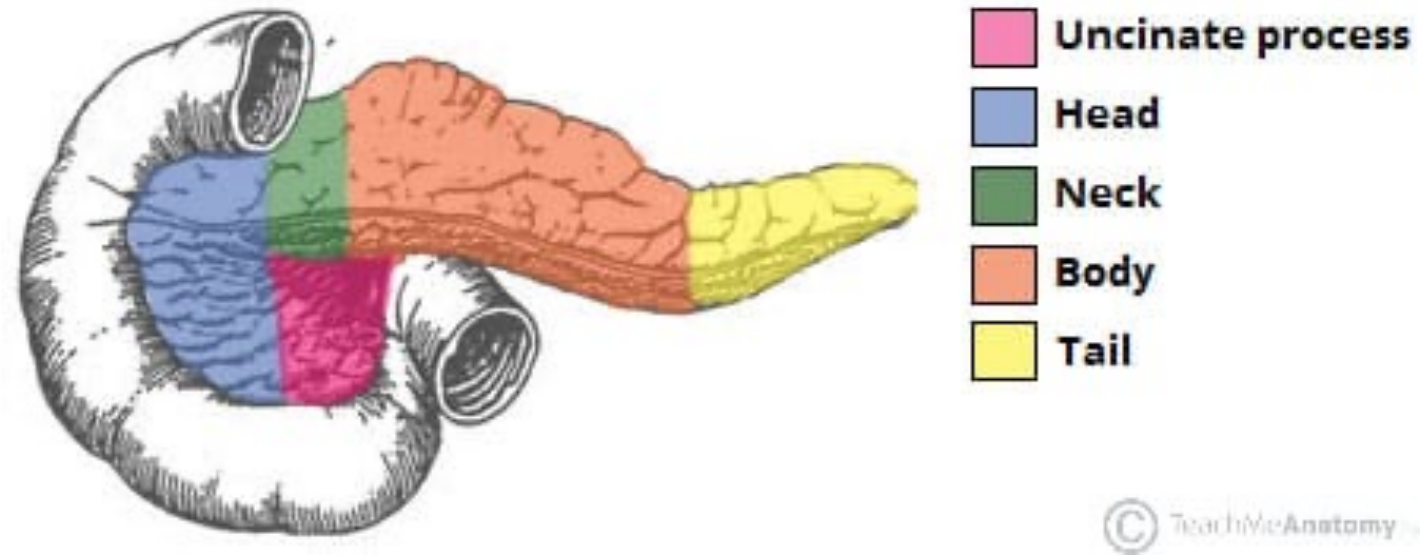
Updates in Gastrointestinal Cancers
Treatment of Localized Pancreatic Cancer

Richard Bold, MD, MBA
Director, Mayo Clinic Comprehensive Cancer Center ARZ

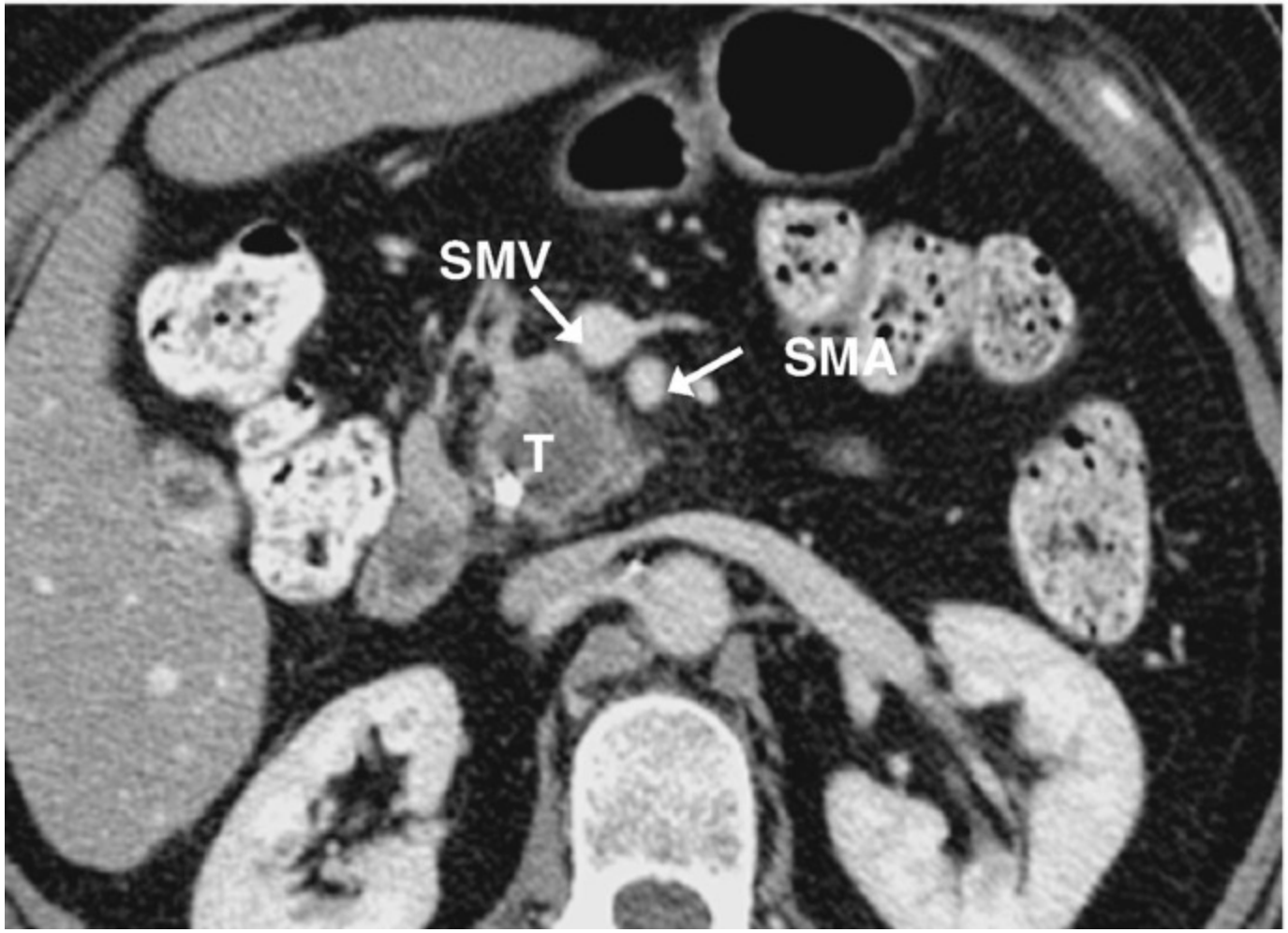


Nearly all clinical trials have focused on cancer of the head of the pancreas

- Most common site of malignancy
- Biology may be different, especially compared to body/tail
- Presentation distinctly different complicating management

NCCN Criteria for PDA Staging

STAGE	ARTERIAL	VENOUS
RESECTABLE	Clear fat planes around Celiac axis(CA), Superior Mesentery artery (SMA), and Hepatic artery (HA)	No SMV/portal vein distortion
BORDERLINE RESECTABLE	Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery without extension to the CA. Tumor abutment of the SMA not to exceed greater than 180° of the circumference of the vessel wall	Venous involvement of the SMV or portal vein with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacemen
UNRESECTABLE	Aortic invasion or encasement. Based on tumor location: Pancreatic head—More than 180° SMA encasement, any CA abutment, IVC Pancreatic body/tail—SMA or CA encasement greater than 180°	Unreconstructible SMV/portal vein occlusion


SMV
SMA
T

Resectable PDAC

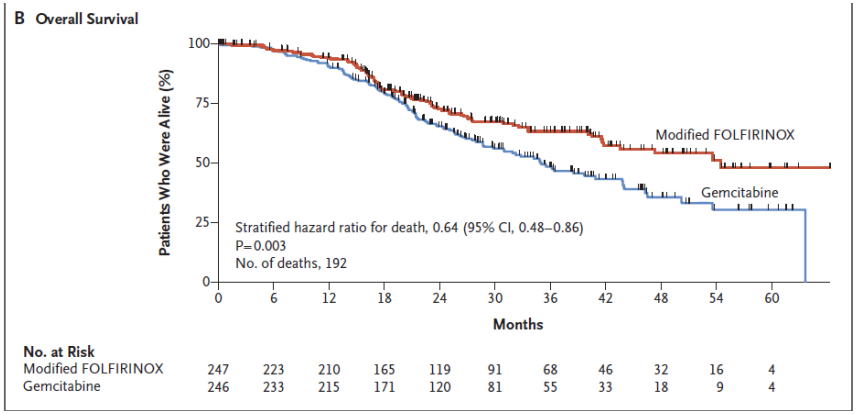
- Adjuvant therapy of proven benefit
- FOLFIRINOX > Gemcitabine
- Not all patients can receive FOLFIRNOX

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 20, 2018 VOL. 379 NO. 25

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

T. Conroy, P. Hammel, M. Hebbar, M. Ben Abdelghani, A.C. Wei, J.-L. Raoul, L. Choné, E. Francois, P. Artru, J.J. Biagi, T. Lecomte, E. Assenat, R. Faroux, M. Ychou, J. Volet, A. Sauvanet, G. Breysacher, F. Di Fiore, C. Cripps, P. Kavan, P. Texereau, K. Bouhier-Leporrier, F. Khemissa-Akouz, J.-L. Legoux, B. Juzyna, S. Gourgou, C.J. O'Callaghan, C. Jouffroy-Zeller, P. Rat, D. Malka, F. Castan, and J.-B. Bachet, for the Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group*

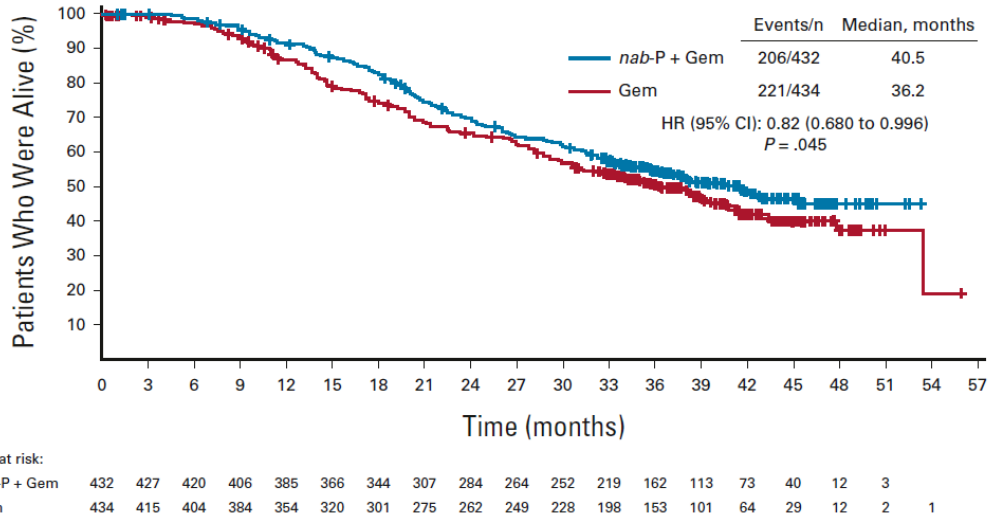


original reports

Adjuvant *nab*-Paclitaxel + Gemcitabine in Resected Pancreatic Ductal Adenocarcinoma: Results From a Randomized, Open-Label, Phase III Trial

Margaret A. Tempero, MD[1]; Uwe Pelzer, MD[2]; Eileen M. O'Reilly, MD[3]; Jordan Winter, MD[4]; Do-Youn Oh, MD[5,6]; Chung-Pin Li, MD, PhD[7,8,9]; Giampaolo Tortora, MD[10,11]; Heung-Moon Chang, MD[12]; Charles D. Lopez, MD, PhD[13]; Tanios Bekaii-Saab, MD[14]; Andrew H. Ko, MD[1]; Armando Santoro, MD[15,16]; Joon Oh Park, MD, PhD[17]; Marcus S. Noel, MD[18]; Giovanni Luca Frassineti, MD[19]; Yan-Shen Shan, MD, PhD[20]; Andrew Dean, MD[21]; Hanno Riess, MD[2]; Eric Van Cutsem, MD, PhD[22]; Jordan Berlin, MD[23]; Philip Philip, MD[24,25]; Malcolm Moore, MD[26]; David Goldstein, MD[27]; Josep Tabernero, MD, PhD[28]; Mingyu Li, PhD[29]; Stefano Ferrara, PharmD[30]; Yvan Le Bruchec, MS[30]; George Zhang, PhD[29]; Brian Lu, MD, PhD[29]; Andrew V. Biankin, MD, PhD[31,32,33]; and Michele Reni, MD[34]; on behalf of the APACT Investigators

C



Note: Primary endpoint of DFS not met; p=0.18)

J Clin Oncol. 2023; 41:2007-2019

original reports

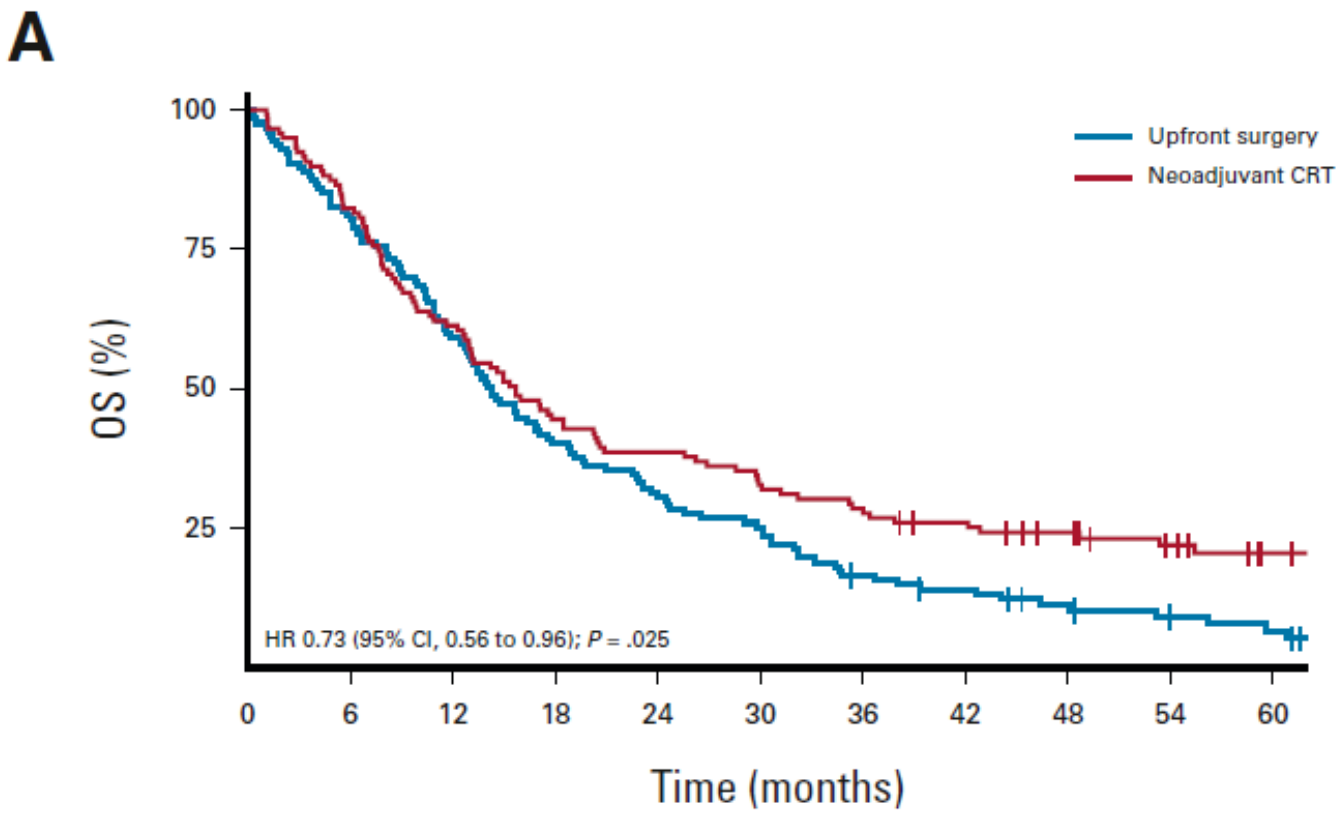
Neoadjuvant Chemoradiotherapy Versus Upfront Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Long-Term Results of the Dutch Randomized PREOPANC Trial

Eva Versteijne, MD, PhD[1]; Jacob L. van Dam, MD[2]; Mustafa Suker, MD, PhD[2]; Quisette P. Janssen, MD[2]; Karin Groothuis, MSc[3]; Janine M. Akkermans-Vogelaar, BSc[3]; Marc G. Besselink, MD, PhD[4]; Bert A. Bonsing, MD, PhD[5]; Jeroen Buijsen, MD, PhD[6]; Olivier R. Busch, MD, PhD[4]; Geert-Jan M. Creemers, MD, PhD[7]; Ronald M. van Dam, MD, PhD[8,9,10]; Ferry A. L. M. Eskens, MD, PhD[11]; Sebastiaan Festen, MD, PhD[12]; Jan Willem B. de Groot, MD, PhD[13]; Bas Groot Koerkamp, MD, PhD[2]; Ignace H. de Hingh, MD, PhD[14]; Marjolein Y. V. Homs, MD, PhD[11]; Jeanin E. van Hooft, MD, PhD[15,16]; Emile D. Kerver, MD[17]; Saskia A. C. Luelmo, MD[18]; Karen J. Neelis, MD, PhD[19]; Joost Nuyttens, MD, PhD[20]; Gabriel M. R. M. Paardekooper, MD[21]; Gijs A. Patijn, MD, PhD[22]; Maurice J. C. van der Sangen, MD, PhD[23]; Judith de Vos-Geelen, MD, PhD[24]; Johanna W. Wilmink, MD, PhD[25]; Aeilko H. Zwinderman, PhD[26]; Cornelis J. Punt, MD, PhD[27]; Geertjan van Tienhoven, MD, PhD[1]; and Casper H. J. van Eijck, MD, PhD[2]; for the Dutch Pancreatic Cancer Group

J Clin Oncol 40:1220-1230.

246 patients accrued across 16 Dutch centers (2013-2017)
Both borderline and upfront resectable PDAC
Neoadjuvant therapy of gemcitabine/radiation therapy

Neoadjuvant chemoradiotherapy has survival benefit……..

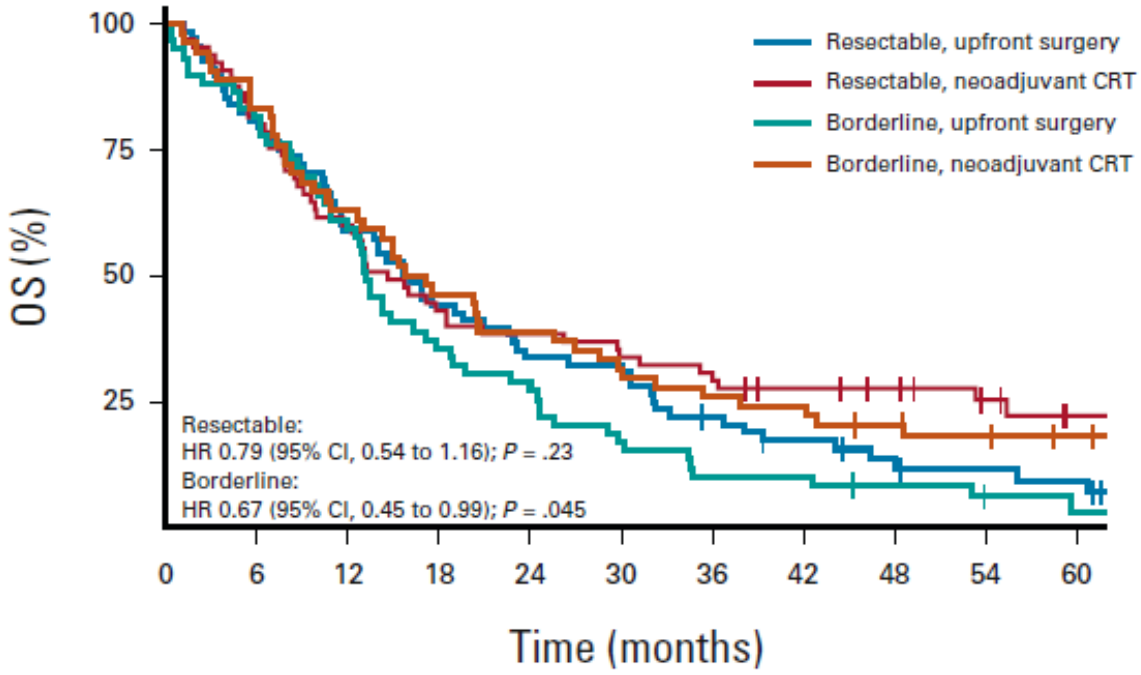


No. at risk:

Upfront surgery	127 (0)	103 (0)	75 (0)	51 (0)	40 (0)	32 (0)	20 (1)	16 (2)	11 (4)	7 (6)	5 (6)
Neoadjuvant CRT	119 (0)	98 (0)	73 (0)	53 (0)	46 (0)	39 (0)	34 (0)	29 (2)	24 (5)	17 (10)	11 (15)

But wait – no benefit in resectable PDAC

B



No. at risk:

Resectable, upfront surgery	68 (0)	55 (0)	40 (0)	30 (0)	23 (0)	22 (0)	14 (1)	10 (2)	7 (3)	5 (4)	4 (4)
Resectable, neoadjuvant CRT	65 (0)	53 (0)	39 (0)	28 (0)	25 (0)	22 (0)	20 (0)	16 (2)	14 (4)	9 (8)	5 (11)
Borderline, upfront surgery	59 (0)	48 (0)	35 (0)	21 (0)	17 (0)	10 (0)	6 (0)	6 (0)	4 (1)	2 (2)	1 (2)
Borderline, neoadjuvant CRT	54 (0)	45 (0)	34 (0)	25 (0)	21 (0)	17 (0)	14 (0)	13 (0)	10 (1)	8 (2)	6 (4)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

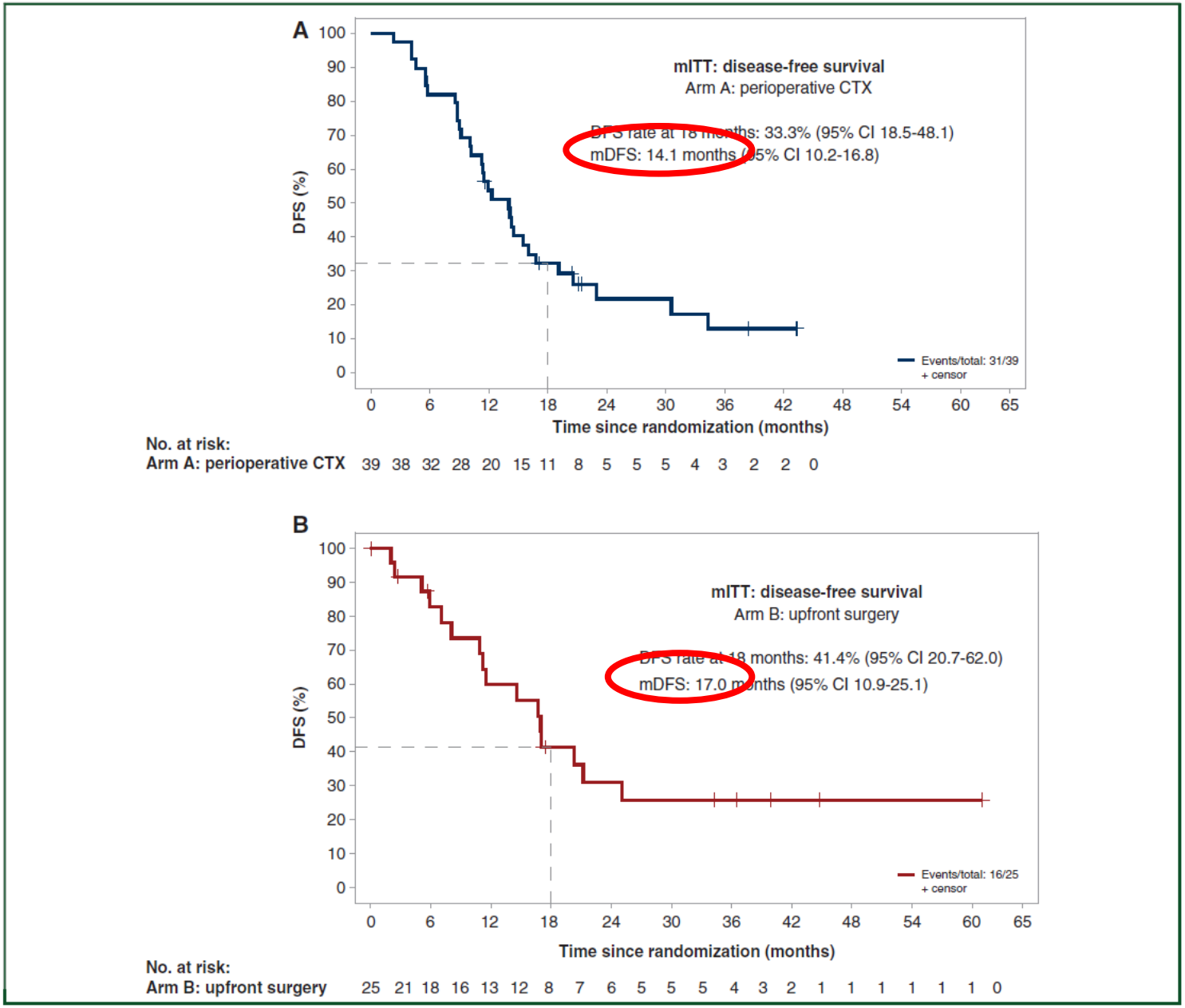
ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

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

T. Seufferlein[1*†], W. Uhl[2†], M. Kornmann[3], H. Algül[4], H. Friess[5], A. König[6], M. Ghadimi[7], E. Gallmeier[8], D. K. Bartsch[9], M. P. Lutz[10], R. Metzger[11], K. Wille[12], B. Gerdes[13], C. C. Schimanski[14], F. Graupe[15], V. Kunzmann[16], I. Klein[17], M. Geissler[18], L. Staib[19], D. Waldschmidt[20], C. Bruns[21], U. Wittel[22], S. Fichtner-Feigl[22], S. Daum[23], A. Hinke[24], L. Blome[25], A. Tannapfel[26], A. Kleger[1], A. W. Berger[1], A. M. R. Kestler[1], J. S. Schuhbaur[1], L. Perkhofer[1], M. Tempero[27], A. C. Reinacher-Schick[28] & T. J. Ettrich[1]

127 patients enrolled (2015 – 2019)
40 completed all protocol therapy
Perioperative – 2 cycles of gemcitabine/nab-paclitaxel
- Goal of 6 cycles of gemcitabine/nab-paclitaxel for all patients


A
mITT: disease-free survival
Arm A: perioperative CTX
DFS rate at 18 months: 33.3% (95% CI 18.5-48.1)
mDFS: 14.1 months (95% CI 10.2-16.8)
DFS (%)
Events/total: 31/39
+ censor
Time since randomization (months)
No. at risk:
Arm A: perioperative CTX 39 38 32 28 20 15 11 8 5 5 5 4 3 2 2 0
B
mITT: disease-free survival
Arm B: upfront surgery
DFS rate at 18 months: 41.4% (95% CI 20.7-62.0)
mDFS: 17.0 months (95% CI 10.9-25.1)
DFS (%)
Events/total: 16/25
+ censor
Time since randomization (months)
No. at risk:
Arm B: upfront surgery 25 21 18 16 13 12 8 7 6 5 5 5 4 3 2 1 1 1 1 1 1 0

STUDY PROTOCOL Open Access

Neoadjuvant chemotherapy versus surgery first for resectable pancreatic cancer (Norwegian Pancreatic Cancer Trial - 1 (NorPACT-1)) – study protocol for a national multicentre randomized controlled trial

Knut Jørgen Labori[1*], Kristoffer Lassen[1], Dag Hoem[2], Jon Erik Grønbech[3,4], Jon Arne Søreide[5,6], Kim Mortensen[7], Rune Smaaland[8], Halfdan Sorbye[9,10], Caroline Verbeke[11,12] and Svein Dueland[13]

140 patients accrued (2016-2022)

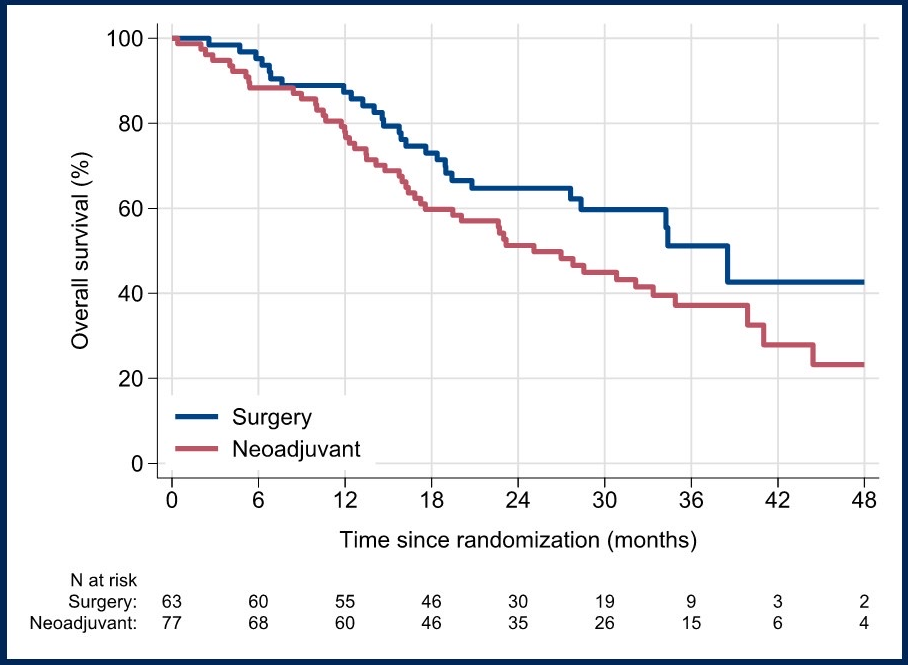
Data not yet published

(presented in abstract form ASCO 2023)

Goal of 12 cycles of mFOLFIRINOX

randomized to 4 cycles preop, or upfront surgery

Overall survival - Intention-to-treat



Median overall survival
25.1 months (neoadjuvant)
38.5 months (upfront surgery)
HR 1.52 (95% CI, 0.94-2.46), p=0.096

Proportion alive at 18 months
60% vs 73%, p=0.1

MORE TO BE DISCUSSED IN GI CASE DISCUSSION

STUDY PROTOCOL Open Access

Resectable pancreatic adenocarcinoma neo-adjuvant FOLF(IRIN)OX-based chemotherapy - a multicenter, non-comparative, randomized, phase II trial (PANACHE01-PRODIGE48 study)

Lilian Schwarz[1,2*], Dewi Vernerey[3], Jean-Baptiste Bachet[4], Jean-Jacques Tuech[1,2], Fabienne Portales[5], Pierre Michel[2,6] and Antonio Sa Cunha[7]

ASCO 2022 Update
153 enrolled

1 yr-OS: 84.1% (mFOLFIRINOX)
71.8% (FOLFOX)
80.8% (Surgery)

FOLFOX arm discontinued

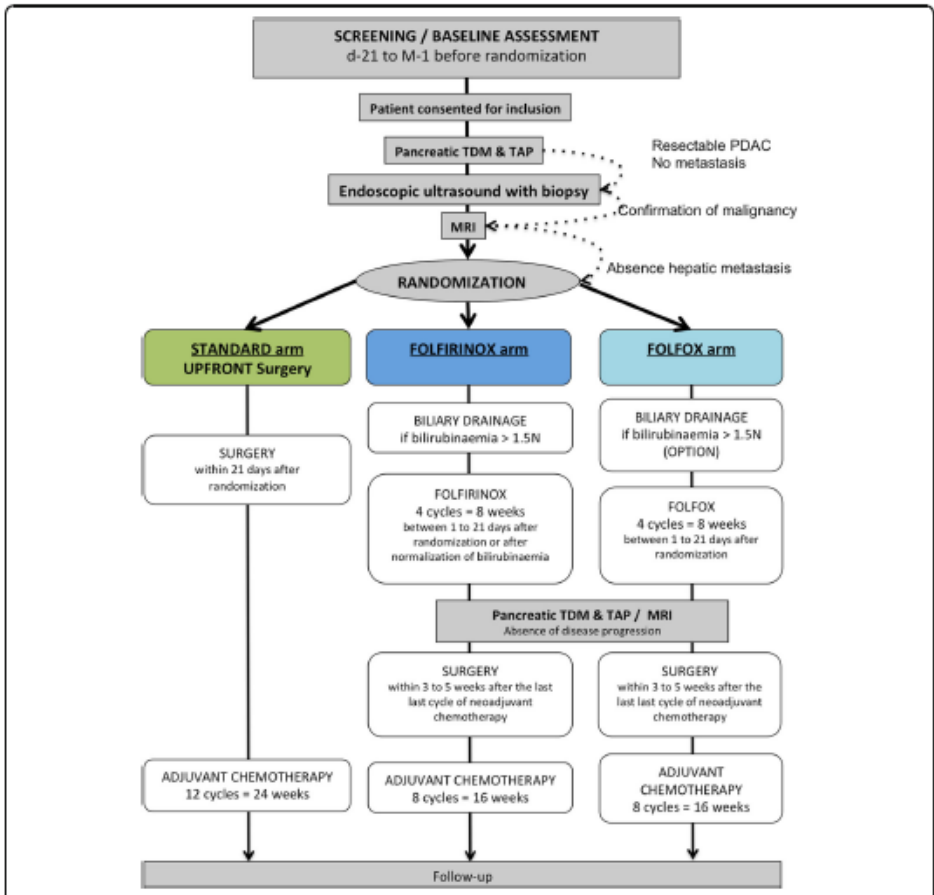


Fig. 1 Protocol overview. MRI: Magnetic resonance imaging; PDAC: Pancreatic duct adenocarcinoma; TDM TAP: CT-scan Thorax Abdomen and Pelvis

Current landscape of clinical trials

Trial	n	Perioperative	Adjuvant	Comment
Germany, Multicenter	66	Gemcitabine/cisplatin/XRT Surgery Gemcitabine	Gemcitabine	Terminated due to poor accrual (p=NS)
Swiss multicenter	37	Gemcitabine/oxaliplatin Surgery Gemcitabine	Gemcitabine	Terminated due to poor accrual (234 assessed)
Bologna	38	Gemcitabine/XRT Surgery Gemcitabine	Gemcitabine	Terminated due to poor accrual (350 assessed)
PACT-15	93	Gem/Epirubicin/Cisplatin Surgery Gem/Epirubicin/Cisplatin	Gemcitabine OR Gem/Epi/Cisplatin	Terminated due to change in SOC (p=NS)
JSAP-05	364	Gemcitabine/S-1 Surgery S1	S1	OS (p=0.15) 36.7 mo vs 26.6 mo (ASCO abstract)
Alliance A021806	352	mFOLFIRINOX x 8 Surgery mFOLFIRINOX x 4	mFOLFIRINOX	Enrollment completion Nov 2030
PREOPANC-3	378	mFOLFIRINOX x 8 Surgery mFOLFIRINOX x 4	mFOLFIRINOX	Enrollment completion July 2029

Resectable PDAC

Areas of unresolved controversy and uncertainty

- Neoadjuvant vs. adjuvant
  - Only 1 positive trial (Japan using S1), all others are negative, abandoned or ongoing
- Optimal regimen
  - FOLFIRINOX vs Gem vs Gem/nab-paclitaxel
  - Role of radiation
- Total neoadjuvant vs. “sandwich”

Borderline Resectable PDAC

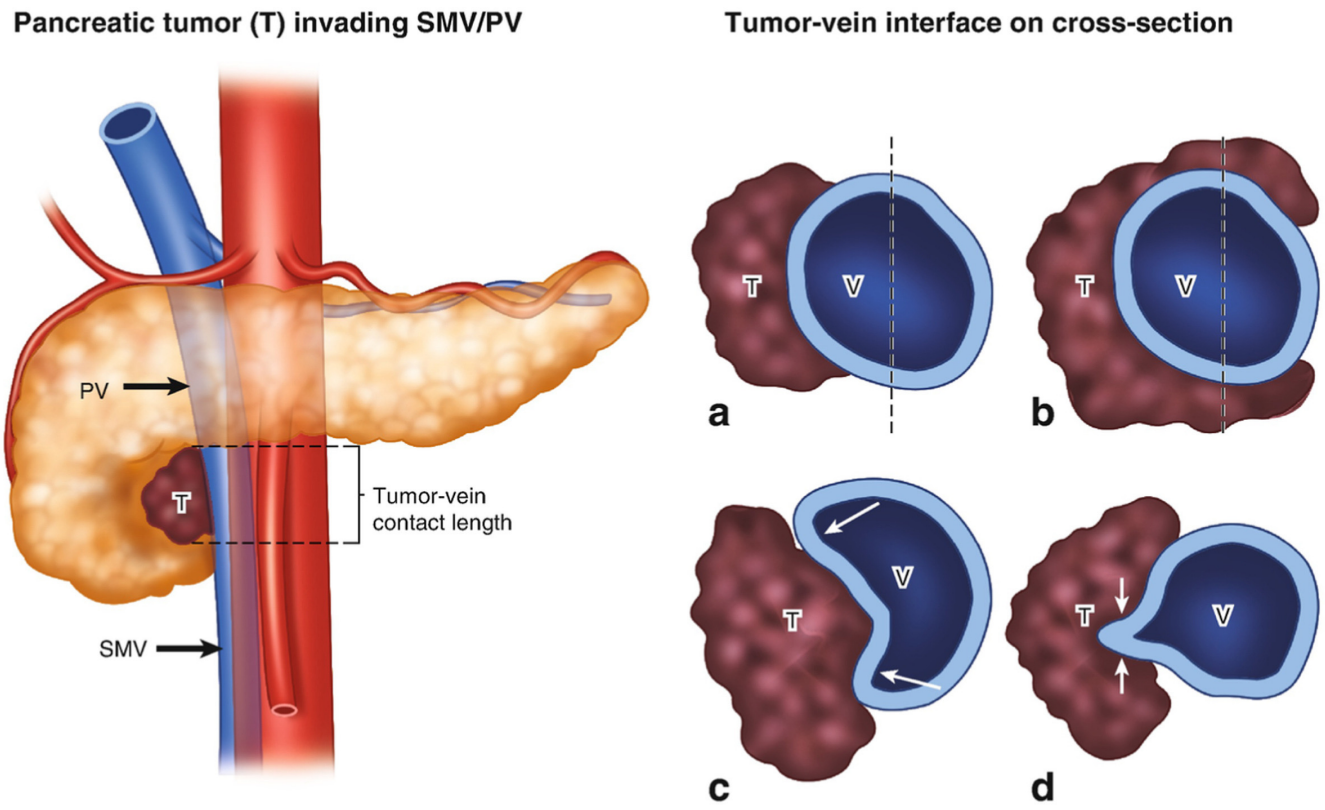
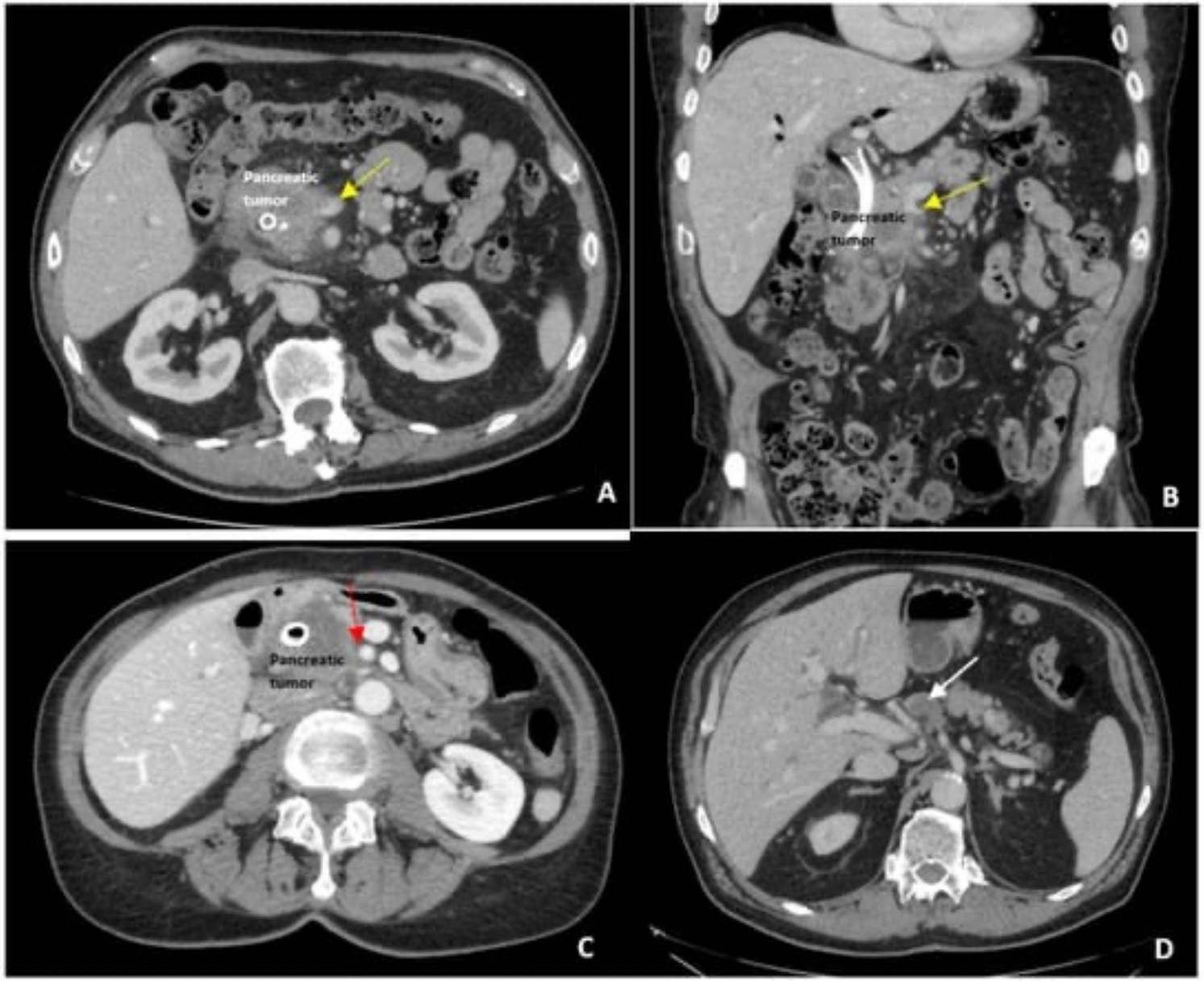


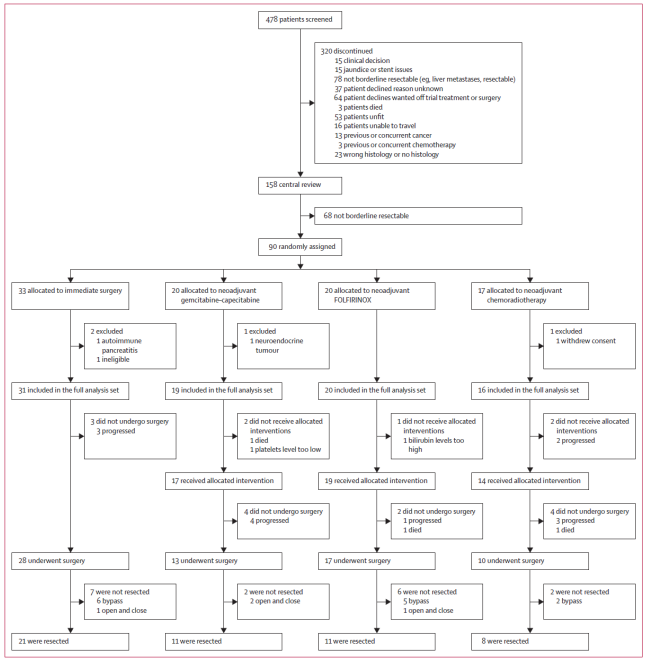
Fig. 1

If you've seen one borderline resectable PDAC,
you've seen one borderline resectable PDAC


Pancreatic tumor
A
Pancreatic tumor
B
Pancreatic tumor
C
D

Immediate surgery compared with short-course neoadjuvant gemcitabine plus capecitabine, FOLFIRINOX, or chemoradiotherapy in patients with borderline resectable pancreatic cancer (ESPAC5): a four-arm, multicentre, randomised, phase 2 trial

Paula Ghaneh, Daniel Palmer, Silvia Cicconi, Richard Jackson, Christopher Michael Halloran, Charlotte Rawcliffe, Rajaram Sripadam, Somnath Mukherjee, Zahir Soonawalla, Jonathan Wadsley, Ahmed Al-Mukhtar, Euan Dickson, Janet Graham, Long Jiao, Harpreet S Wasan, Iain S Tait, Andreas Prachalias, Paul Ross, Juan W Valle, Derek A O'Reilly, Bilal Al-Sarireh, Sarah Gwynne, Irfan Ahmed, Kate Connolly, Kein-Long Yim, David Cunningham, Thomas Armstrong, Caroline Archer, Keith Roberts, Yuk Ting Ma, Christoph Springfeld, Christine Tjaden, Thilo Hackert, Markus W Büchler, John P Neoptolemos, for the European Study Group for Pancreatic Cancer

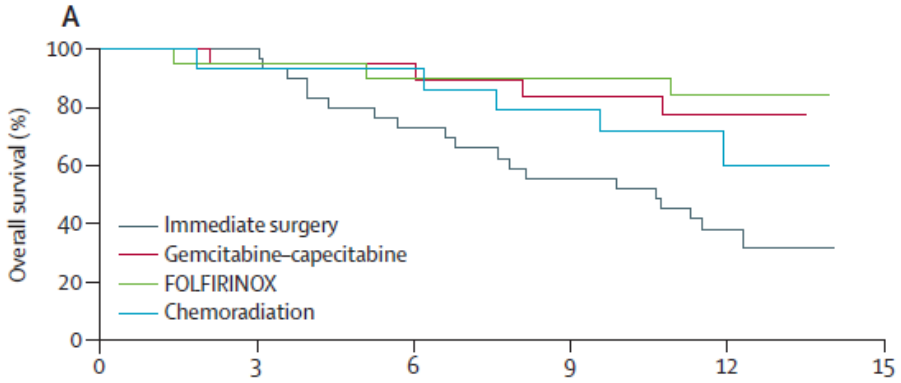


Accrual was difficult

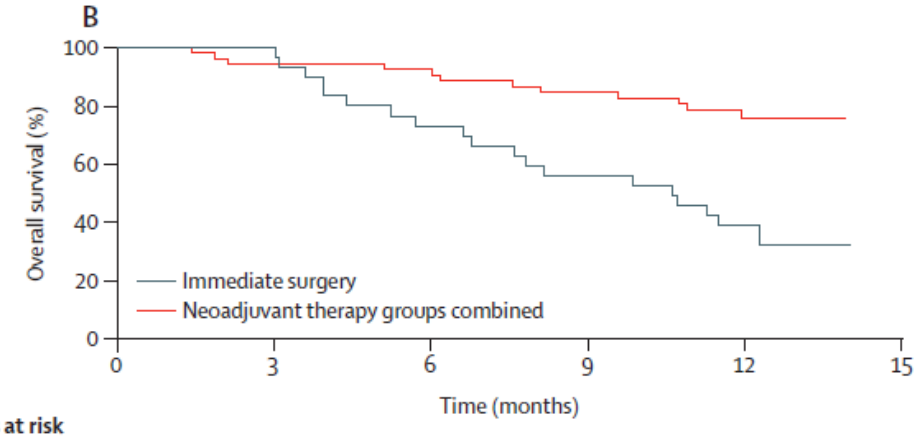
Significant number of patients excluded/removed

Low R0 resection rate in all groups (p=NS)

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



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

Results of a Phase II Study on the Use of Neoadjuvant Chemotherapy (FOLFIRINOX or GEM/nab-PTX) for Borderline-resectable Pancreatic Cancer (NUPAT-01)

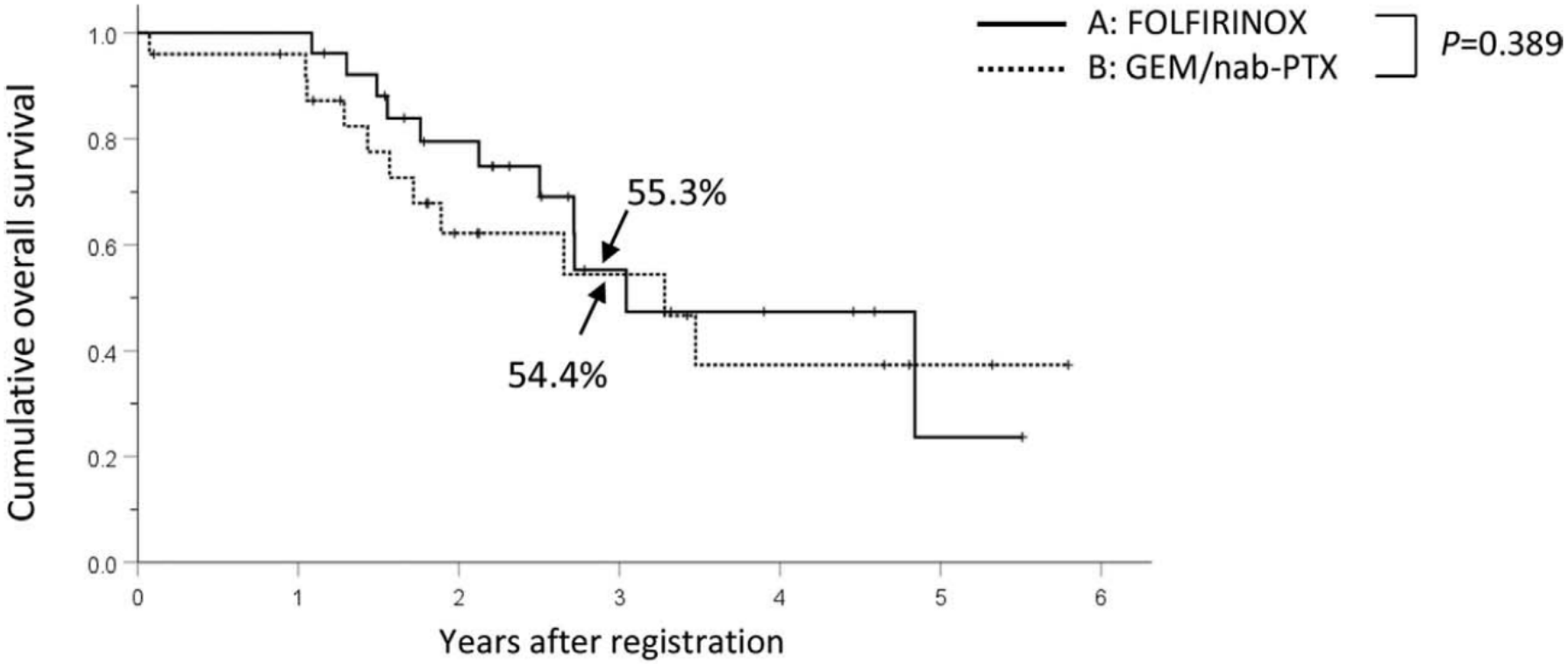
Junpei Yamaguchi, MD,✉ *Yukihiro Yokoyama, MD,* *Tsutomu Fujii, MD,* *Suguru Yamada, MD,*
Hideki Takami, MD, *Hiroki Kawashima, MD,* *Eizaburo Ohno, MD,* *Takuya Ishikawa, MD,*
Osamu Maeda, MD, *Hiroshi Ogawa, MD,* *Yasuhiro Kodera, MD,*
Masato Nagino, MD, *and Tomoki Ebata, MD**

FOLFIRINOX (4) → Surgery → Chemotherapy (typically S-1) N= 26

VS

Gemcitabine/nab-paclitaxel → Surgery → Chemotherapy (typically S-1) N=25

Dang it – but this is why we do clinical trials!



JAMA Oncology | Original Investigation

Efficacy of Preoperative mFOLFIRINOX vs mFOLFIRINOX Plus Hypofractionated Radiotherapy for Borderline Resectable Adenocarcinoma of the Pancreas

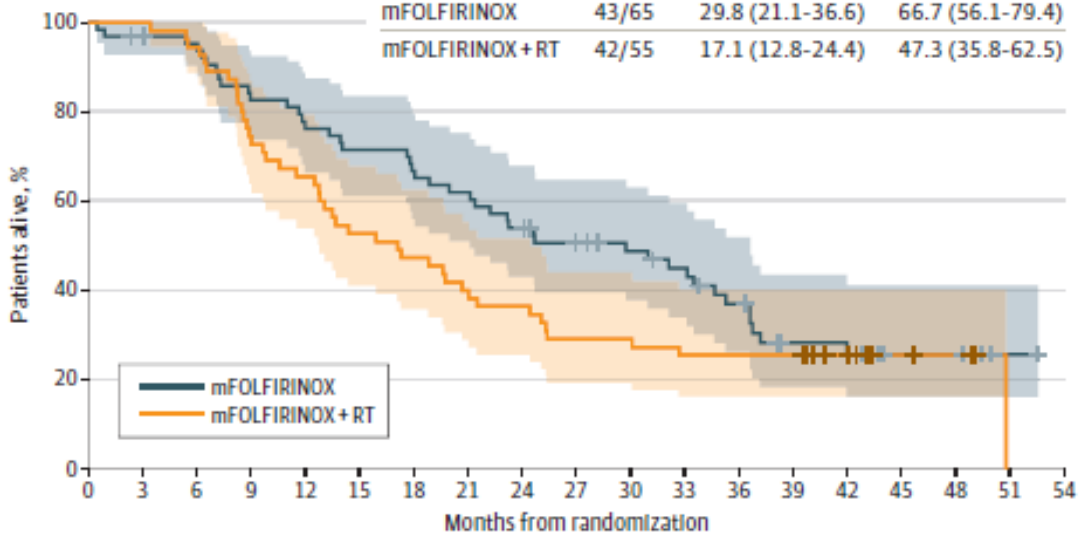
The A021501 Phase 2 Randomized Clinical Trial

Matthew H. G. Katz, MD; Qian Shi, PhD; Jeff Meyers, BS; Joseph M. Herman, MD; Michael Chuong, MD; Brian M. Wolpin, MD, MPH; Syed Ahmad, MD; Robert Marsh, MD; Larry Schwartz, MD; Spencer Behr, MD; Wendy L. Frankel, MD; Eric Collisson, MD; James Leenstra, MD; Terence M. Williams, MD; Gina Vaccaro, MD; Alan Venook, MD; Jeffrey A. Meyerhardt, MD, MPH; Eileen M. O'Reilly, MD

JAMA Oncol. 2022;8(9):1263-1270. doi:10.1001/jamaoncol.2022.2319

A Overall survival

Arm	Events/ total	Median (95% CI), mo	18-mo OS rate (95% CI), %
mFOLFIRINOX	43/65	29.8 (21.1-36.6)	66.7 (56.1-79.4)
mFOLFIRINOX + RT	42/55	17.1 (12.8-24.4)	47.3 (35.8-62.5)



No. at risk

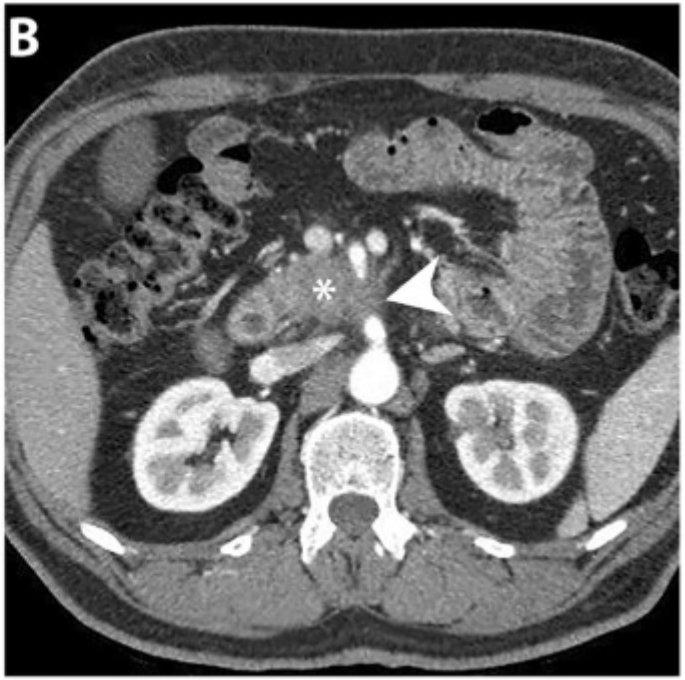
mFOLFIRINOX	65	62	60	52	48	45	42	39	34	29	26	23	18	11	10	4	4	1	0
mFOLFIRINOX + RT	55	55	52	41	36	29	26	22	20	16	16	14	14	14	9	4	3	0	

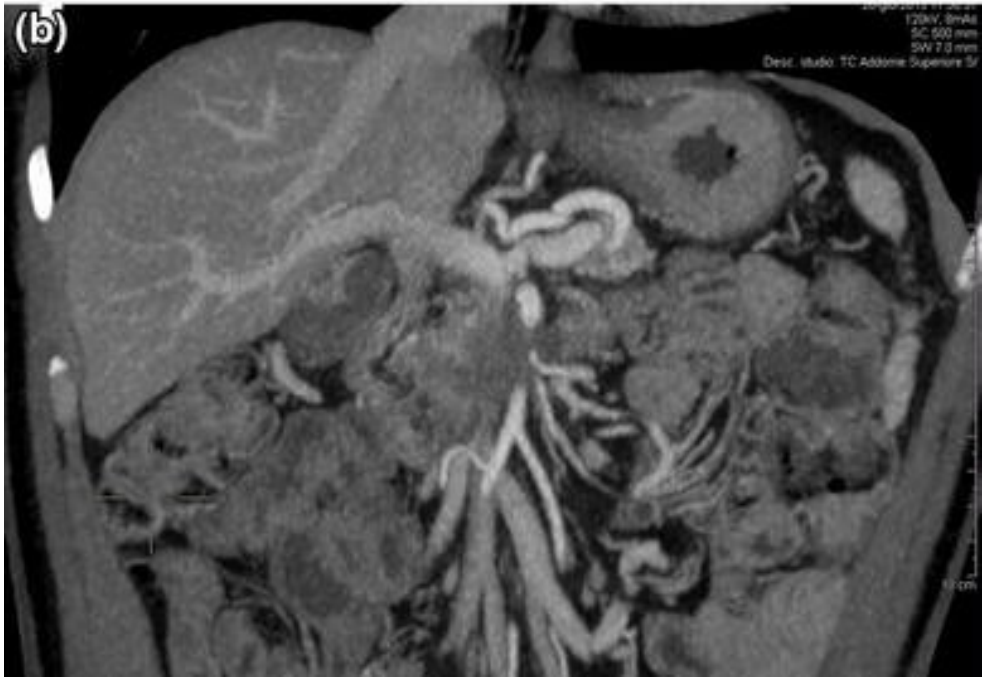
Borderline Resectable PDAC

Areas of unresolved controversy and uncertainty

- Some chemotherapy is beneficial, but how much and which regimen is unclear
- Overall role of radiation therapy is unclear

Locally advanced PDAC





Generally, these patients don't get to surgical resection

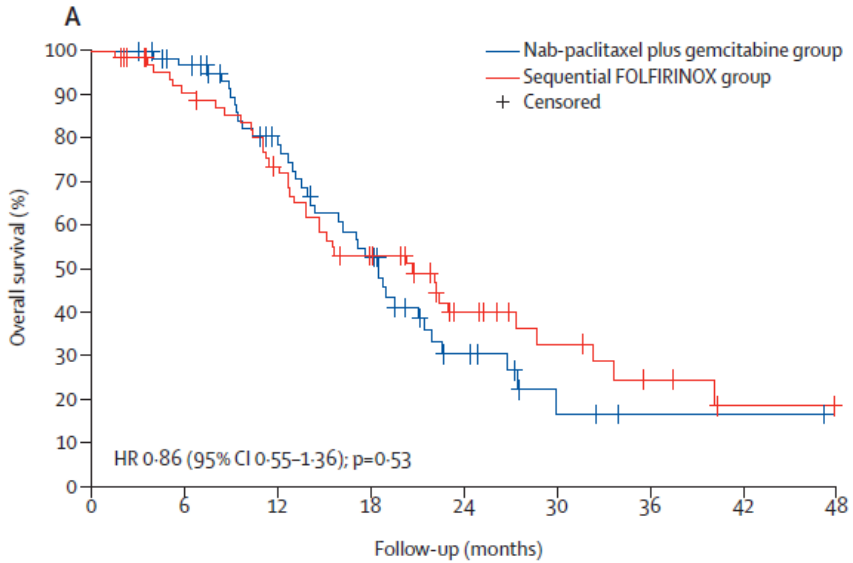
Bob Wolff – "All of these patients are metastatic, we just can't see it"

Nab-paclitaxel plus gemcitabine versus nab-paclitaxel plus gemcitabine followed by FOLFIRINOX induction chemotherapy in locally advanced pancreatic cancer (NEOLAP-AIO-PAK-0113): a multicentre, randomised, phase 2 trial

Volker Kunzmann, Jens T Siveke, Hana Algül, Eray Goekkurt, Gabriele Siegler, Uwe Martens, Dirk Waldschmidt, Uwe Pelzer, Martin Fuchs, Frank Kullmann, Stefan Boeck, Thomas J Ettrich, Swantje Held, Ralph Keller, Ingo Klein, Christoph-Thomas Germer, Hubert Stein, Helmut Friess, Marcus Bahra, Ralf Jakobs, Ingo Hartlapp, Volker Heinemann, on behalf of the German Pancreatic Cancer Working Group (AIO-PAK) and NEOLAP investigators

More is not necessarily better

- No difference in surgery rate
- No difference in survival



Number at risk (number censored)									
Nab-paclitaxel plus gemcitabine group	64 (0)	58 (4)	41 (12)	26 (13)	10 (20)	3 (24)	1 (26)	1 (26)	0 (27)
Sequential FOLFIRINOX group	66 (0)	55 (5)	43 (7)	29 (9)	15 (17)	9 (21)	5 (23)	2 (25)	2 (25)

R0 resection following chemo (radio)therapy improves survival of primary inoperable pancreatic cancer patients. Interim results of the German randomized CONKO-007± trial

R. Fietkau[1] · R. Grützmann[2] · U. A. Wittel[3] · R. S. Croner[4] · L. Jacobasch[5] · U. P. Neumann[6] · A. Reinacher-Schick[7] · D. Imhoff[8] · S. Boeck[9] · L. Keilholz[10] · H. Oettle[11] · W. M. Hohenberger[2] · H. Golcher[2] · W. O. Bechstein[12] · W. Uhl[13] · A. Pirkl[14] · W. Adler[15] · S. Semrau[1] · S. Rutzner[1] · M. Ghadimi[16] · D. Lubgan[1]

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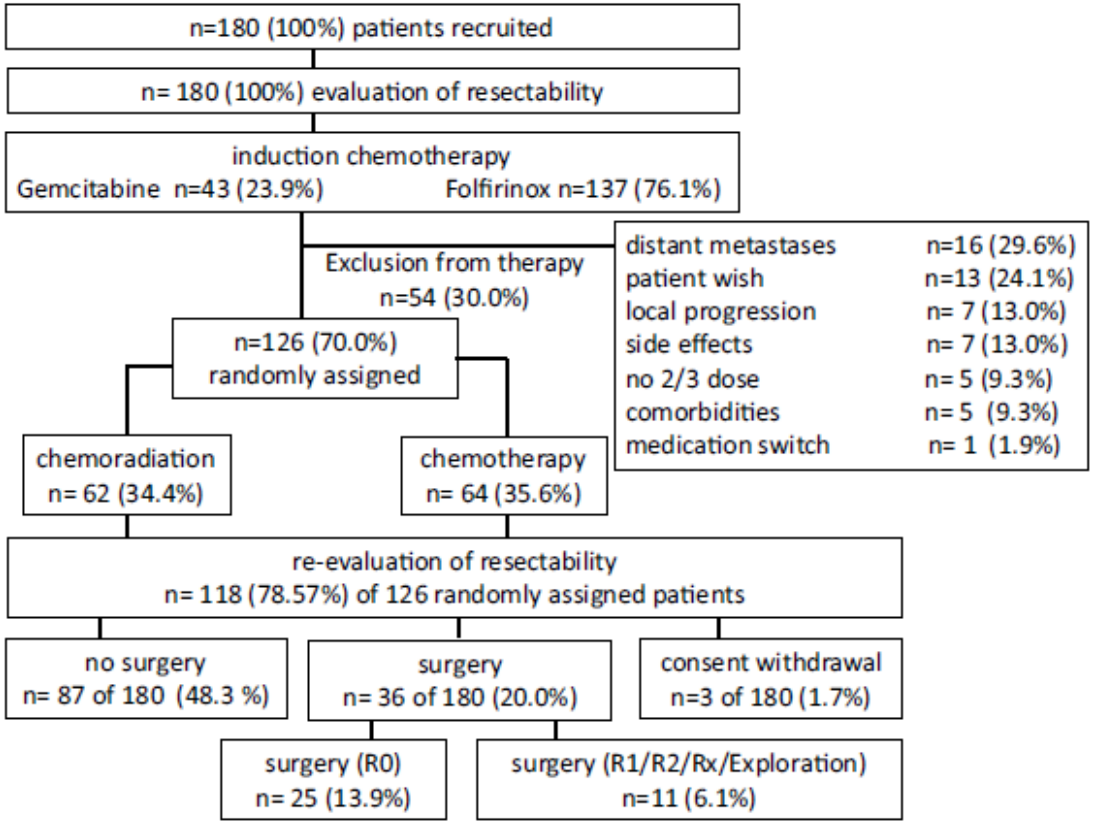
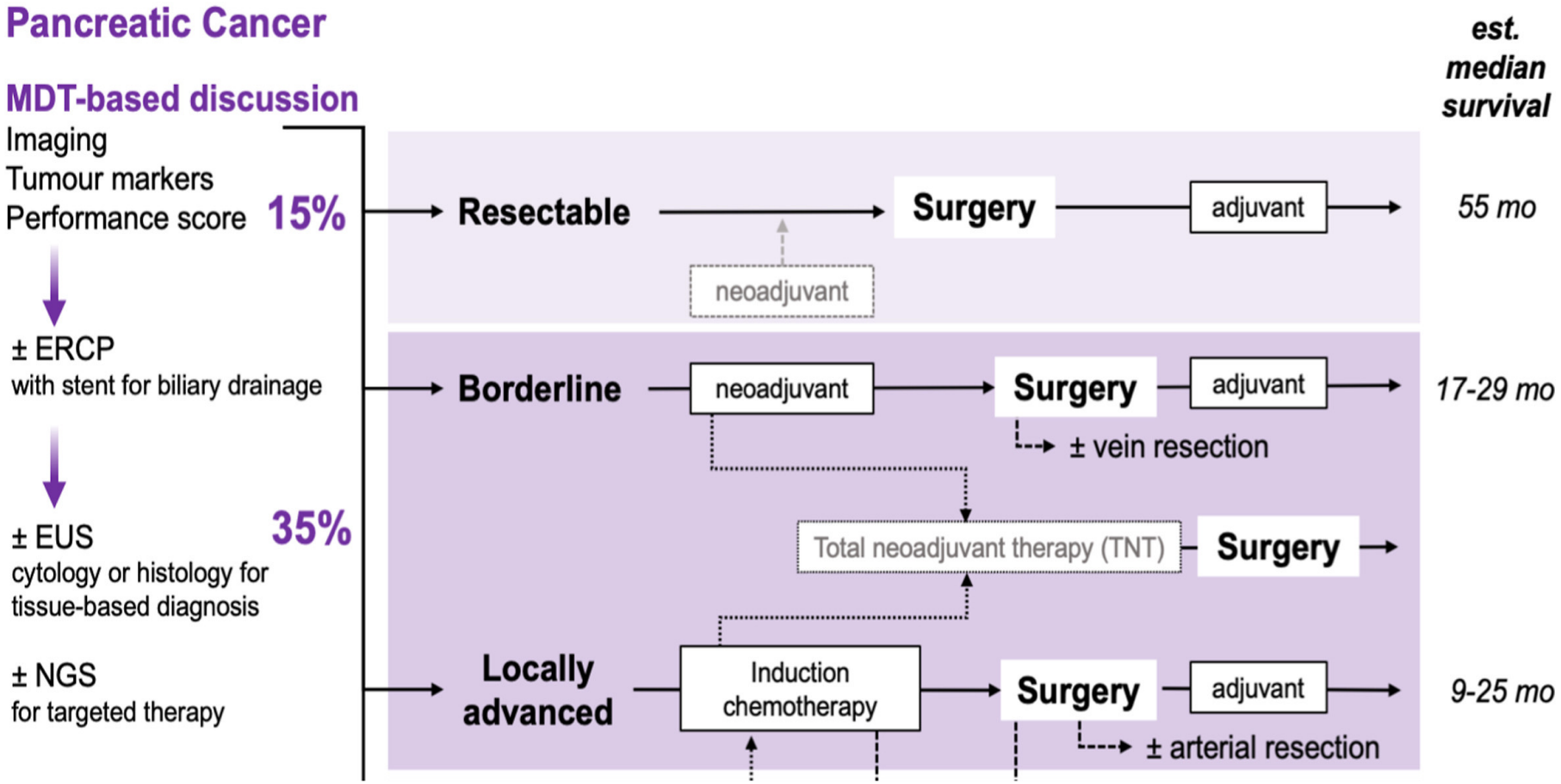


CONKO-007 Results (ASCO 2022)

	CT	CRT	p
Total (n)	167	168	
Surgery (n)	60 (35.9%)	61 (36.3 %)	1.000
R0	30 (18.0%)	42 (25.0%)	0.1433
R0 CRM – (n)	15 (9.0%)	33 (19.6%)	0.0015
R0 CRM + (n)	15 (9.0%)	9 (5.4%)	0.1777
R1 (n)	16 (9.6%)	5 (3.0%)	0.0085
pCR (n)	0	10 (6.0%)	0.0013
1-yr PFS rates	59.0 ± 0.04%	56.3 ± 0.04%	
2-yr PFS rates	17.5 ± 0.04%	24.1 ± 0.04%	
1-yr OS rates	71.3 ± 0.04%	71.1 ± 0.04%	
2-yr OS rates	32.5 ± 0.04%	34.8 ± 0.04%	

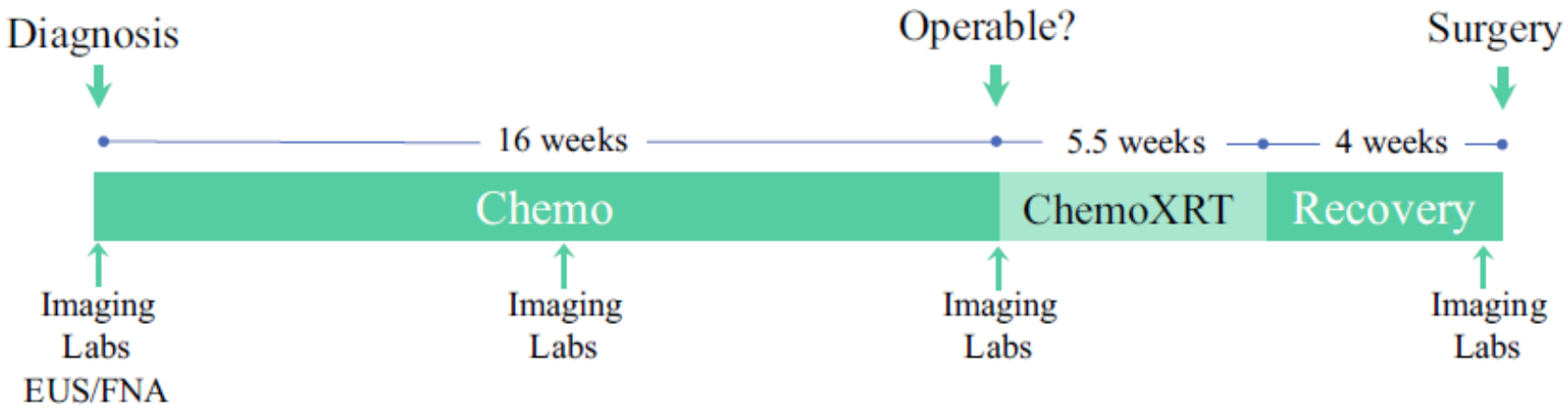
Addition of radiation may have increased R0 resection rate,
……but no impact on PFS or OS


Pancreatic Cancer
MDT-based discussion
Imaging
Tumour markers
Performance score
15%
± ERCP
with stent for biliary drainage
± EUS
cytology or histology for tissue-based diagnosis
35%
± NGS
for targeted therapy
est. median survival
Resectable
Surgery
adjuvant
55 mo
neoadjuvant
Borderline
neoadjuvant
Surgery
adjuvant
17-29 mo
± vein resection
Total neoadjuvant therapy (TNT)
Surgery
Locally advanced
Induction chemotherapy
Surgery
adjuvant
9-25 mo
± arterial resection

Total Neoadjuvant Therapy for Operable Pancreatic Cancer

Rebecca Y. Kim, MD, MPH[1], Kathleen K. Christians, MD[1], Mohammed Aldakkak, MD[1], Callisia N. Clarke, MD[1], Ben George, MD[2], Mandana Kamgar, MD, MPH[2], Abdul H. Khan, MD[3], Naveen Kulkarni, MD[4], William A. Hall, MD[5], Beth A. Erickson, MD[5], Douglas B. Evans, MD[1], and Susan Tsai, MD, MHS[1]

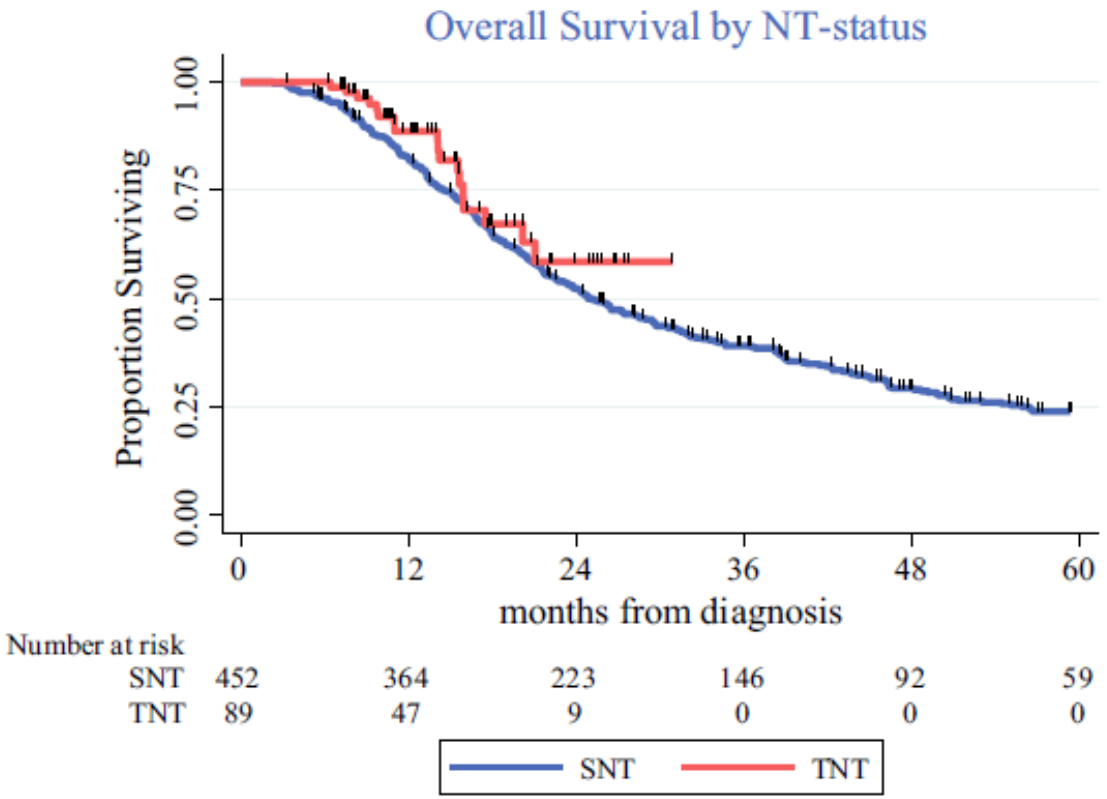
Ann Surg Oncol (2021) 28:2246–2256



MCW Experience

Resectable and Borderline Resectable

TNT = 64 patients (Standard neoadjuvant = 322 patients)



Thank you!