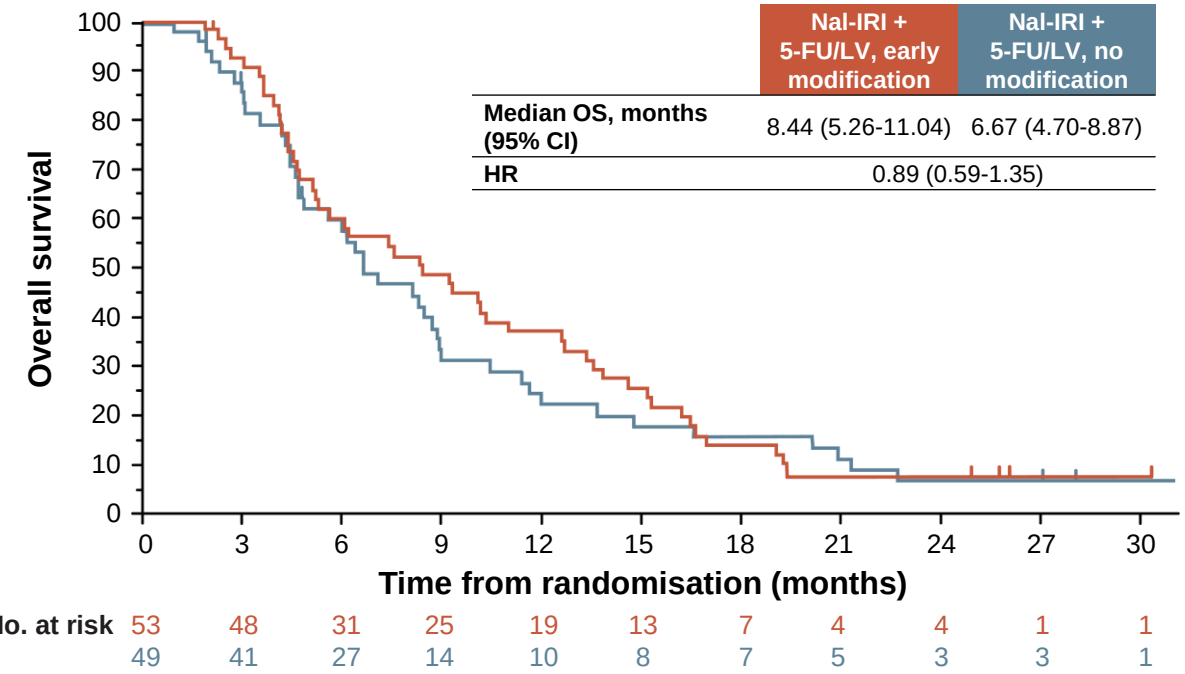
	Nal-IRI + 5-FU/LV	5-FU/LV
	Nal-IRI dose delay	
Median overall survival, mos	8.4 (N=49)	4.2 (N=105)
Hazard ratio (95% CI)	0.66 (0.46, 0.94)	
	Nal-IRI dose reduction	
Median overall survival, mos	9.4 (N=34)	4.2 (N=105)
Hazard ratio (95% CI)	0.58 (0.38, 0.88)	

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

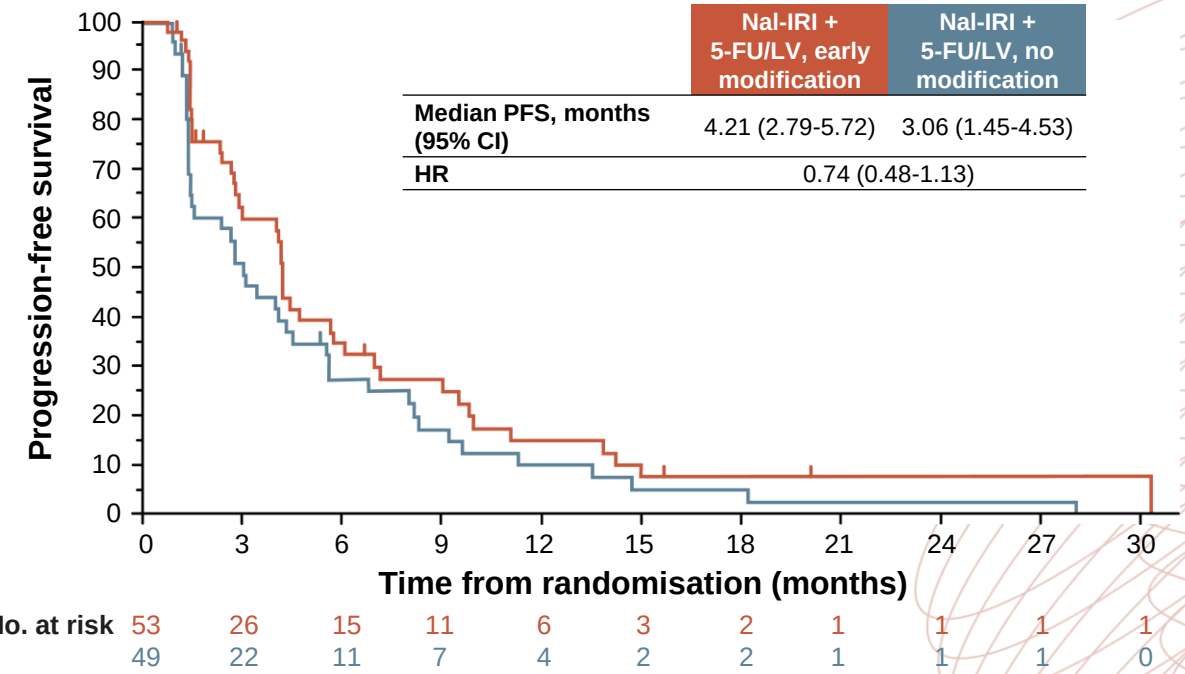
NAPOLI-1: DOSE MODIFICATIONS OF NAL-IRI + 5-FU/LV

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)	

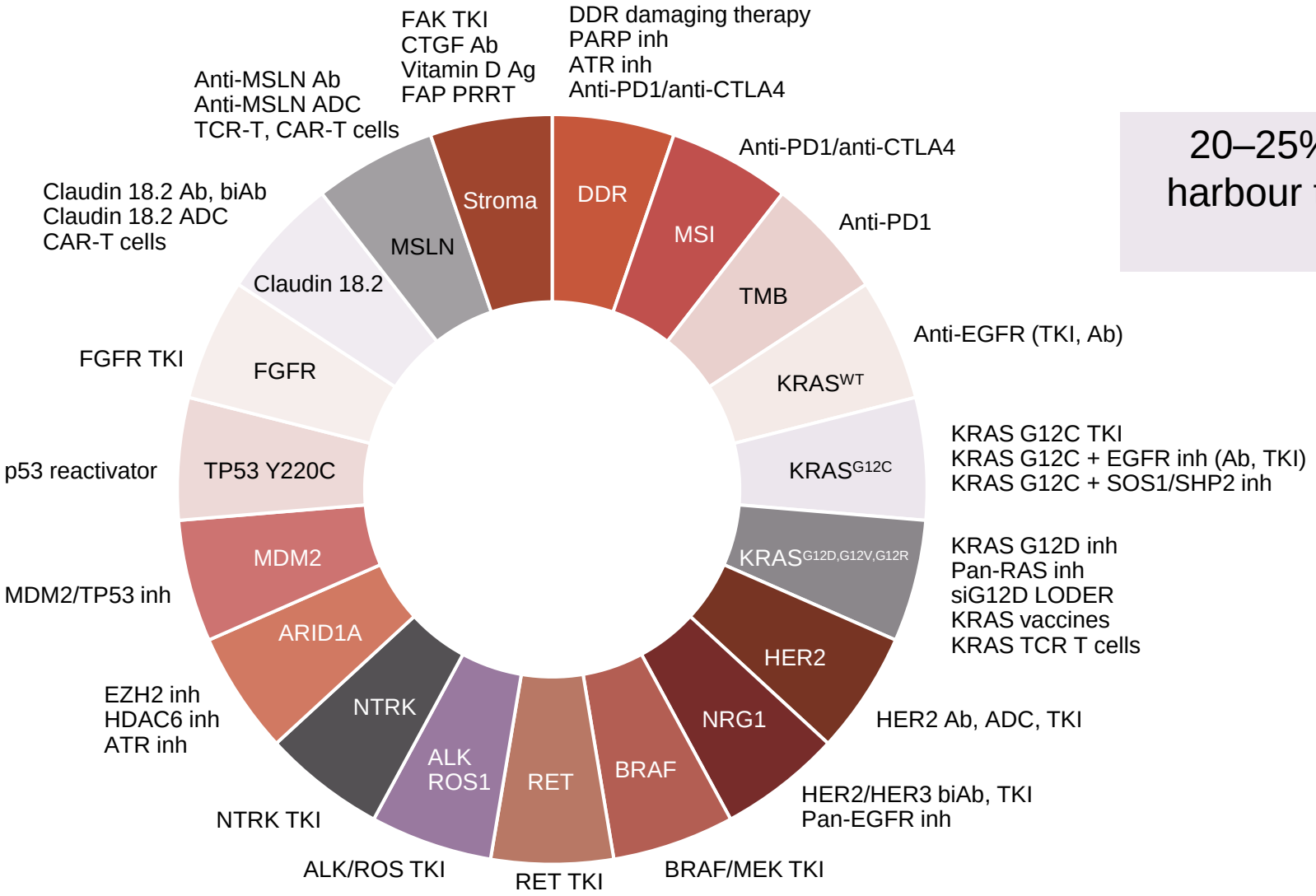
No. at risk											
Nal-IRI + 5-FU/LV, early modification	53	26	15	11	6	3	2	1	1	1	1
Nal-IRI + 5-FU/LV, no modification	49	22	11	7	4	2	2	1	1	1	0

- 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

POTENTIAL MOLECULAR TARGETS IN PDAC



20–25% of PDAC patients harbour targetable molecular alterations

ADC, antibody-drug conjugate; ALK, anaplastic lymphoma kinase; ARID1A, AT-rich interaction domain 1A; ATR, ataxia telangiectasia and Rad3-related protein; (bi)Ab, (bi-specific) antibody; BRAF, B-Raf proto-oncogene serine/threonine kinase; CAR-T, chimeric antigen receptor T-cell therapy; CTLA-4; cytotoxic T-lymphocyte-associated protein 4; DDR, DNA damage repair; EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; FAP, fibroblast activation protein; FGFR, fibroblast growth factor receptor; HDAC, histone deacetylase 6; inh, inhibitor; HER2/3, human epidermal growth factor receptor 2/3; KRAS, Kirsten rat sarcoma viral oncogene homolog; MEK, mitogen-activated protein kinase kinase; MSI, microsatellite instability; MSLN, mesothelin; NRG1, neuregulin-1; NTRK, neurotrophic tyrosine receptor kinase; PARP, poly(ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PDAC, pancreatic ductal adenocarcinoma; PRRT, peptide receptor radionuclide therapy; RAS, rat sarcoma; RET, rearranged during transfection; ROS, ROS proto-oncogene receptor tyrosine kinase; siG12D LODER, small interfering RNA G12D Local Drug EluteR; TCR, T-cell receptor; TKI, tyrosine kinase inhibitor; TMB, tumour mutational burden; TP53, tumour protein p53 gene; WT, wild-type

Zhen DB, et al. Therap Adv Gastroenterol 2023;16:17562848231171456

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
- The choice of second-line therapy depends on which treatments the patient has received in the first-line setting and therefore which options are left available to them
- Treatment selection depends on several other 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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