Systemtherapie beim Pancreaskarzinom

5 Szenarien

Primärtherapie metastasiertes Pancreaskarzinom
Zweitlinientherapie metastasiertes Pancreaskarzinom
Adjuvante Therapie
Borderline resektabel / Neoadjuvant
Inoperabel, aber lokal begrenzt

St. Bernward Krankenhaus
Für Leib und Seele

Akademisches Lehrkrankenhaus für die Universität Göttingen

EV Elisabeth Vinzenz Verbund

Onkologisches Zentrum Hildesheim

Pankreaskarzinom – Leitlinien 2023

AWMF online
Das Portal der wissenschaftlichen Medizin

Leitlinienprogramm Onkologie

~~2021~~

2023

S3-Leitlinie zum exokrinen Pankreaskarzinom

Kurzversion 2.0 – Dezember 2021
AWMF-Registernummer: 032/010OL

onkopedia

2018

onkopedia leitlinien

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Pancreatic Adenocarcinoma

Version 2.2022 — December 6, 2022

NCCN.org

Pankreaskarzinom

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v56–v68, 20
doi:10.1093/annonc/mdv2

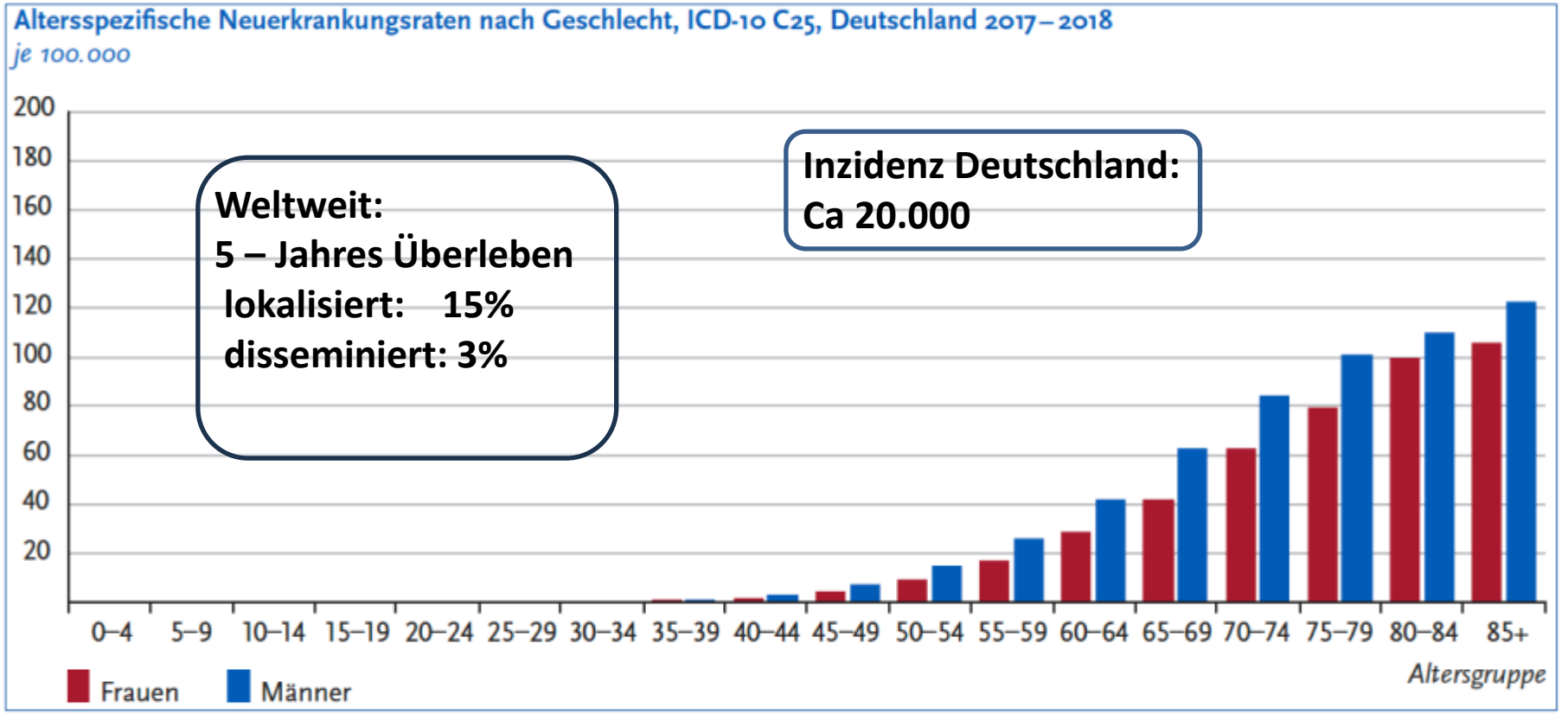
Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. Ducreux[1,2], A. Sa. Cuhna[2,3], C. Caramella[4], A. Hollebecque[1,5], P. Burtin[1], D. Goéré[6], T. Seufferlein[7], K. Haustermans[8], J. L. Van Laethem[9], T. Conroy[10] & D. Arnold[11], on behalf of the ESMO Guidelines Committee*

September 2023

~~2015~~

Pankreaskarzinom – Epidemiologie (RKI)

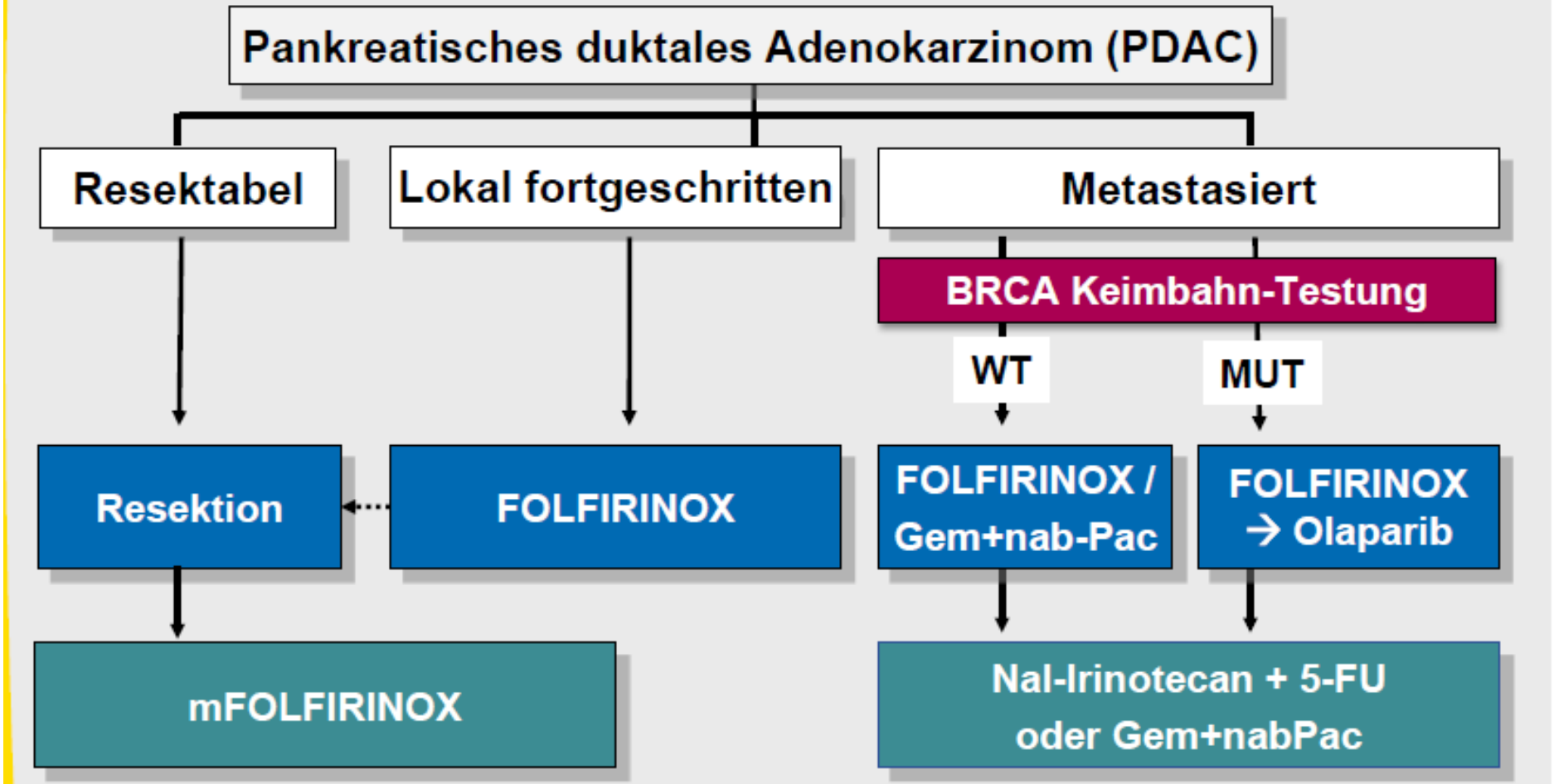


Weltweit:
5 – Jahres Überleben
lokalisiert: 15%
disseminiert: 3%

Inzidenz Deutschland:
Ca 20.000

www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2021/kid_2021_c25_bauchspeicheldruese.pdf?__blob=publicationFile

State of the Art



F. Lordick – Onko Update 2022

Szenario 1

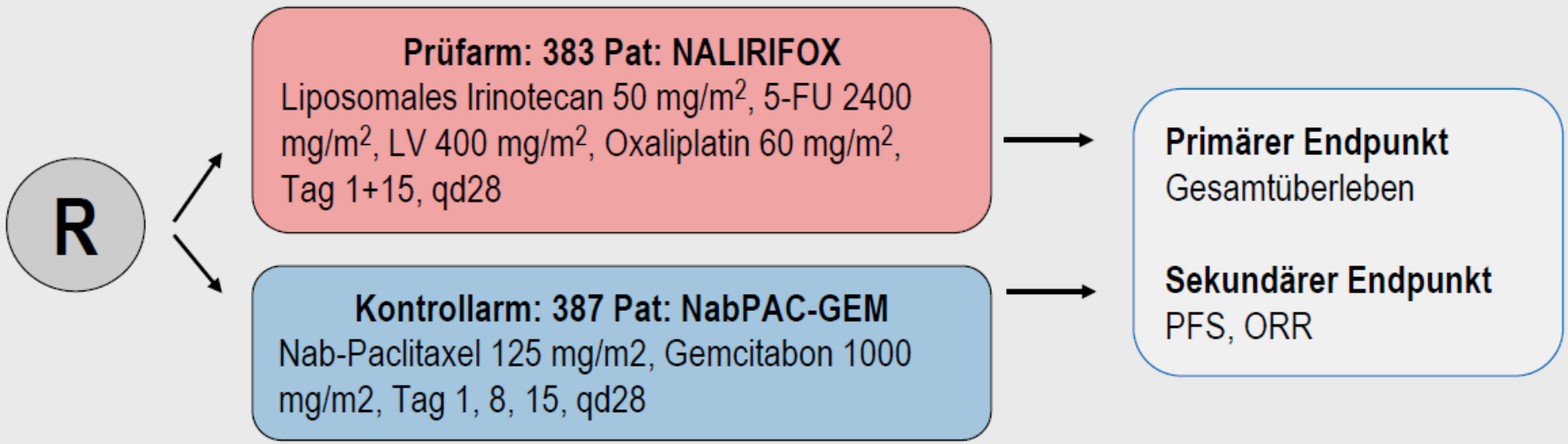
- **Primärtherapie metastasiertes Pancreaskarzinom**

THERAPIE	PALLIATIV
	Erstlinie med. ÜL
„keine“	(3-5 Mo)
Gemcitabin*	**5,7-7,2 Mo**
5-FU	4,4 Mo
5FU / Folinsäure	
5-FU/Erlotinib	**6,4 Mo**
Gemcitabin/Capecitabin	8,4 Mo
nab-Paclitaxel/Gemcitabin	**8,5 – 9,2 Mo**
nab-Paclitacel/5-FU/Folinsäure#	((12,0 Mo))
FOLFIRINOX	**11,1 Mo**
mFOLFIRINOX	(?)
NALIRIFOX	**11,1 Mo**

Stadium IV – Standard 1st-line

Wainberg Z et al., ASCO GI 2023, LBA 661

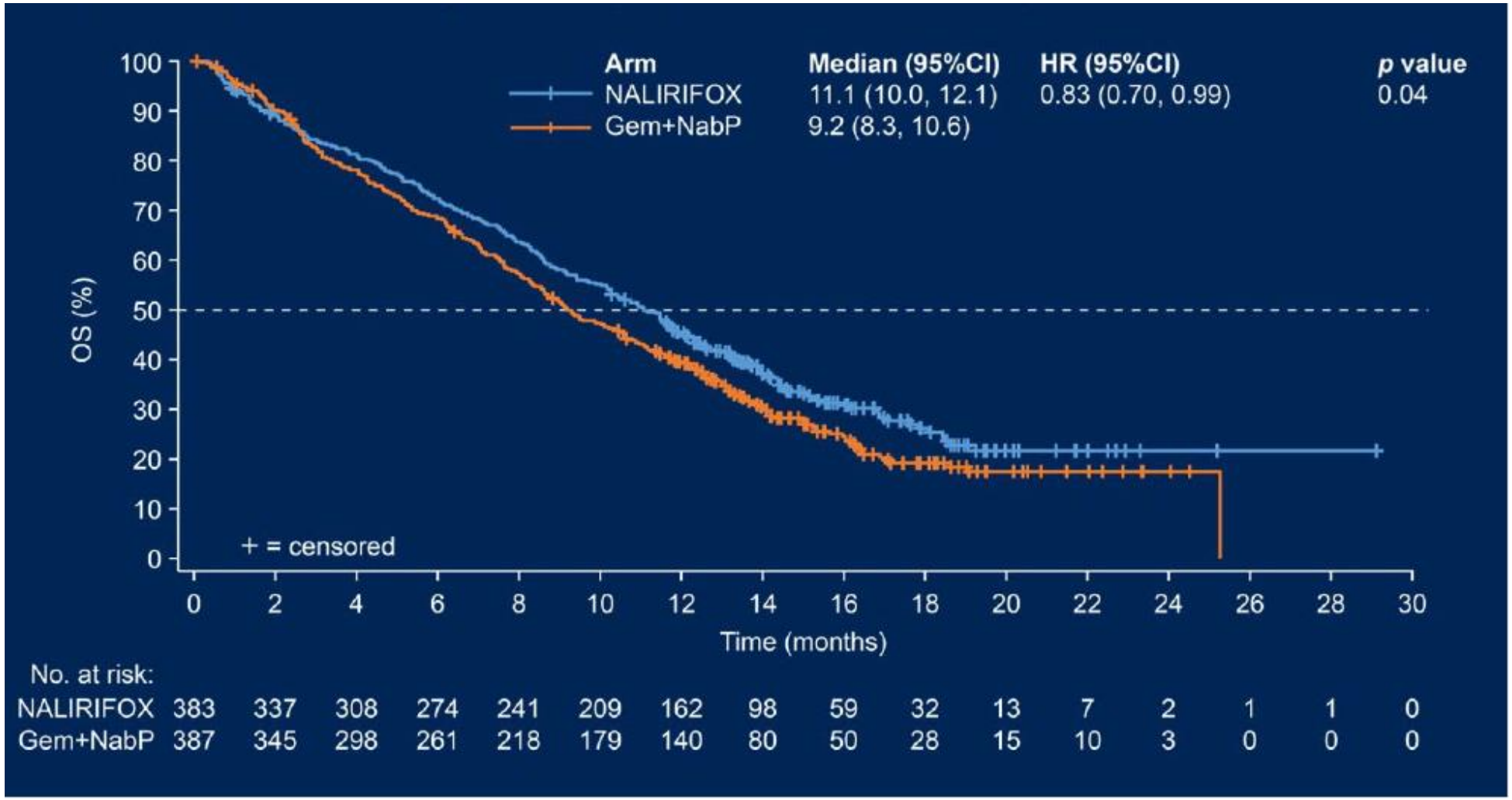
NAPOLI-3 Studie



770 Patienten:Innen mit histologisch gesichertes PDAC, Stadium IV, nicht vorbehandelt

NAPOLI-3 Ergebnisse

	NALIRIFOX	nabPAC-GEM	
Überleben, Mon	**11,1**	**9,2**	**HR 0,84, p=0,04**
PFS, Mon	**7,4**	**5,6**	**HR 0,7, p=0,0001**
Responserate, %	41,8	36,2	
TRAEs G3/4 ≥10%			
Diarrhoe	20,3%	4,5%	
Nausea	11,9%	2,6%	
Hypokaliämie	15,1%	4,0%	
Anämie	10,5%	17,4%	
Neutropenie	14,1%	25,4%	



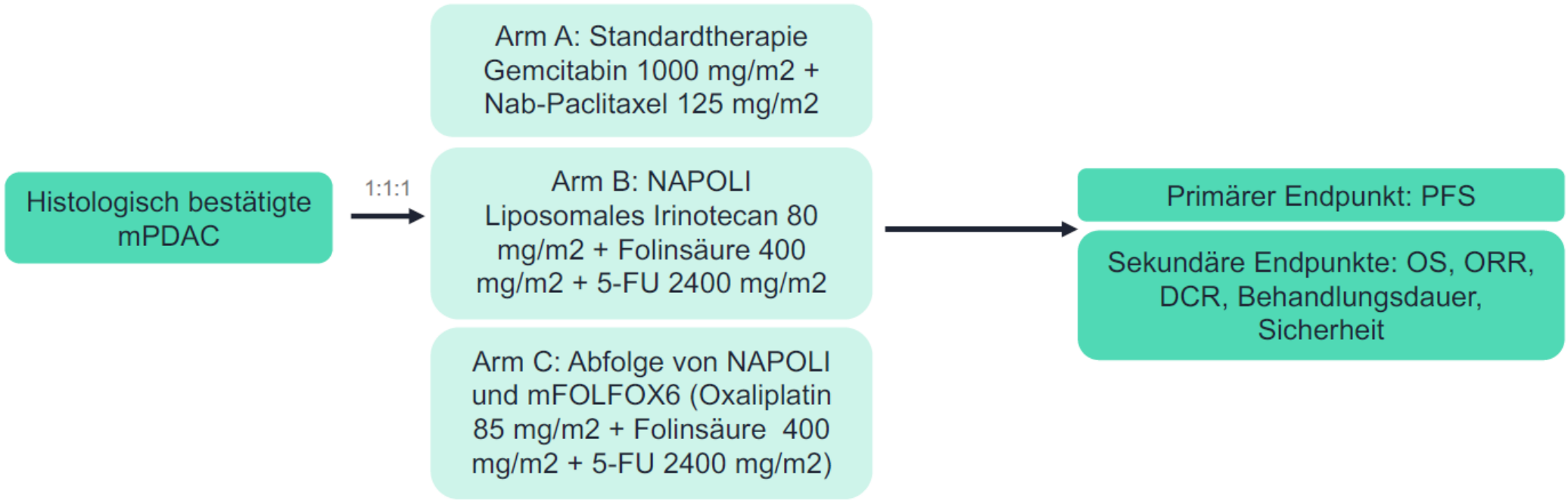
POSITIVE STUDIE OS

ASCO 2023

FOOTPATH: A randomized, open-label phase-2 study of liposomal irinotecan + 5-FU and folinic acid (NAPOLI) versus sequential NAPOLI and mFOLFOX6 versus gemcitabine/nab-paclitaxel in treatment-naïve metastatic pancreatic cancer (mPDAC)

Benedikt Westphalen et al.

FOOTPATH Studie | Studiendesign



FOOTPATH – Studie

Sequenzielle Chemotherapie im Stadium IV

	Arm A (Gem/nabPac)	Arm B (NAPOLI)	Arm C (NAPOLI/FOLFOX)
Median PFS, Mo	4,3	3,1 (HR 1,1224, p=0,2123)	6,0 (HR 0,864, p=0,0720)
Behandlungsdauer, (Mo, Median)	3,5	2,0	3,7
Median OS, (Mo; 95 % CI)	8,7 (7,1-11,9)	7,9 (6,6-12,3)	11,0 (8,4-13,6) (HR 0,879, p=0,154)

	Arm A (Gem/nabPac)		Arm B (NAPOLI)		Arm C (NAPOLI/FOLFOX)	
AE/SAE	Gesamt	Grad 3-4	Gesamt	Grad 3-4	Gesamt	Grad 3-4
Neutropenie	30,3%	**21,3%**	9,3%	5,8%	13,3%	6,7%
Diarrhoe	38,2%	3,4%	58,1%	**11,6%**	52,2%	**12,2%**
Erbrechen	21,3%	1,1%	27,9%	**4,7%**	28,9%	**4,4%**
Periphere Neuropathie	40,4%	6,7%	14%	n/a	34,4%	3,3%

ESMO 2023

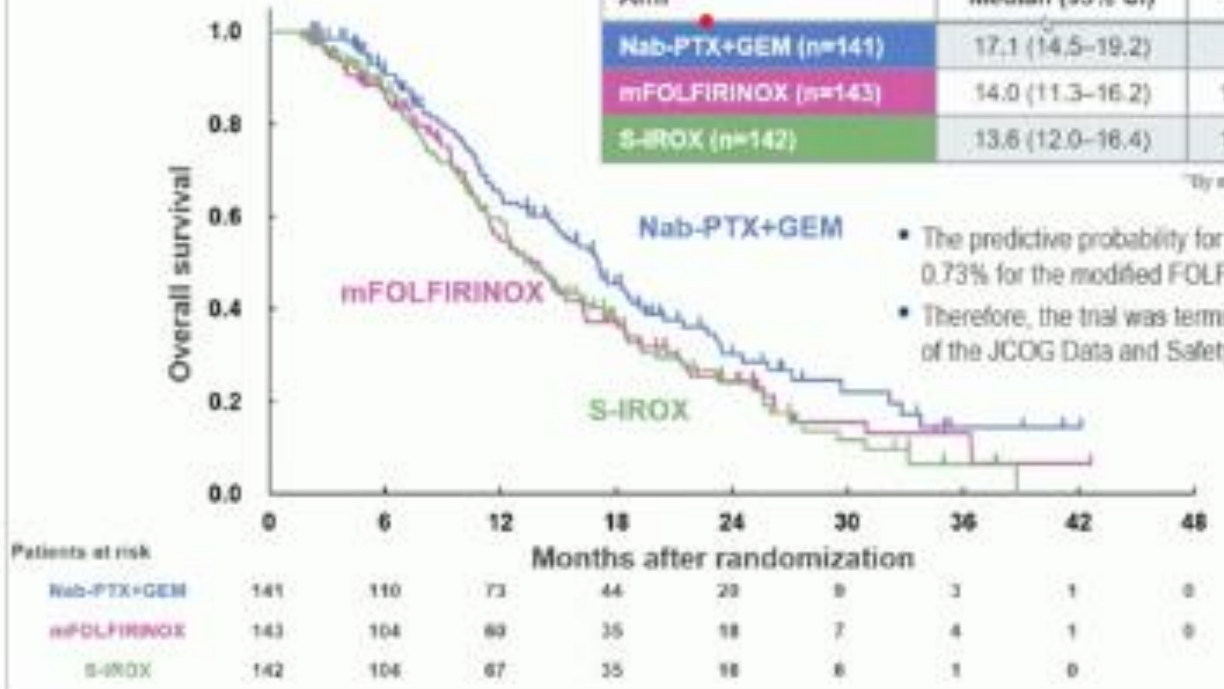
Metastasiertes Pancreascarcinom

nab-Pacli/Gem versus mFOLFIRINOX versus S-IROX

Overall Survival (Interim Analysis: Mar 2023)

Arm	Median (95% CI)	HR (95% CI)*1	One-sided p*2
Nab-PTX+GEM (n=141)	17.1 (14.5–19.2)	–	
mFOLFIRINOX (n=143)	14.0 (11.3–16.2)	1.31 (0.97–1.77)	0.9622
S-IROX (n=142)	13.6 (12.0–16.4)	1.35 (1.00–1.82)	0.9768

*1By stratified Cox regression model, *2By stratified log-rank test



- The predictive probability for achieving superiority at the final analysis was 0.73% for the modified FOLFIRINOX arm and 0.48% for the S-IROX arm.
- Therefore, the trial was terminated for futility based on the recommendation of the JCOG Data and Safety Monitoring Committee.

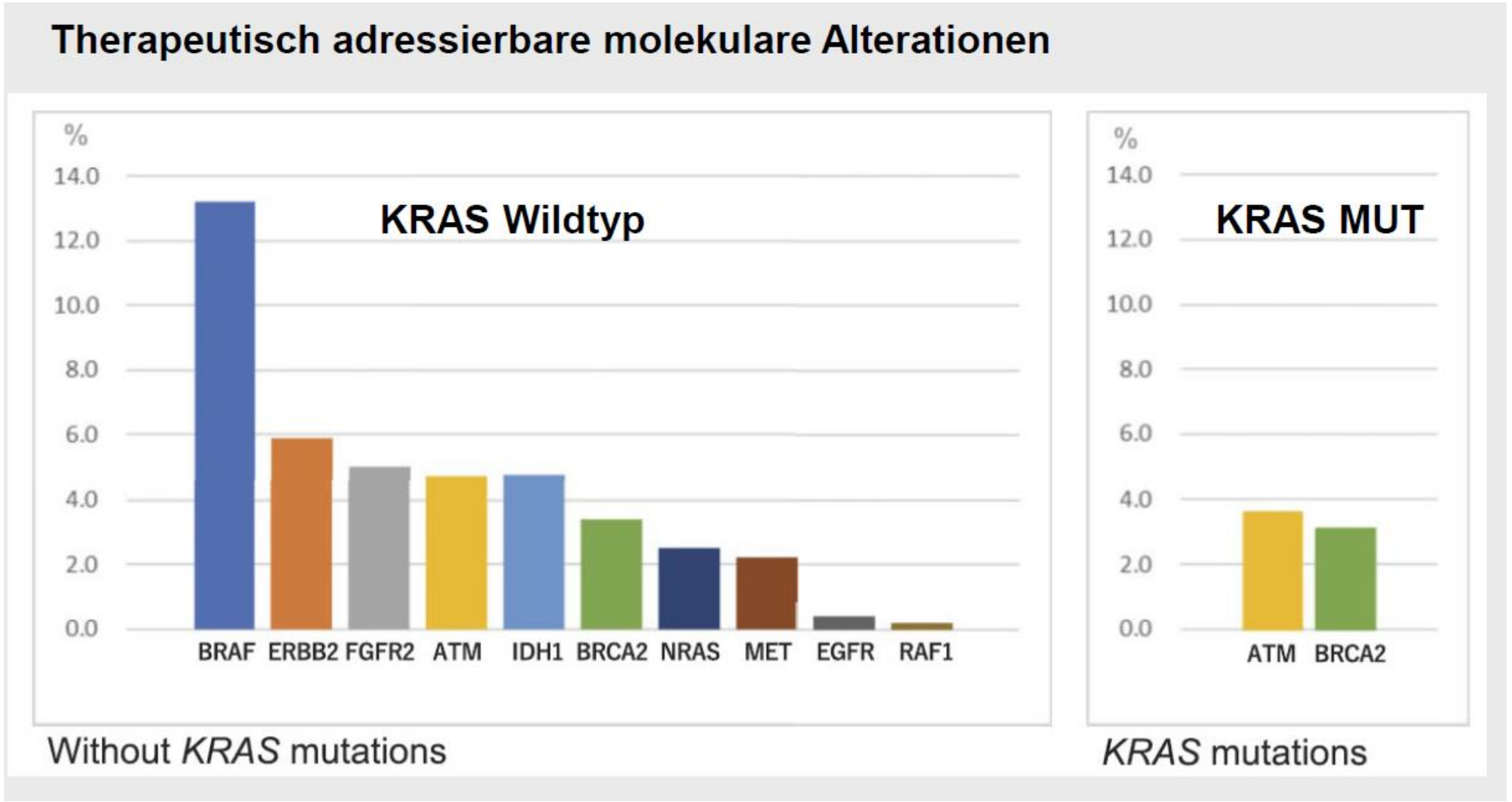
POSITIVE STUDIE OS

Molekulare Therapieansätze

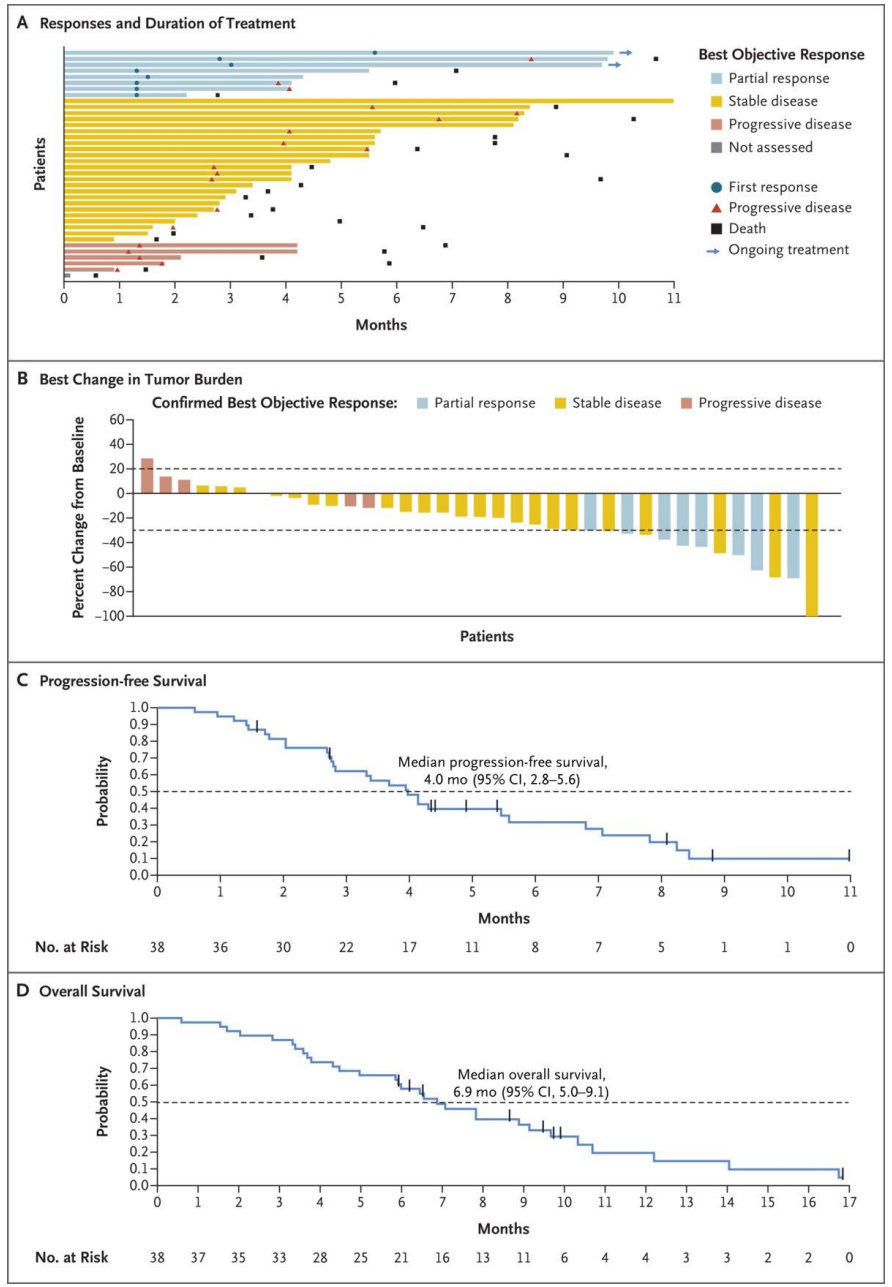
- **90% aktivierende K-RAS Mutation**
- 1-2% K-RAS G12C — Sotorasib, Adagrasib

- **10 % K-RAS- Wildtyp:**
- BRAF-Mutation V600 E — Dabrafenib and Trametinib
- Mikrosatelliten — Immuncheckpoint Therapie
- NTRK — Larotrectinib, Entrectinib
- FGFR2 – Mutation — Erdafitinib

Molekulare Therapieansätze



Sotorasib in *KRAS* p.G12C–Mutated Advanced Pancreatic Cancer



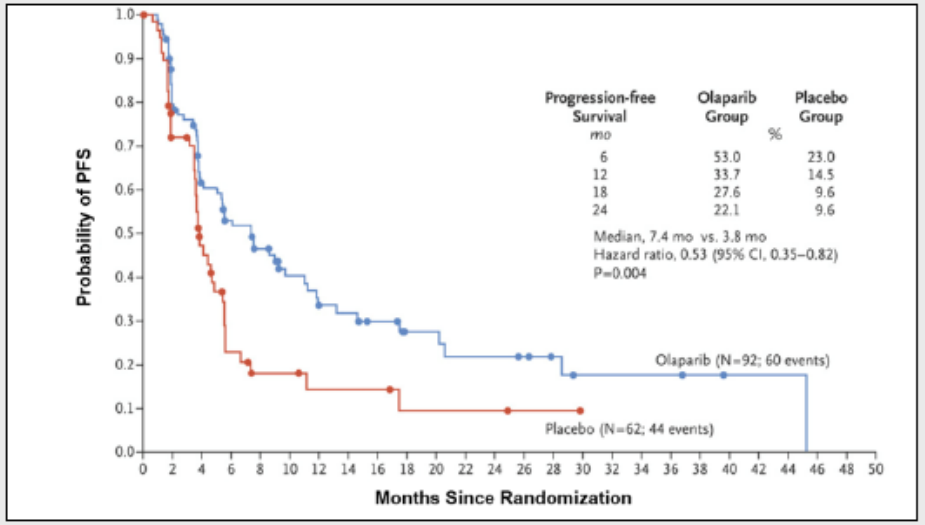
POLO: BRACmut Pankreas-CA

Metastatic PDAC
Germline BRCA(+)
Prior Platinum ≥ 4m
ECOG 0-1
N= 145

RANDOMIZE

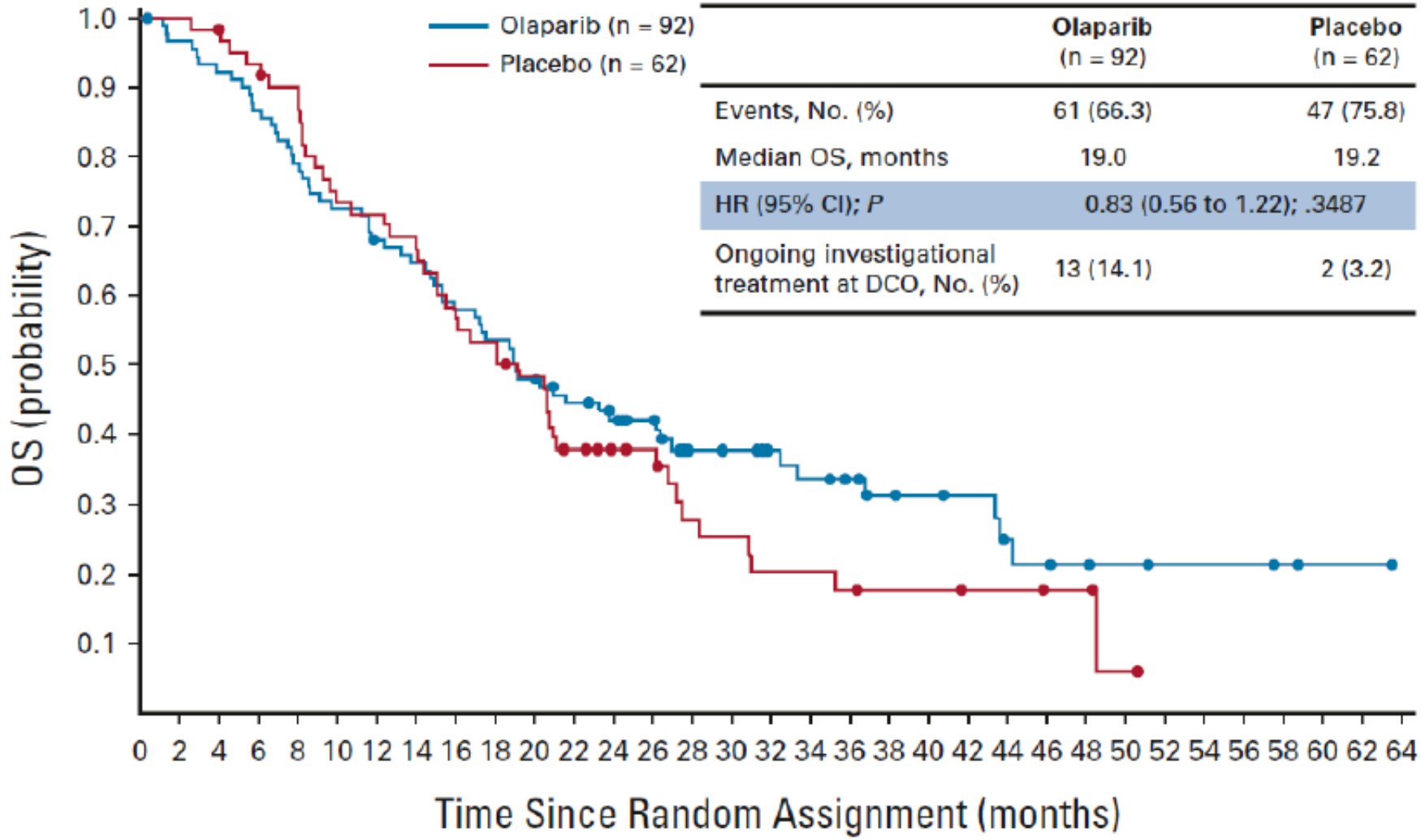
Olaparib
300 mg PO BID

Placebo



Golan T et al. N Engl J Med. 2019 Jul 25;381(4):317-327

POSITIVE STUDIE PFS



	Olaparib (n = 92)	Placebo (n = 62)
Events, No. (%)	61 (66.3)	47 (75.8)
Median OS, months	19.0	19.2
HR (95% CI); *P*	0.83 (0.56 to 1.22); .3487	
Ongoing investigational treatment at DCO, No. (%)	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						

Szenario 2

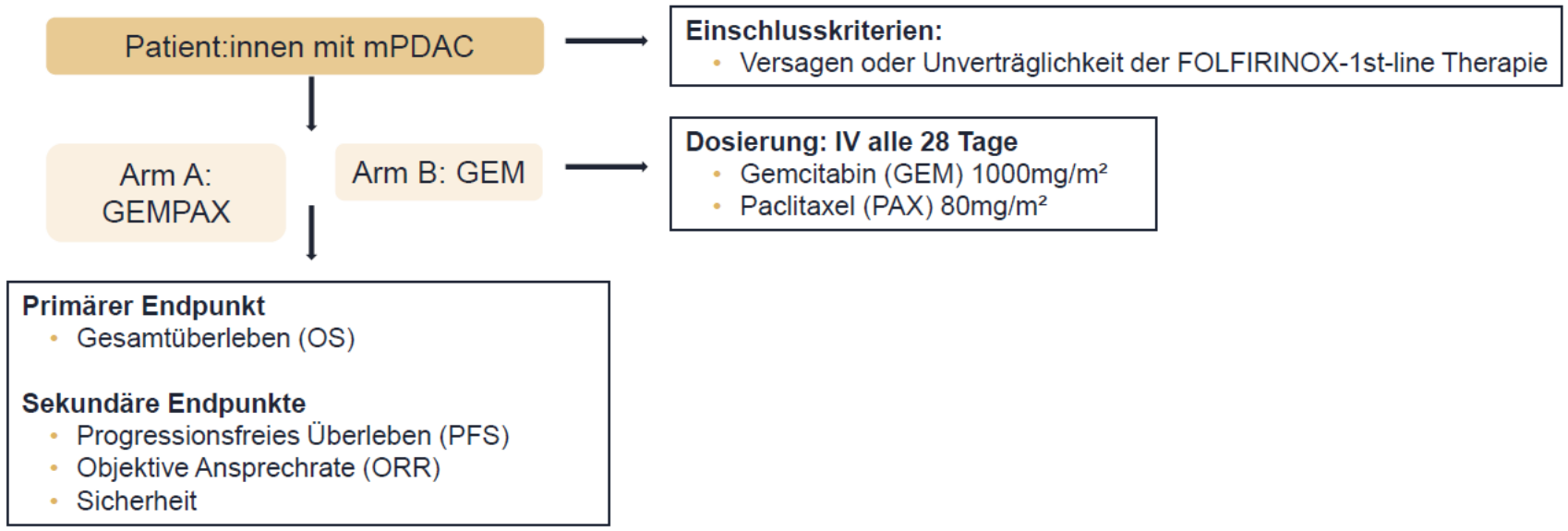
- **Zweitlinientherapie metastasiertes Pancreascarzinom**

- **Gem**
- **Gem / nabPaclitaxel**
- **liposomales Irinotecan / 5- FU**
- **OFF**

ESMO 2022

LBA60: Evaluation of gemcitabine and paclitaxel versus gemcitabine alone after FOLFIRINOX failure or intolerance in metastatic Pancreatic Ductal Adenocarcinoma: Results of the randomized phase III PRODIGE 65 – UCGI 36 – GEMPAX UNICANCER study.

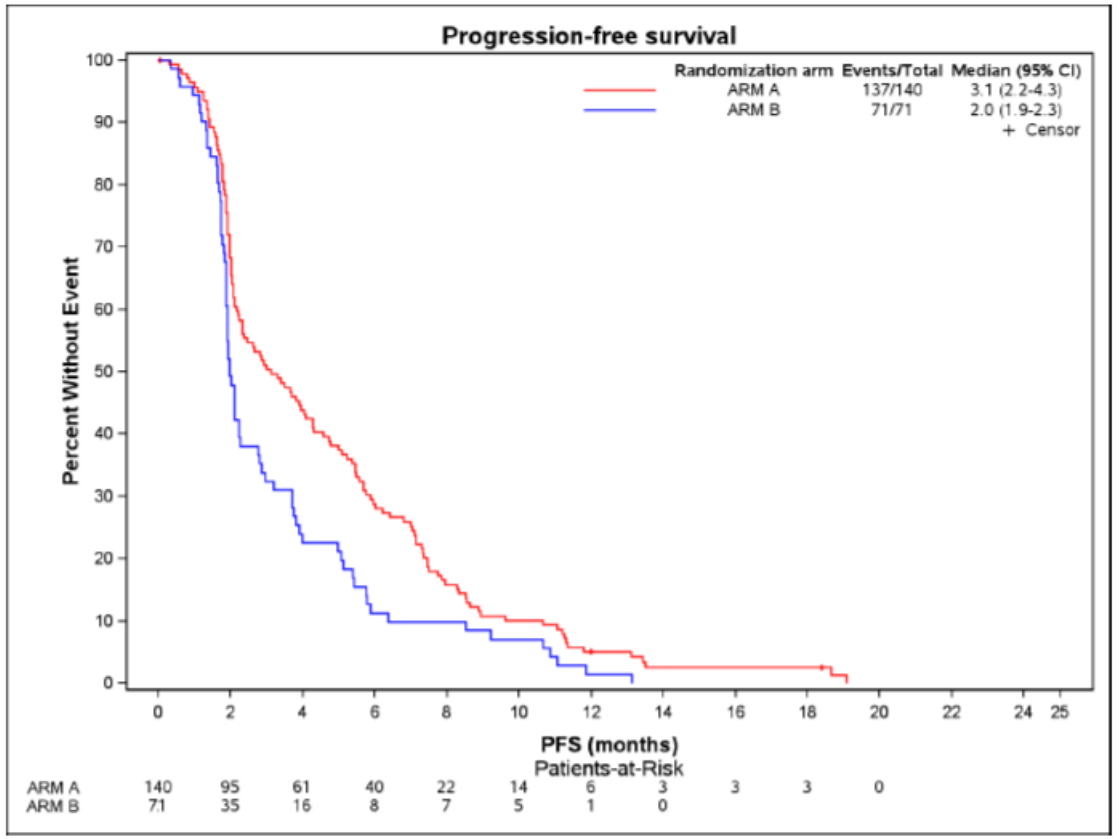
C. de la Fouchardiere et al., Lyon, Frankreich



- 208 PFS events / 211 pts (99.6% maturity)

- **Median PFS (95% CI)**
- **Arm A: 3.1 months (2.2 – 4.3)**
- **Arm B: 2.0 months (1.9 – 2.3)**

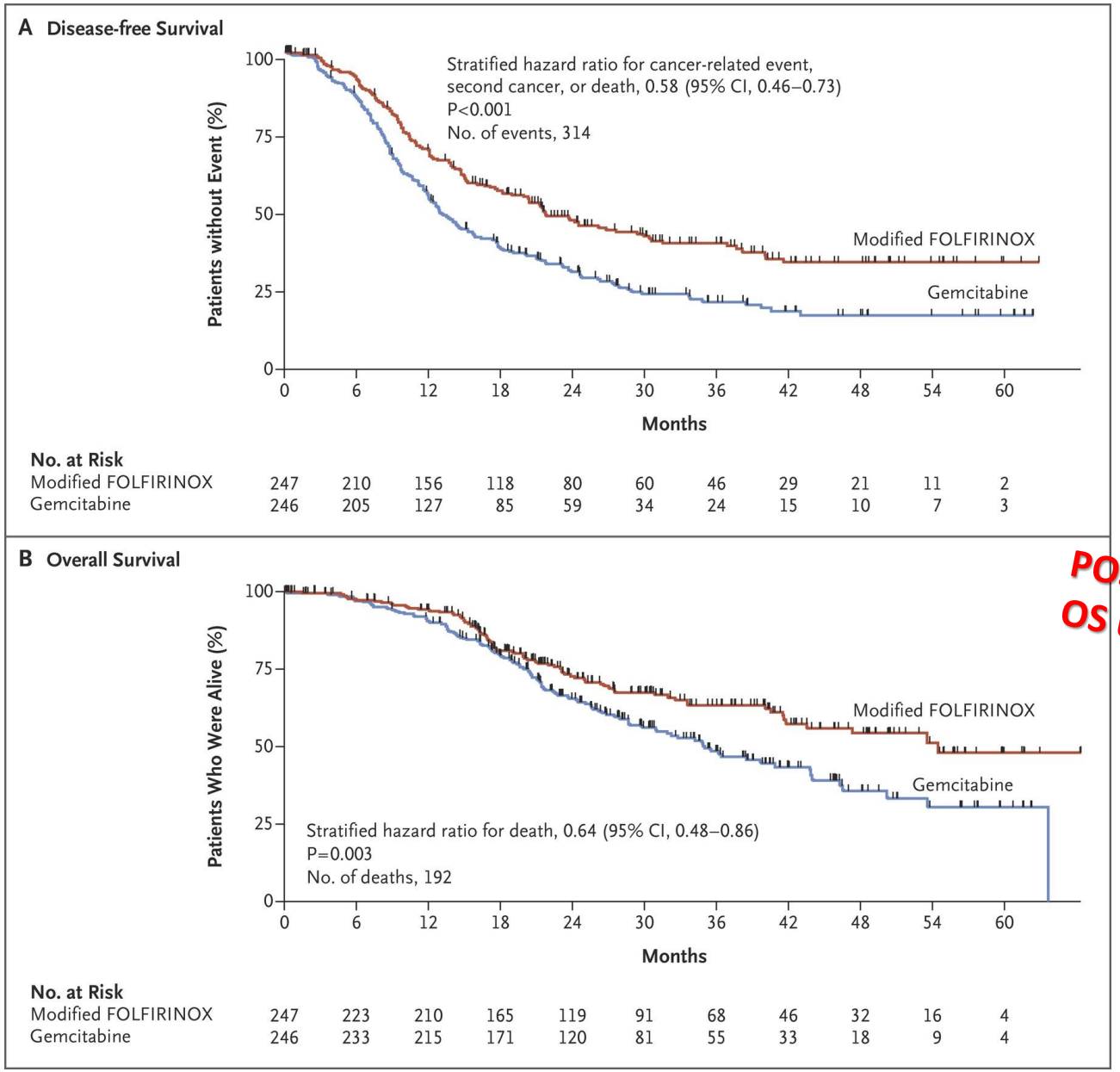
- **Stratified HR = 0.64** (95% CI, 0.47-0.89)



POSITIVE STUDIE PFS

Szenario 3

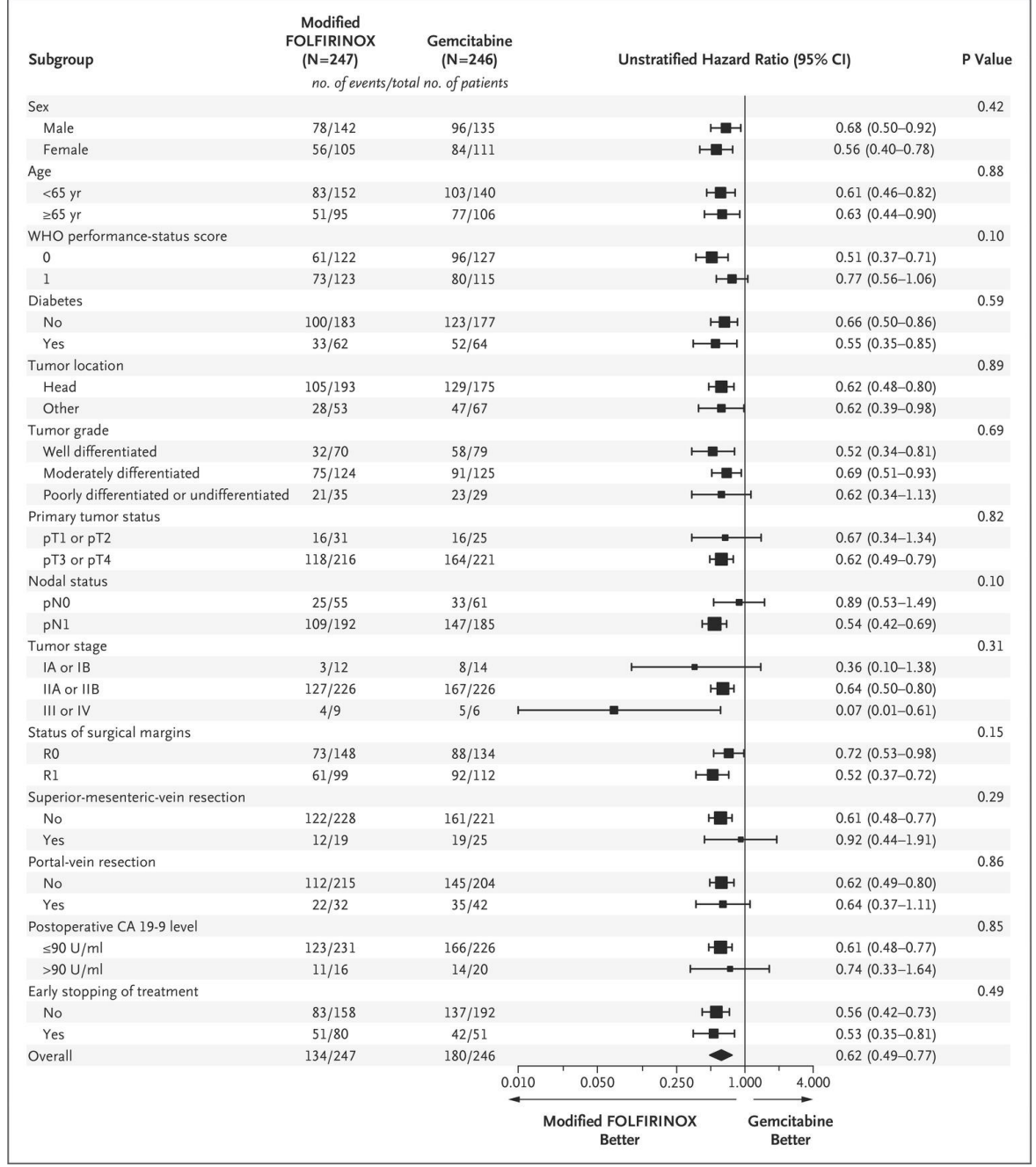
- **Adjuvante Therapie**



POSITIVE STUDIE
OS und DFS

mFOLFIRINOX versus Gemcitabine

T. Conroy and Others N Engl J Med 2018; 379:2395-2406



Forest Plot of the Treatment Effect on Disease-free Survival in Subgroup Analyses.

RCT: Five-Year Outcomes of FOLFIRINOX vs Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

POPULATION

277 Males, 216 Females

Age <79 y; WHO 0-1; <12 wk after R0 or R1 resection of pancreatic cancer; CA 19-9 <180 U/mL

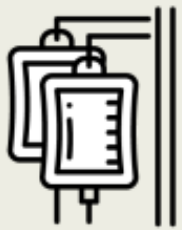
Mean age, 62 y

SETTINGS / LOCATIONS

77 Hospitals, (France, Canada)

INTERVENTION

493 Patients randomized



247 Adjuvant mFOLFIRINOX
Oxaliplatin, 85 mg/m²; leucovorin, 400 mg/m²; irinotecan, 150-180 mg/m²; and fluorouracil, 2400 mg/m² for 24 wk (12 cycles)

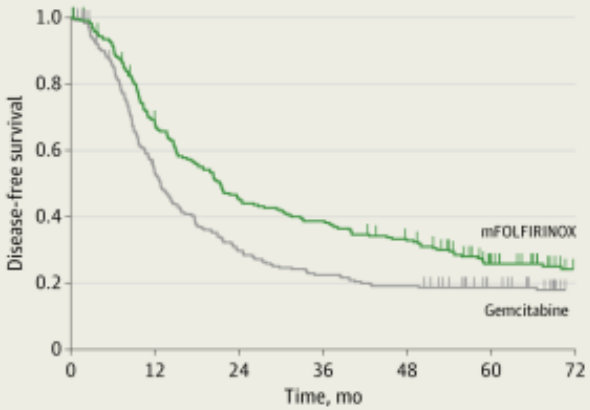
246 Adjuvant gemcitabine
Gemcitabine, 1000 mg/m², on days 1, 8, and 15 every 28 d for 24 wk (6 cycles)

PRIMARY OUTCOME

Disease-free survival (DFS) calculated from the date of randomization to first cancer-related event, second cancer, or death from any cause

FINDINGS

Median DFS was longer for patients receiving mFOLFIRINOX compared with those receiving gemcitabine



Median DFS

mFOLFIRINOX: 21.4 mo
Gemcitabine: 12.8 mo
HR, 0.66; 95% CI, 0.54-0.82; *P*<.001

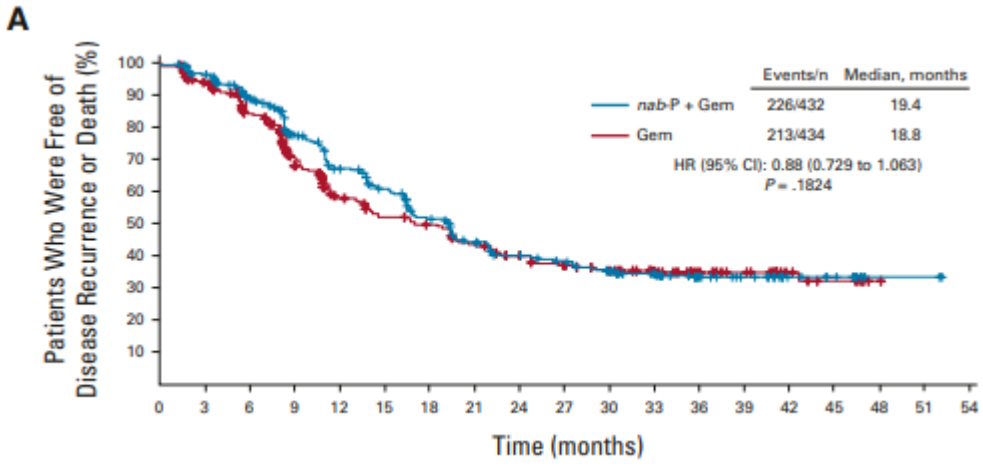
Conroy T, Castan F, Lopez A, et al; for the Canadian Cancer Trials Group and the Unicancer-GI-PRODIGE Group. Five-year outcomes of FOLFIRINOX vs gemcitabine as adjuvant therapy for pancreatic cancer: a randomized clinical trial. *JAMA Oncol*. Published online September 1, 2022. doi:10.1001/jamaoncol.2022.3829

Adjuvante Therapie mit Gem / nab Paclitaxel ?

ADAPT Studie

Gem / nab Paclitaxel versus Gem

J Clin Oncol 41: 2007 2023



NEGATIVE STUDIE DFS

Szenario 4

- **Borderline resektabel / Neoadjuvant**
- **Borderline:**

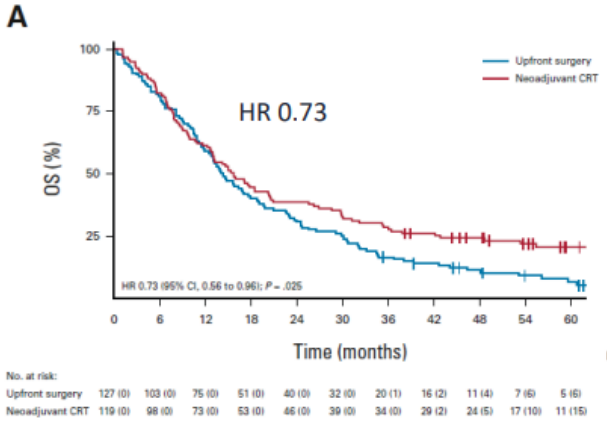
nach anatomischen Kriterien potenziell resektabel, Ca 19-9 <500, ECOG 0 oder 1

Resektabilität	A (anatomisch)	B (biologisch)	C (konditional)
Resektabel (R, resectable)	R-Typ A	Neg: R-Typ A	Neg: R-Typ A
		Pos: BR-Typ B	Pos: BR-Typ C
Grenzwertig-resektabel (BR, borderline resectable)	BR-Typ A	Neg: BR-Typ A	Neg: BR-Typ A
		Pos: BR-Typ AB	Pos: BR-Typ AC
Lokal-fortgeschritten (LA, locally advanced)	LA-Typ A	Neg: LA-Typ A	Neg: LA-Typ A
		Pos: LA-Typ AB	Pos: LA-Typ AC

Abkürzungen:
A: „anatomical": Verhältnisse zu den Gefäßen
B: „biological": CA19-9 > 500 IU/ml oder befallen regionäre Lymphknoten (PET-CT oder bioptisch)
C: „conditional": ECOG-Performance-Status 2 oder höher
Neg: negativ für die o.g. Parameter
Pos: positiv für die o.g. Parameter
Weitere Kombinationen möglich: z.B. BR-BC, BR-ABC, LA-ABC etc.

Neoadjuvante Therapie beim operablen Pancreaskarzinom ?

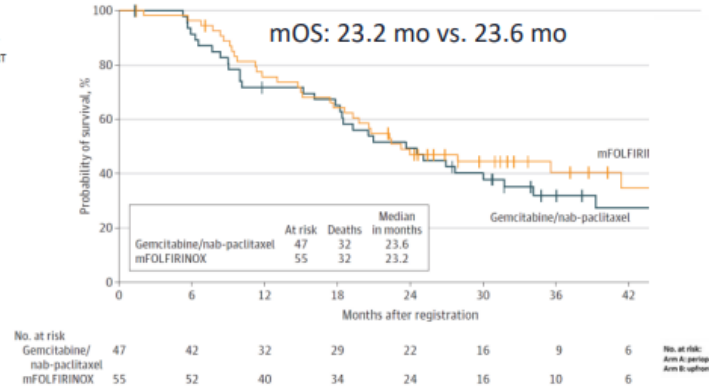
PREOPANC



Versteijne, JCO 2022

Neoadjuvante Radiochemotherapie mit Gemcitabine

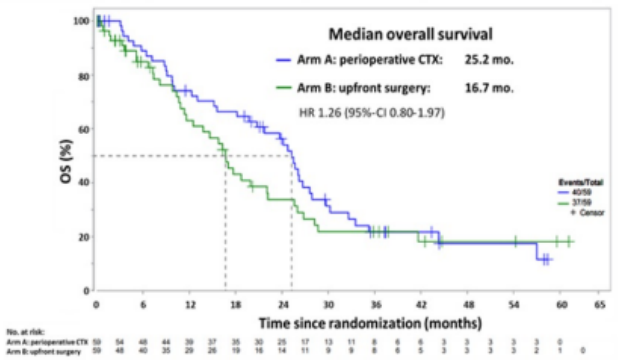
SWOG 1505



Sohal et al., JAMA Oncol 2021

Perioperative Chemotherapie Gem/nabPaclitaxel oder mFOLFIRINOX

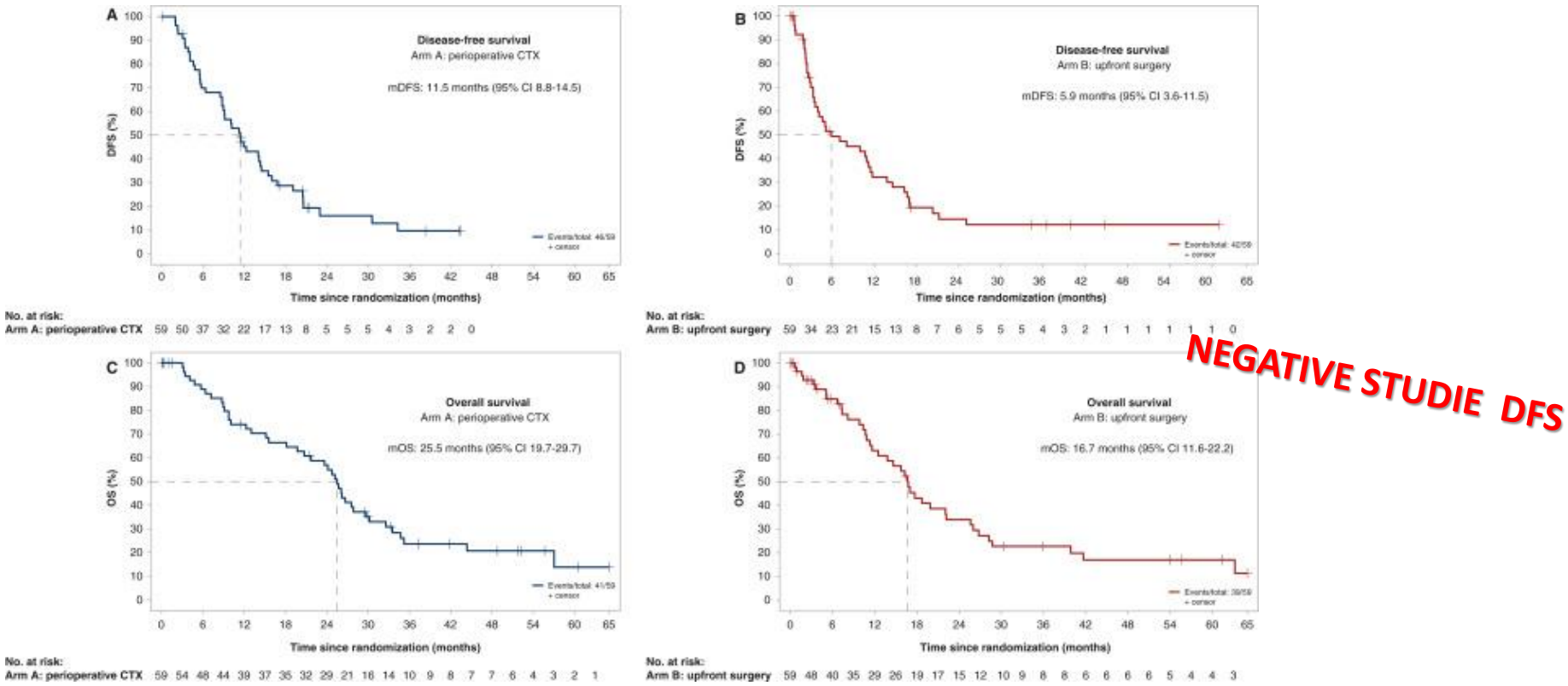
NEONAX



Seufferlein et al., Annals Oncology 2022

Prä-OP 2 Zyklen Gem/nab-Paclitaxel gefolgt von 4 Zyklen post OP *versus* Adjuvant Gem/nabPaclitaxel

Perioperative or only adjuvant gemcitabine plus nab-paclitaxel for resectable pancreatic cancer (NEONAX)—a randomized phase II trial of the AIO pancreatic cancer group



NEGATIVE STUDIE DFS

Perioperative or only adjuvant gemcitabine plus nab-paclitaxel for resectable pancreatic cancer:

- Did not meet its primary endpoint in either arm of the study (DFS rate at 18 months of 55% in the mITT population).
- Showed that pre-operative chemotherapy can be completed by the majority of patients (90%).
- Showed an mOS as a secondary endpoint of 25.5 months in arm A (perioperative) and 16.7 months in arm B (upfront surgery).
- Gemcitabine and nab-paclitaxel were safe and well tolerated both in the perioperative as well as the adjuvant setting

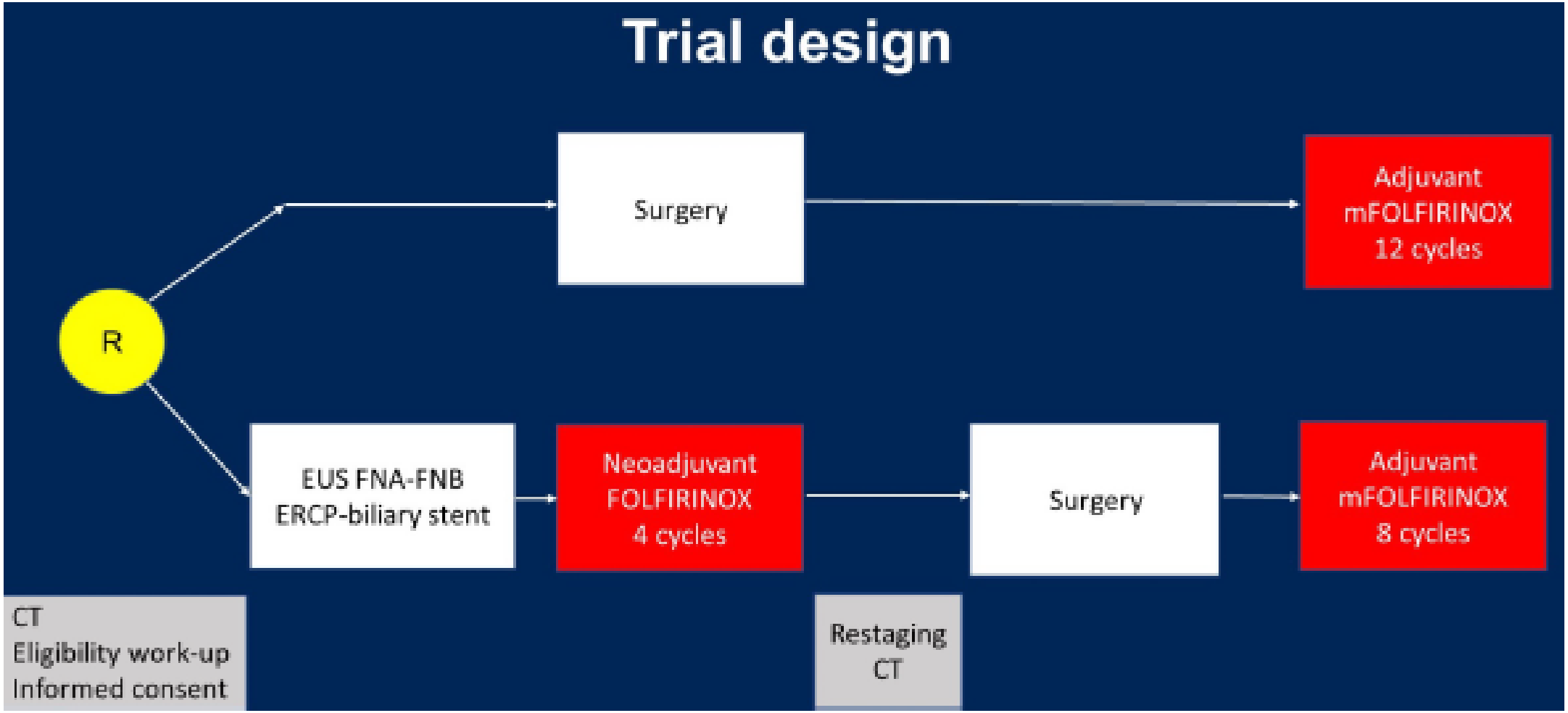
2023 ASCO ANNUAL MEETING

Short-course neoadjuvant FOLFIRINOX versus upfront surgery for resectable pancreatic head cancer -

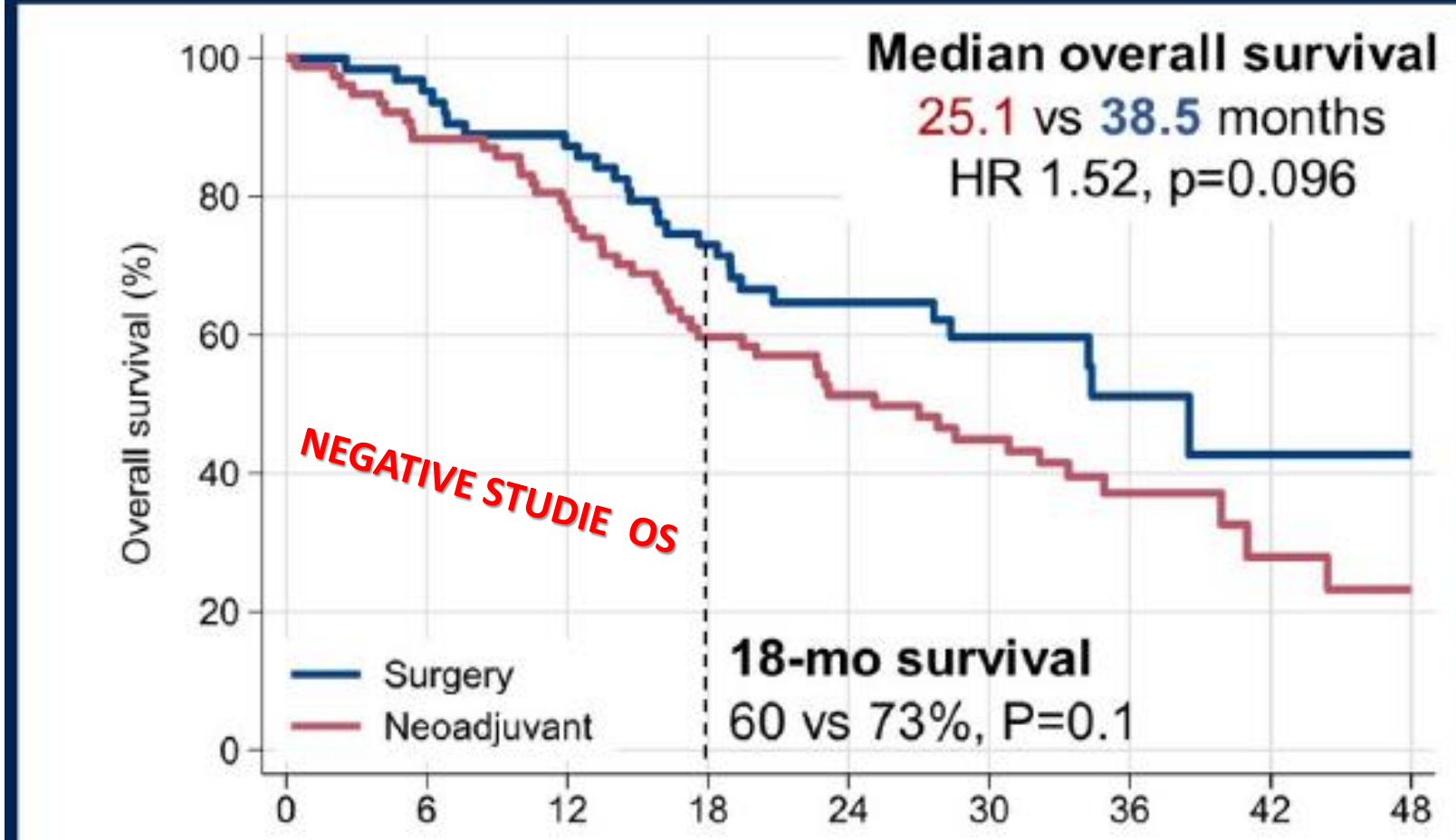
A multicenter randomized phase-2 trial (NORPACT-1)

KJ Labori, SO Bratlie, C Biörserud, B Björnsson, EA Bringeland, N Elander, JE Grønbech, J Haux, O Hemmingsson, LS Nymo, P Pfeiffer, V Sallinen, E Sparrelid, K Søreide, B Tingstedt, C Verbeke, L Klint, S Dueland, and K Lassen for the **NORPACT-1 study group**

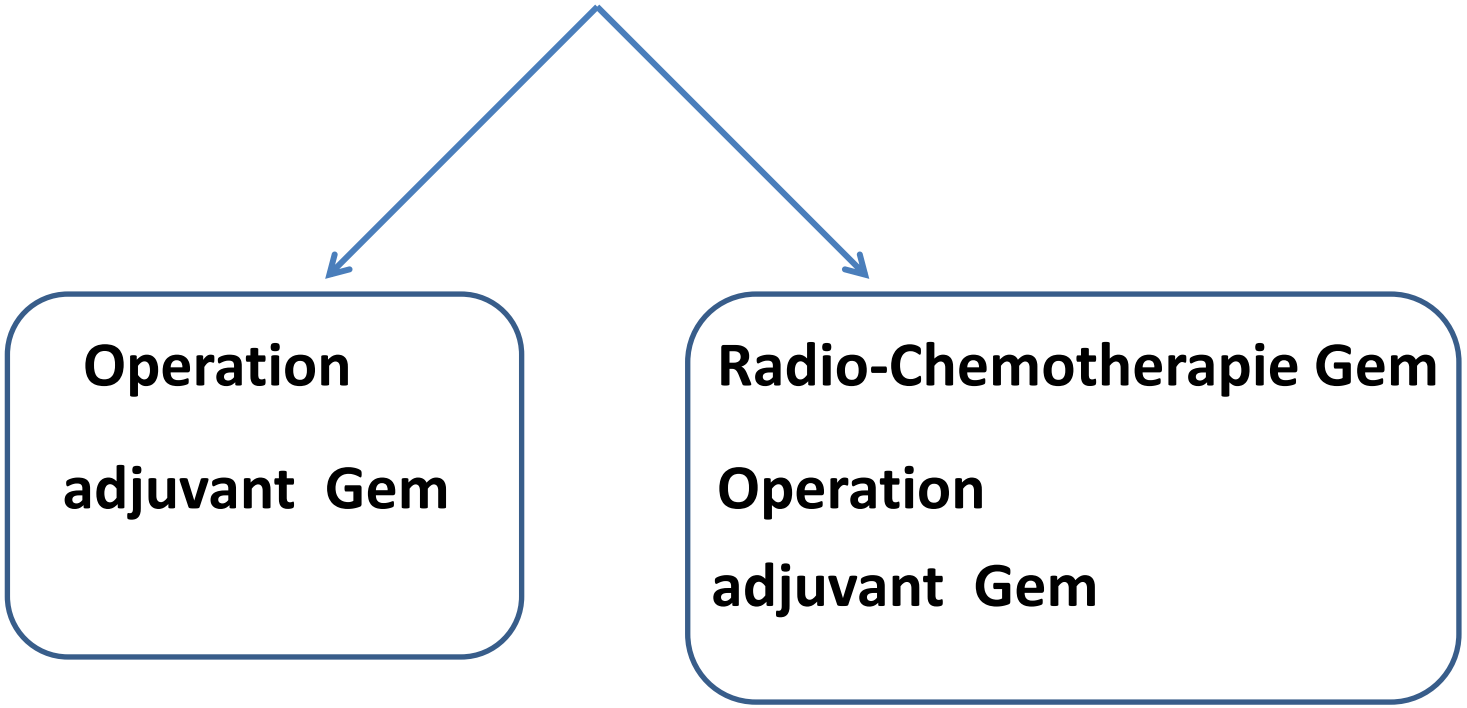
PRESENTED BY: Knut Jørgen Labori, Dept. of HPB Surgery, Oslo University Hospital and University of Oslo, Norway


Trial design
Surgery
Adjuvant
mFOLFIRINOX
12 cycles
R
EUS FNA-FNB
ERCP-biliary stent
Neoadjuvant
FOLFIRINOX
4 cycles
Surgery
Adjuvant
mFOLFIRINOX
8 cycles
CT
Eligibility work-up
Informed consent
Restaging
CT

Intention to treat



Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial



Journal of Clinical Oncology 40, no. 11 (April 10, 2022) 1220-1230.

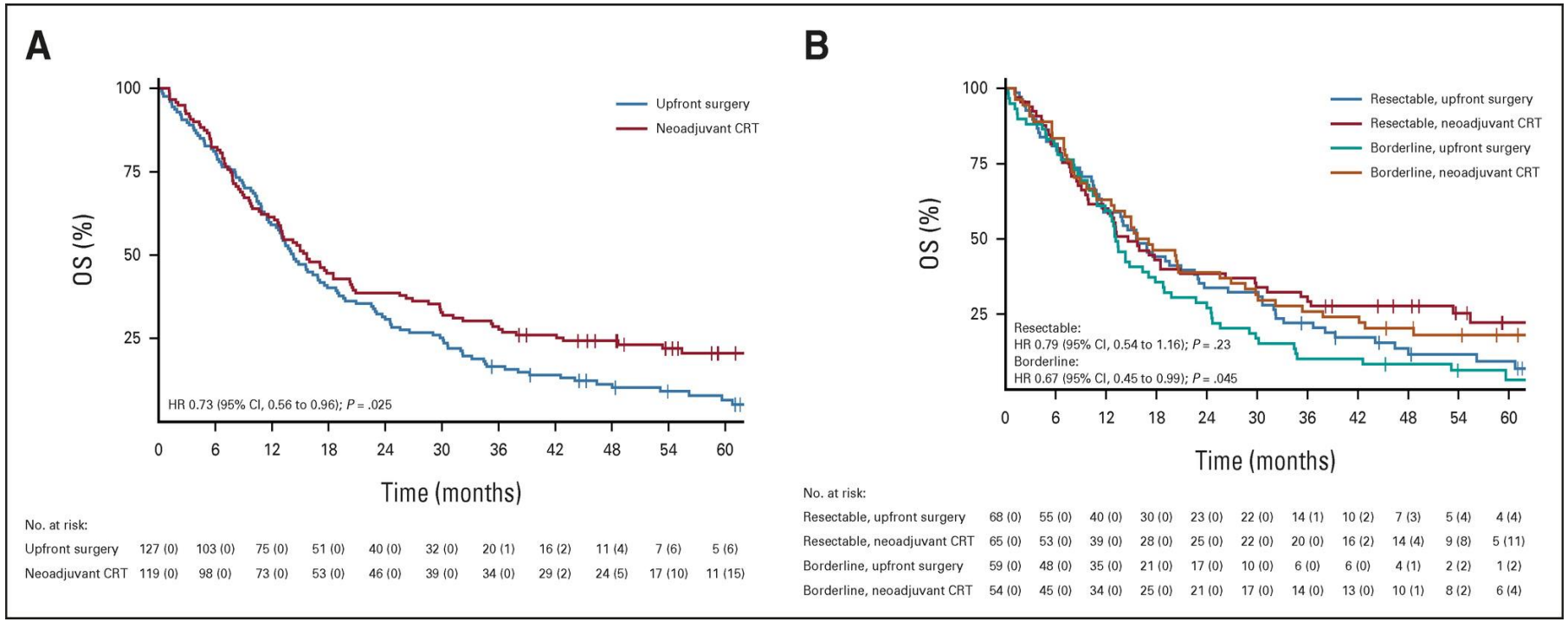


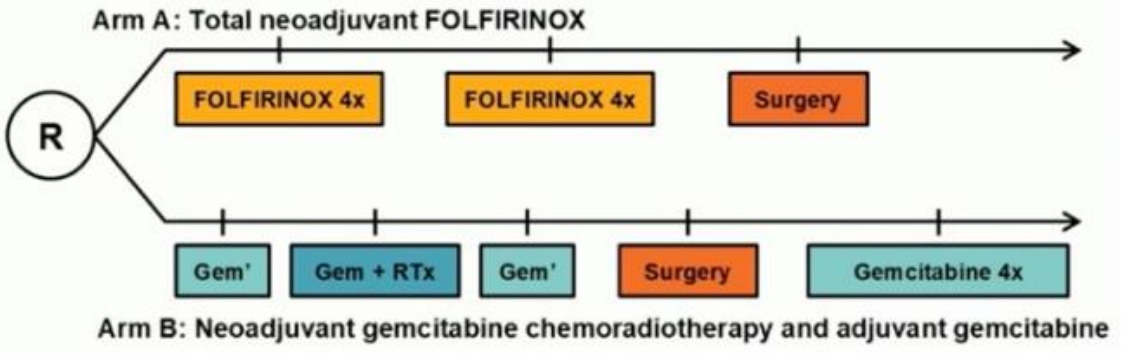
FIG 2. Kaplan-Meier estimates of OS by (A) treatment group and (B) by resectability and treatment group. CRT, chemoradiotherapy; HR, hazard ratio; OS, overall survival.

POSITIVE STUDIE OS

Published in: Eva Versteijne; Jacob L. van Dam; Mustafa Suker; Quisette P. Janssen; Karin Groothuis; Janine M. Akkermans-Vogelaar; Marc G. Besselink; Bert A. Bonsing; Jeroen Buijsen; Olivier R. Busch; Geert-Jan M. Creemers; Ronald M. van Dam; Ferry A. L. M. Eskens; Sebastiaan Festen; Jan Willem B. de Groot; Bas Groot Koerkamp; Ignace H. de Hingh; Marjolein Y. V. Homs; Jeanin E. van Hooft; Emile D. Kerver; Saskia A. C. Luelmo; Karen J. Neelis; Joost Nuyttens; Gabriel M. R. M. Paardekooper; Gijs A. Patijn; Maurice J. C. van der Sangen; Judith de Vos-Geelen; Johanna W. Wilmink; Aeilko H. Zwinderman; Cornelis J. Punt; Geertjan van Tienhoven; Casper H. J. van Eijck; *Journal of Clinical Oncology* 2022 401220-1230.
DOI: 10.1200/JCO.21.02233

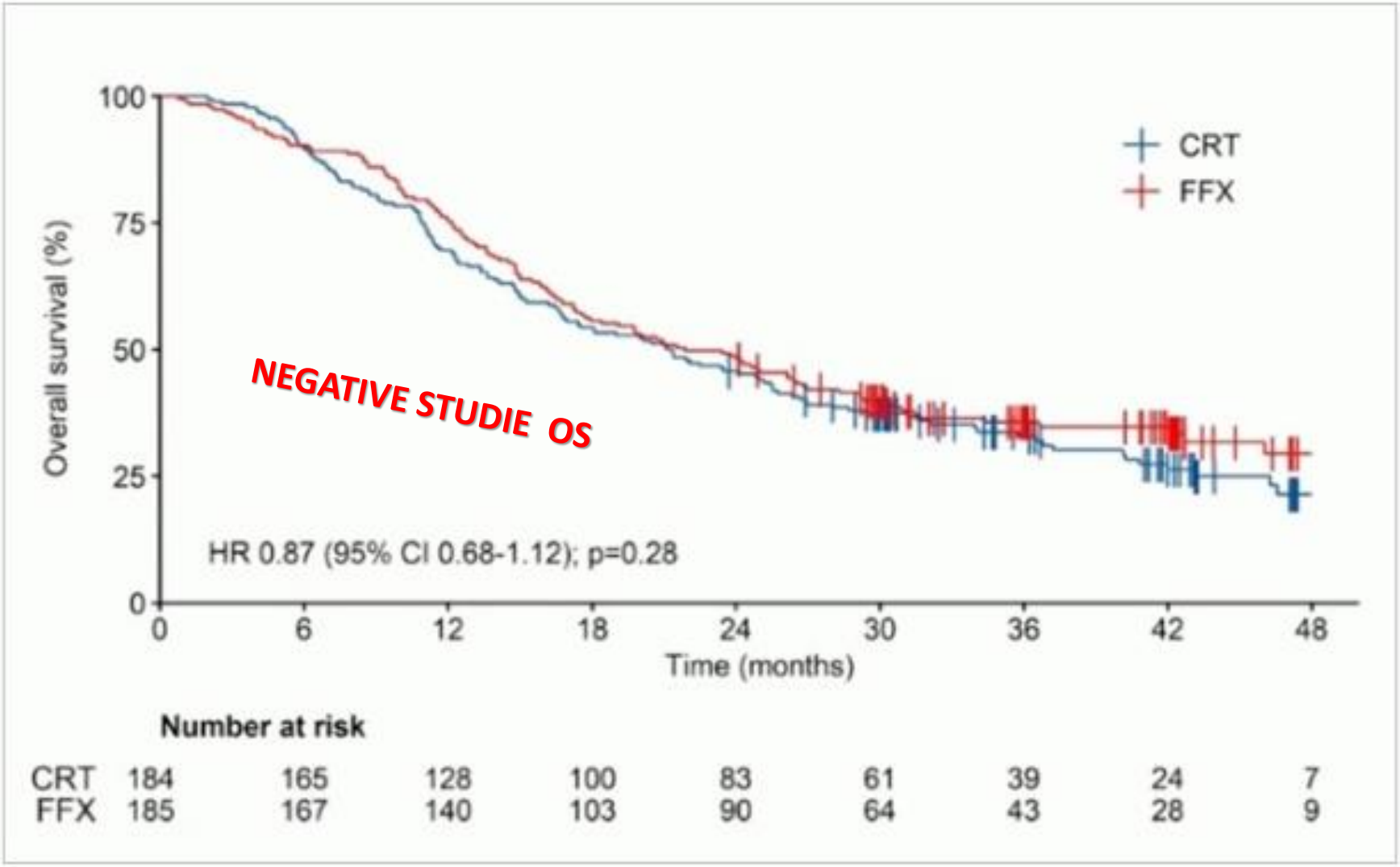
ESMO 2023
PREOPANC -2

- Nationwide phase III trial, n = 368
- (Borderline) resectable pancreatic cancer; <270 venous and <90 arterial
- Randomization 1:1



Primärer Endpunkt:
OS

Sekundäre Endpunkte:
Resektionsrate, SAE-Rate

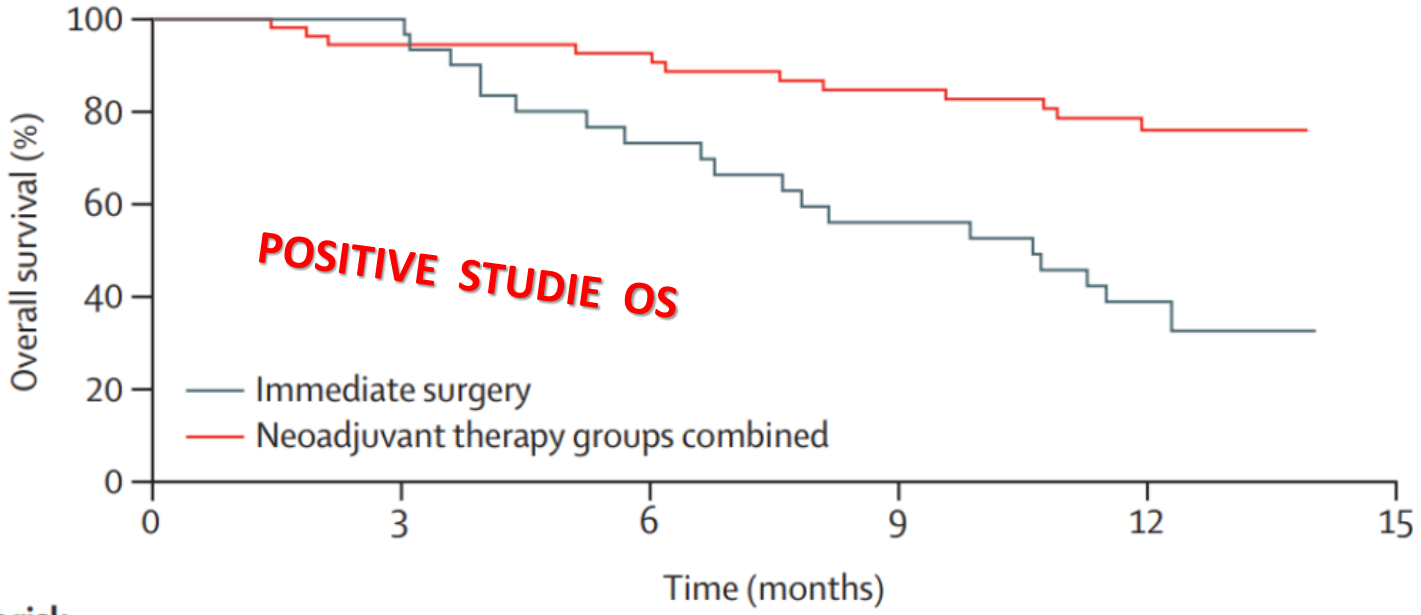

100
75
50
25
0
Overall survival (%)
CRT
FFX
NEGATIVE STUDIE OS
HR 0.87 (95% CI 0.68-1.12); p=0.28
0
6
12
18
24
30
36
42
48
Time (months)
Number at risk
CRT 184 165 128 100 83 61 39 24 7
FFX 185 167 140 103 90 64 43 28 9

	FOLFIRINOX	GEM-CRT	P-value
ypN0 ypN1 ypN2	47% 33% 20%	58% 35% 7%	<0.01
R0	61%	67%	0.28
Complete PR	11%	5%	0.26

- **No difference in OS.**
- At least 4 cycles of FOLFIRINOX in 81%.
- Resection in 77% vs 75%.
- In gem-CRT arm; 72% started adjuvant gem.
- Gem-CRT more N0; R0 and CPR were similar.
- SAE and grade 3-4 AE similar.

ESPAC-5: Borderline resectable

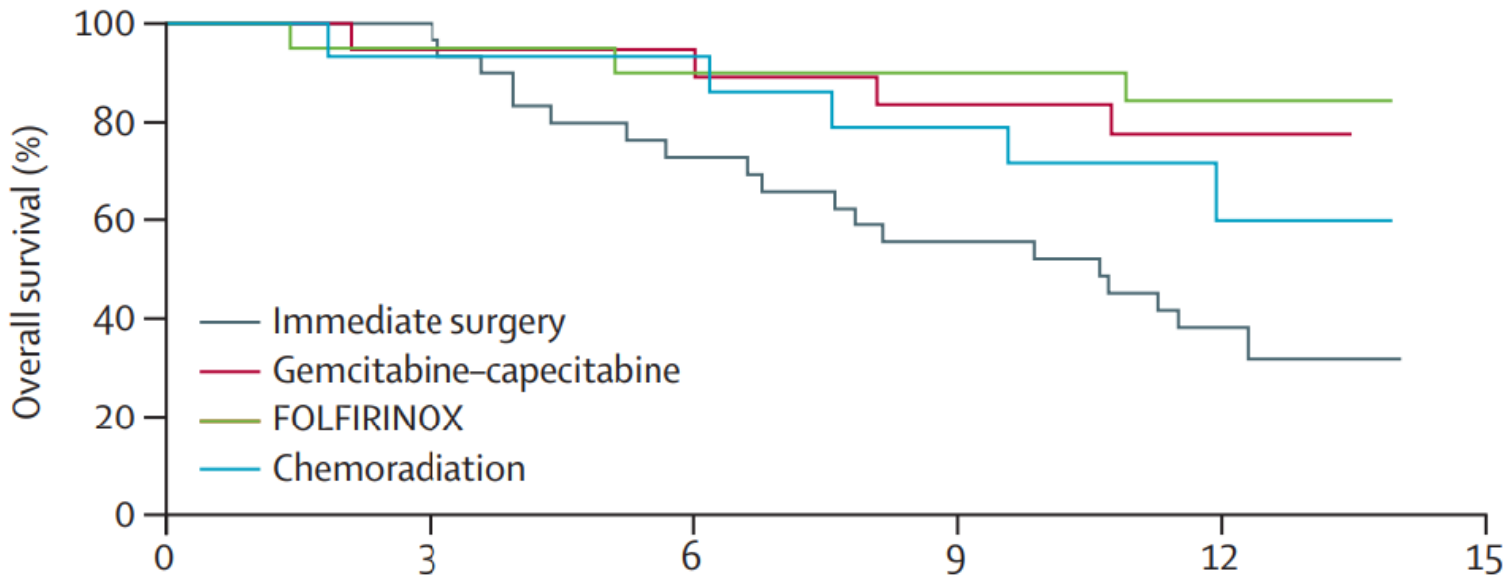
Ghaneh P et al., Lancet Gastroenterol Hepatol 2023; 8: 157–68



Numbers at risk (number censored)						
Neoadjuvant therapy groups combined	55 (1)	51 (3)	47 (1)	42 (15)	23 (23)	0
Immediate surgery	31 (1)	30 (1)	21 (0)	16 (4)	7 (6)	0

ESPAC-5: Borderline resectable

Ghaneh P et al., Lancet Gastroenterol Hepatol 2023; 8: 157–68



Numbers at risk (number censored)						
Surgery	31 (1)	30 (1)	21 (0)	16 (4)	7 (6)	0
Gemcitabine–capecitabine	19 (0)	18 (1)	17 (0)	15 (9)	5 (5)	0
FOLFIRINOX	20 (0)	19 (1)	17 (1)	16 (2)	13 (13)	0
Chemoradiation	16 (1)	14 (1)	13 (0)	11 (4)	5 (5)	0

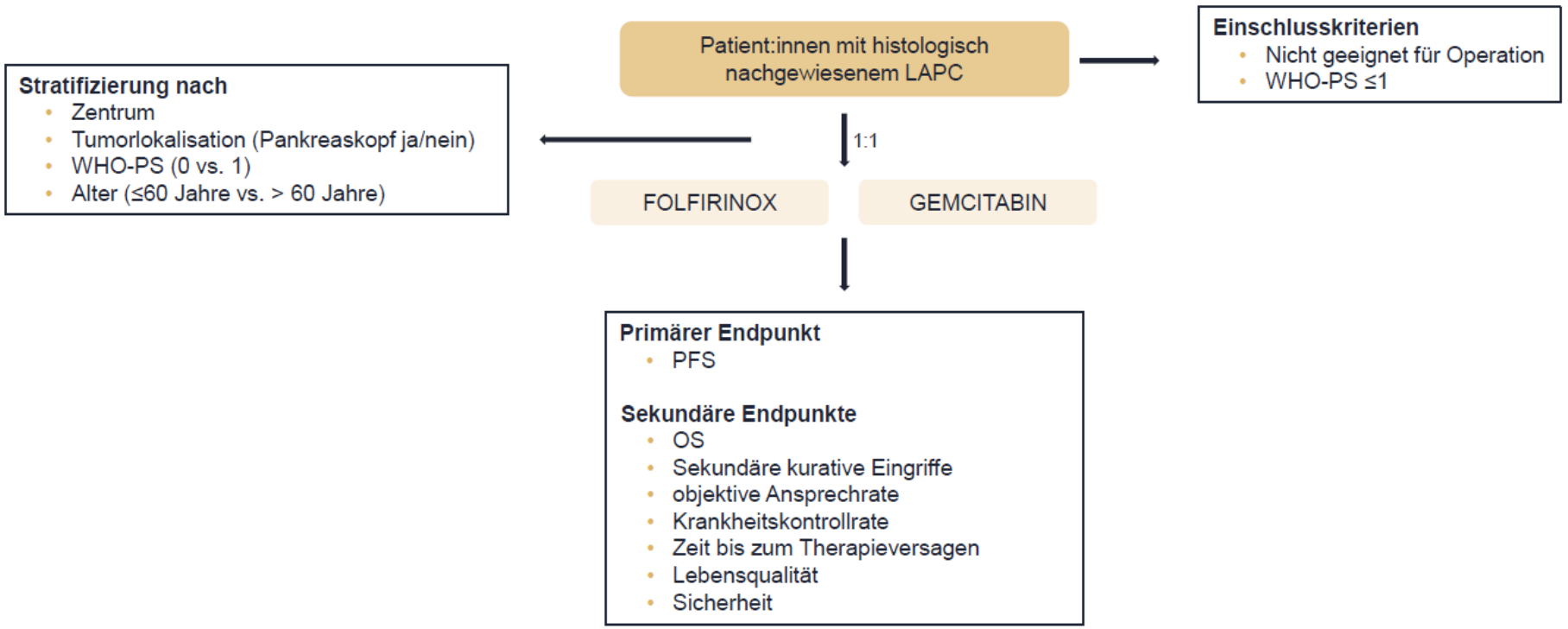
Szenario 5

- **Inoperabel, aber lokal begrenzt**

ESMO 2022

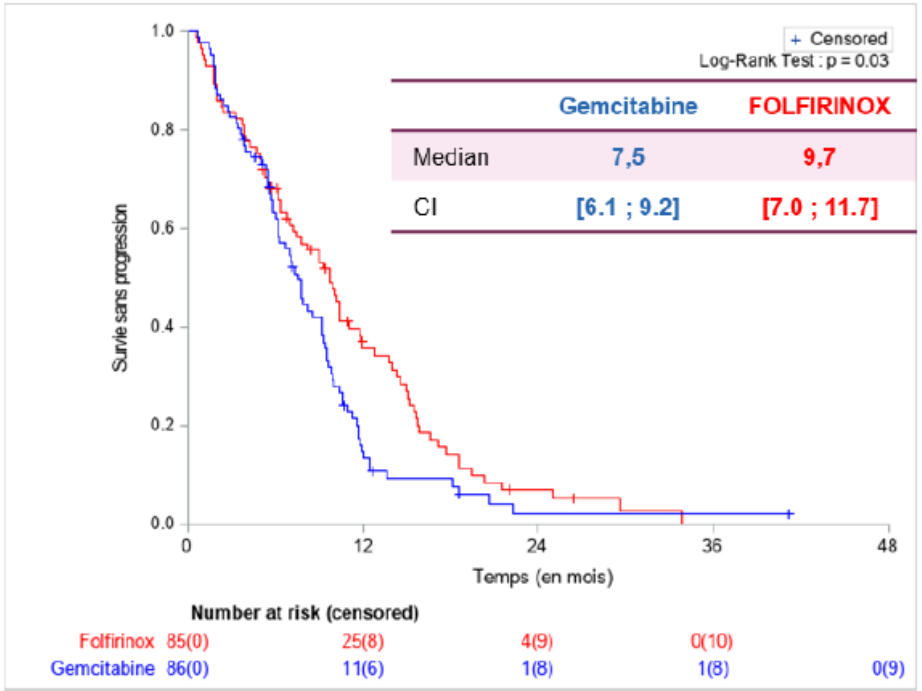
1296MO: PRODIGE 29-UCGI 26 (NEOPAN): A Phase III randomised trial comparing chemotherapy with Folfirinox or gemcitabine in locally advanced pancreatic carcinoma (LAPC).

M. Ducreux et al., Villejuif, Frankreich

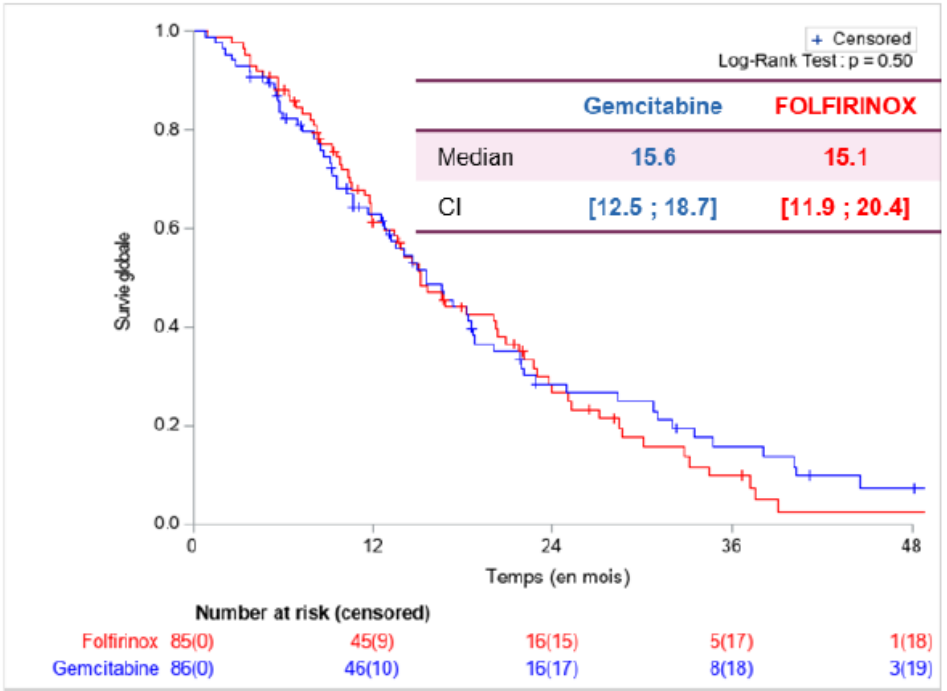


Median follow-up : 41,1 months

PFS



OS

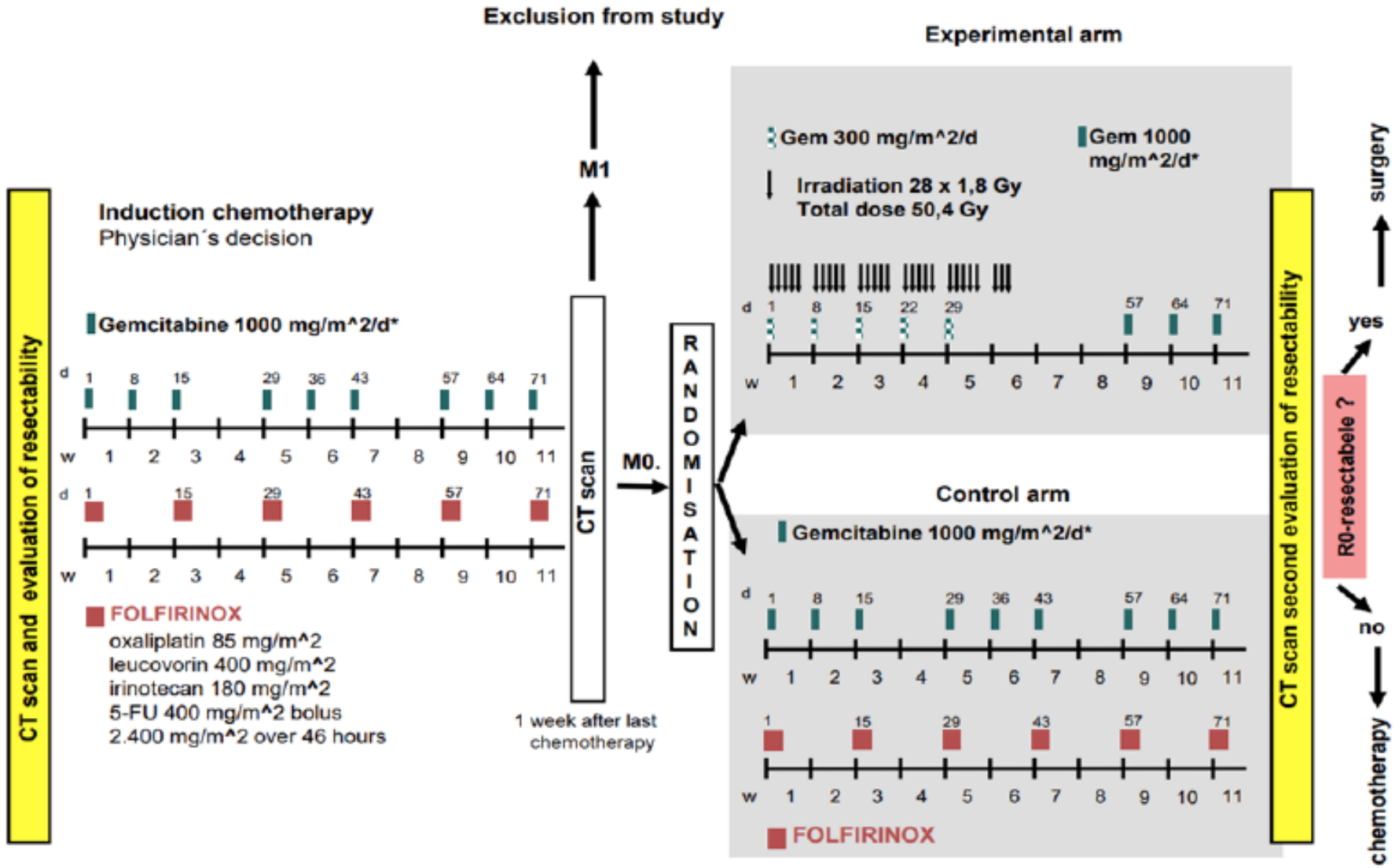


POSITIVE STUDIE PFS

CONKO-007

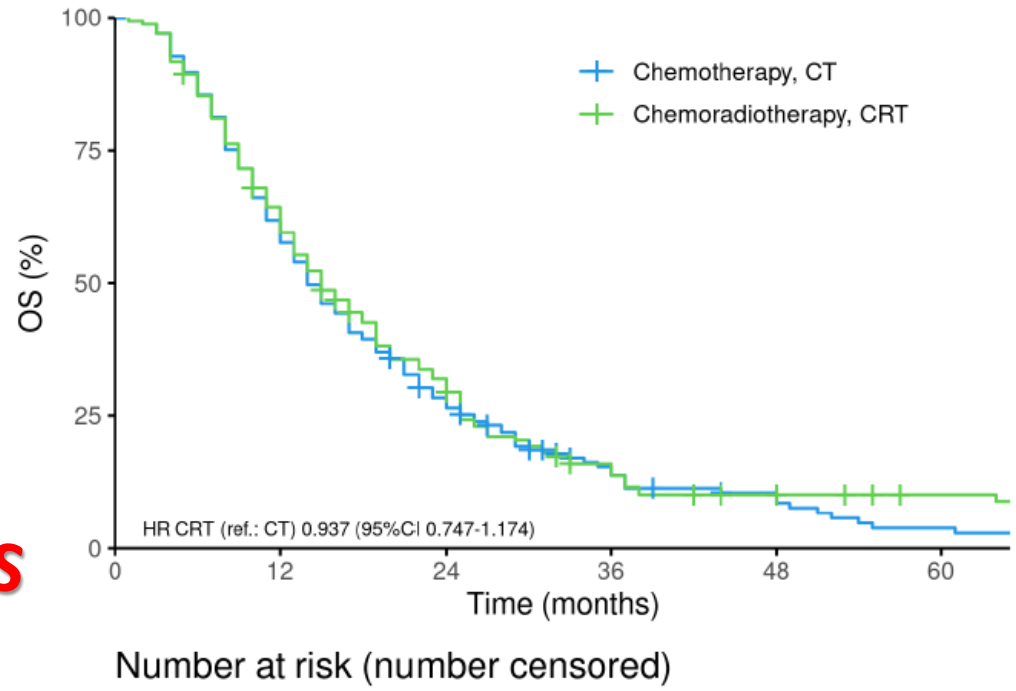
Randomisierte Phase-III-Studie zum Stellenwert einer Radiochemotherapie nach Induktionschemotherapie beim lokal begrenzten, inoperablen Pankreaskarzinom: Chemotherapie gefolgt von Radiochemotherapie im Vergleich zur alleinigen Chemotherapie

EudraCT: 2009-014476-21


Exclusion from study
M1
Experimental arm
Gem 300 mg/m^2/d
Gem 1000 mg/m^2/d*
Irradiation 28 x 1,8 Gy
Total dose 50,4 Gy
CT scan and evaluation of resectability
Induction chemotherapy
Physician´s decision
Gemcitabine 1000 mg/m^2/d*
FOLFIRINOX
oxaliplatin 85 mg/m^2
leucovorin 400 mg/m^2
irinotecan 180 mg/m^2
5-FU 400 mg/m^2 bolus
2.400 mg/m^2 over 46 hours
CT scan
1 week after last chemotherapy
M0.
RANDOMISATION
Control arm
Gemcitabine 1000 mg/m^2/d*
FOLFIRINOX
CT scan second evaluation of resectability
R0-resectabele ?
yes
surgery
no
chemotherapy

Gesamtüberleben,
Randomisierte Patienten (n = 336) (Update: 06/2023)

NEGATIVE STUDIE OS



Zusammenfassung 2023

Primärtherapie metastasiertes Pancreaskarzinom
FOLFIRINOX, Gem/nab Paclitaxel, Gem, Molekularbiologie: Olaparib

Zweitlinientherapie metastasiertes Pancreaskarzinom
Gem, Gem/nab Paclitaxel, 5-FU / Naliri, OFF

Adjuvante Therapie
mFOLFIRINOX, Gem, (Gem / nab Paclitaxel)

Borderline resektabel
Chemotherapie: (m)FOLFIRINOX

Neoadjuvant
Kein Standard außerhalb von Studien

Inoperabel, aber lokal begrenzt
Chemotherapie, Chemo/Radiotherapie