Updates in pancreas cancer

Pancreas Fest, University of Pittsburgh, 7/22/2022

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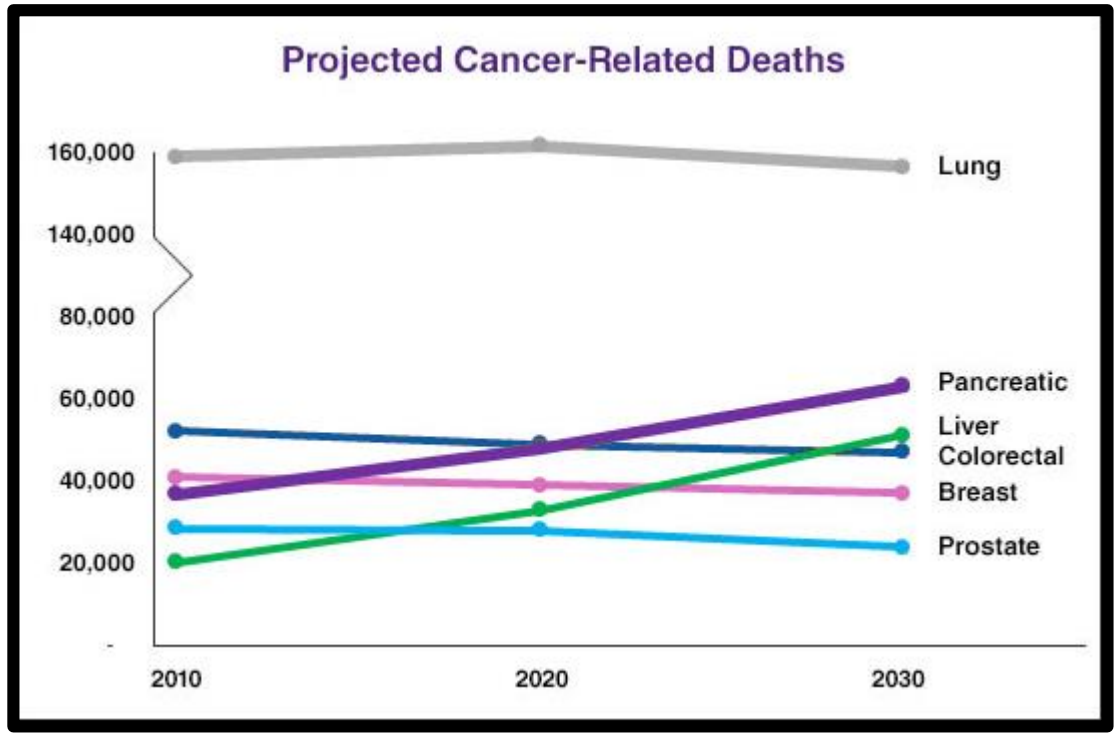
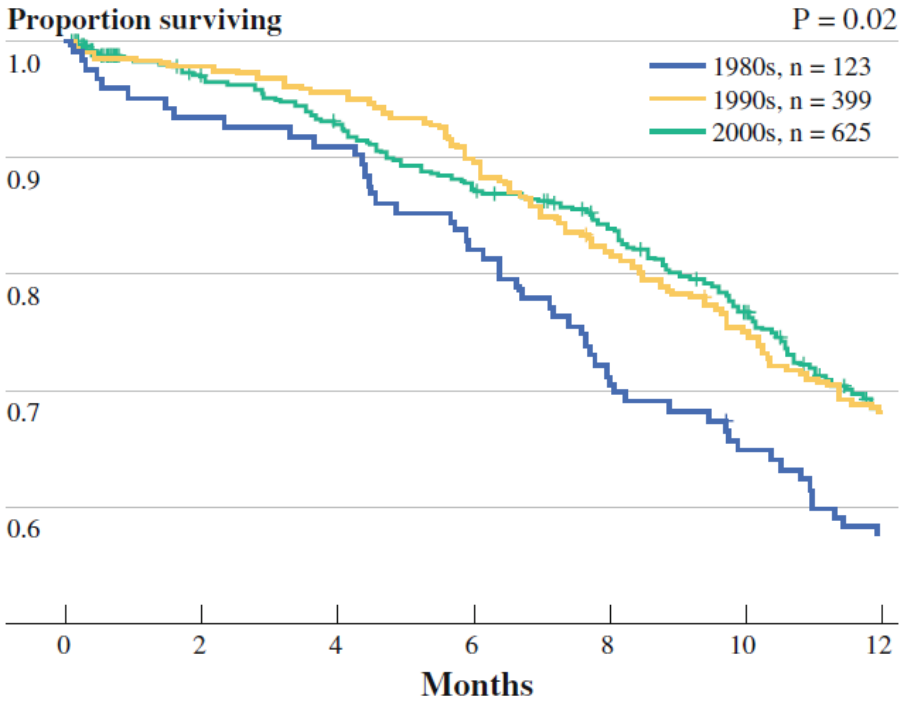
Pancreatic Adenocarcinoma

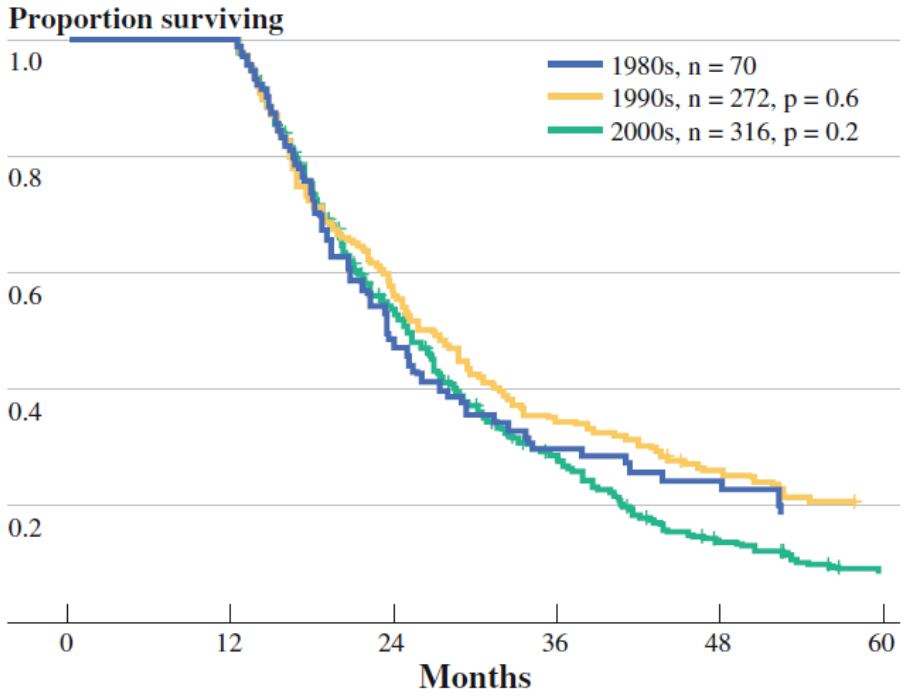
- Projected to be the 2nd leading cause of cancer death in US by 2030
- Overall 5 year survival <5%
- Resection is only chance for survival
- Minority of pts (10%) are resectable
- Best long-term outcome with multimodality therapy



Rahib et al, JAMA Network Open 2021

Pancreas Cancer Survival over 3 Decades

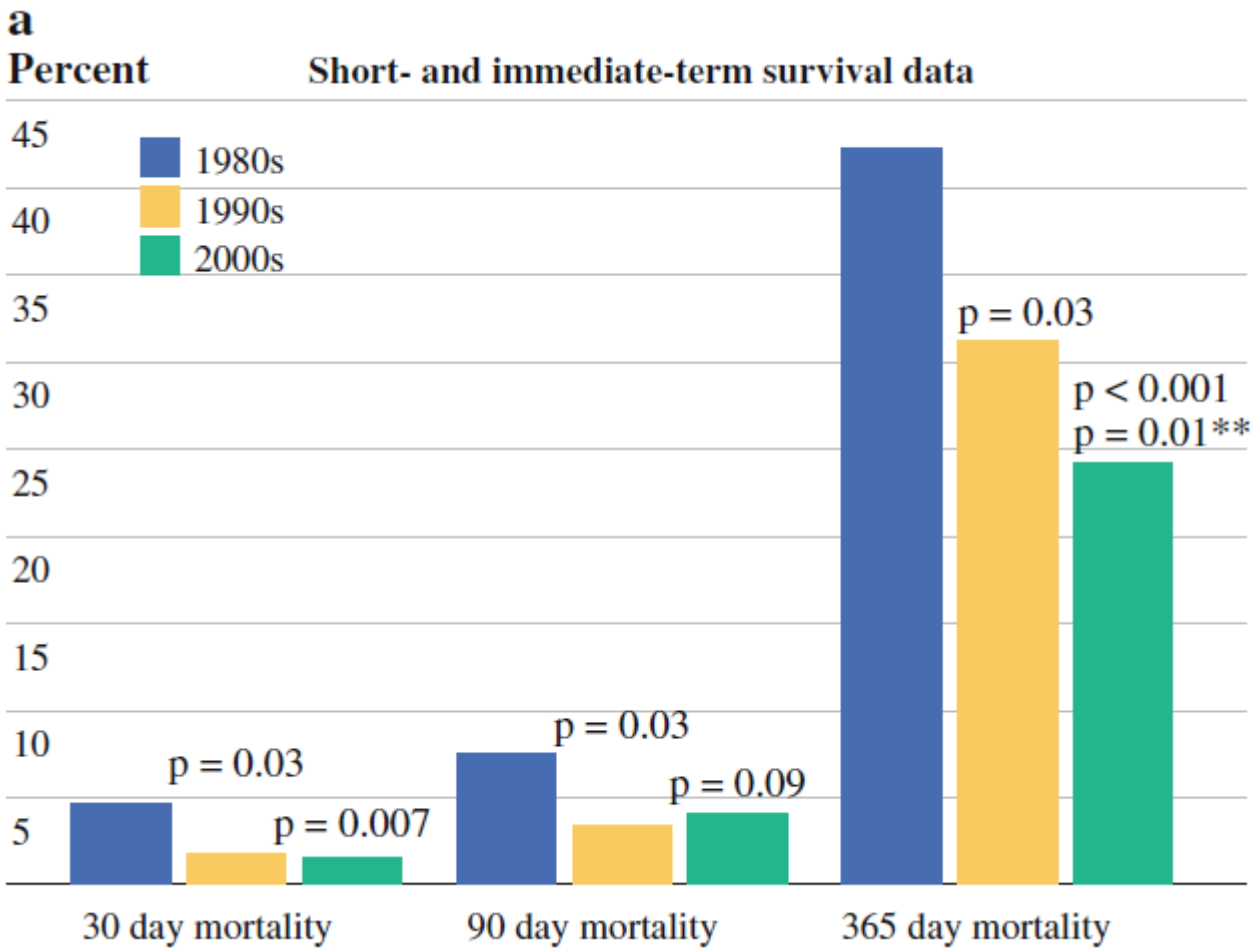




Decade	1 yr survival	Median survival
1980s	58%	23.2 months
1990s	68%	25.6 months
2000s	68%	24.5 months

Winter et al, Ann Surg Onc 2012

Pancreas Cancer Mortality over 3 Decades



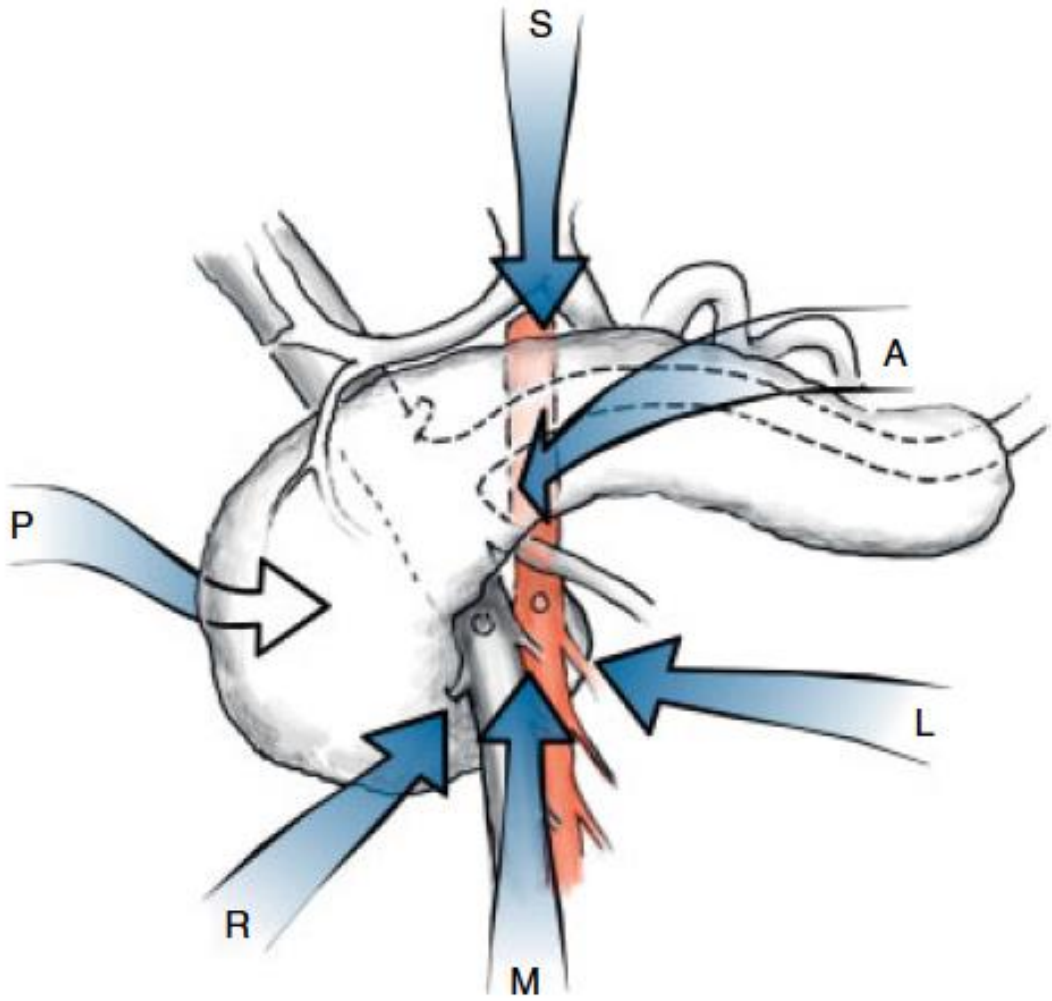
Winter et al, Ann Surg Onc 2012

How we can improve outcomes

- Make the operation safer
  - Reduce complications and rescue patients
  - Vascular resection and reconstruction techniques
- Improve patient selection
  - Preoperative staging with CT/MRI/EUS/PET
  - Pre-therapy and intraoperative staging with laparoscopy
- Add combination chemo/targeted/immuno/therapy
  - Extrapolate agents from metastatic disease
  - Determine optimal treatment sequencing
  - Find novel biomarkers for response

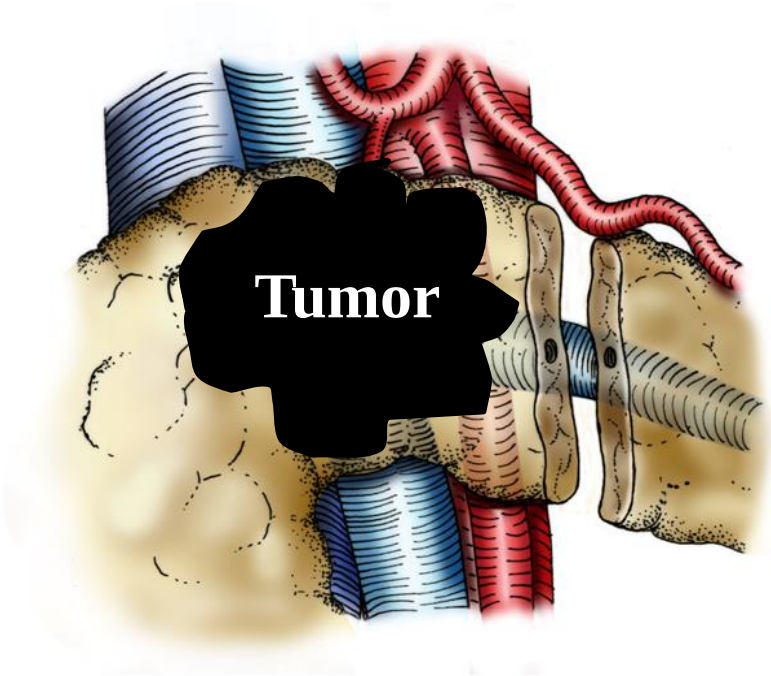
Vascular Resection

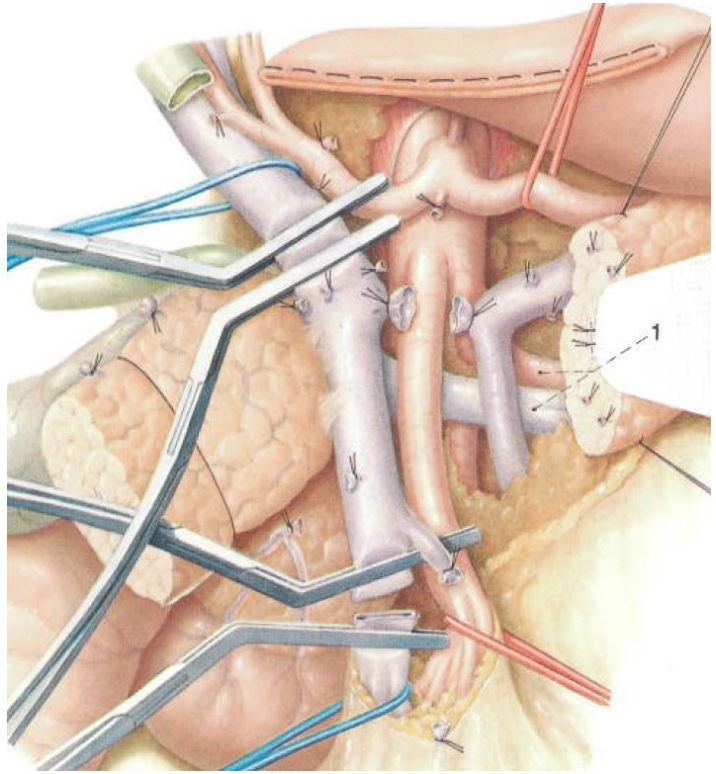
SMA First Approaches



Sanjay et al, BJS 2012

Anterior Approach: SMA Dissection
"WATSA"



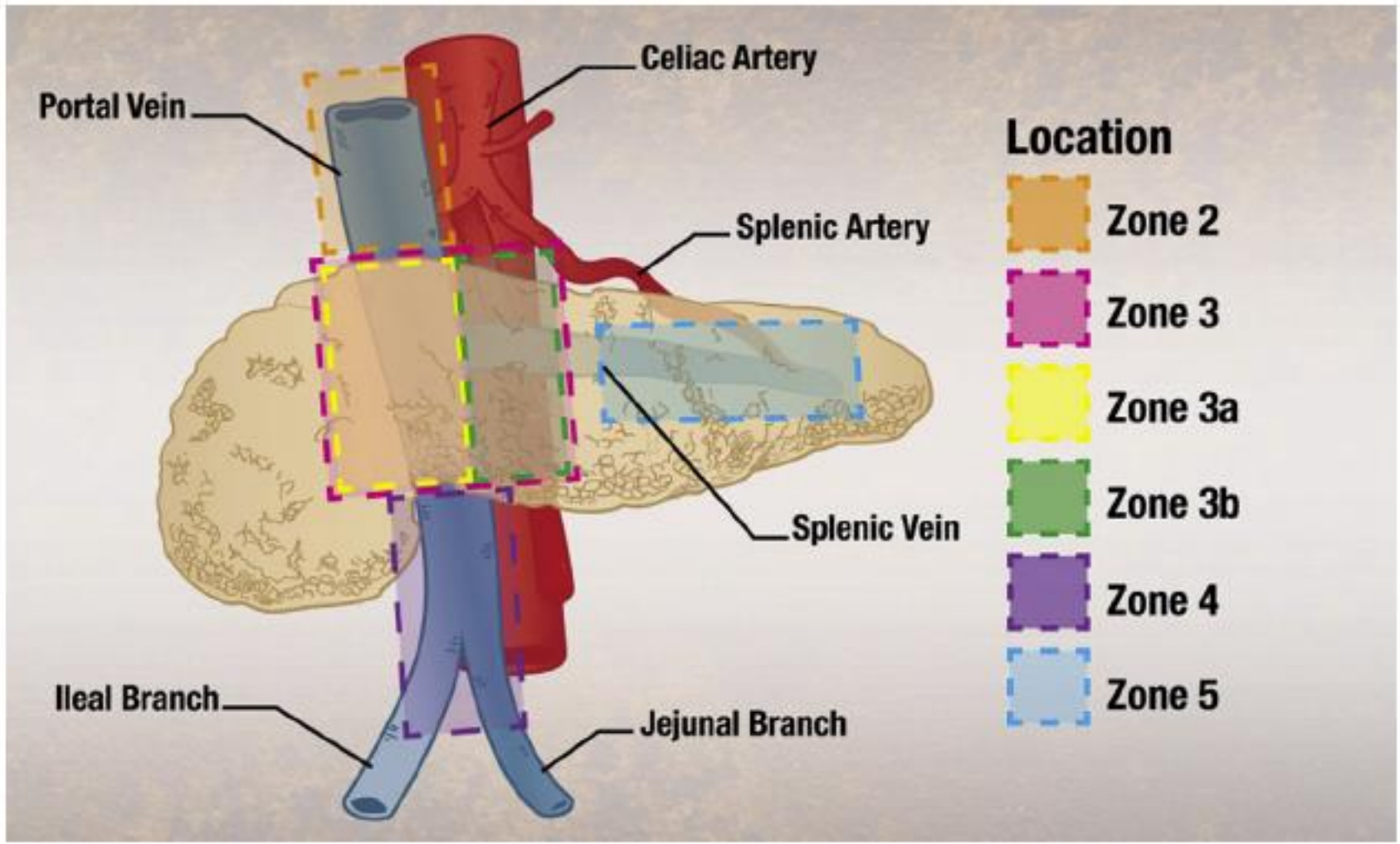


Strasberg SM, J Gastrointest Surg, 2012

ORIGINAL ARTICLE

Classification and techniques of en bloc venous reconstruction for pancreaticoduodenectomy

Farzad Alemi[1], Flavio G. Rocha[2], William S. Helton[2], Thomas Biehl[2] & Adnan Alseidi[2]



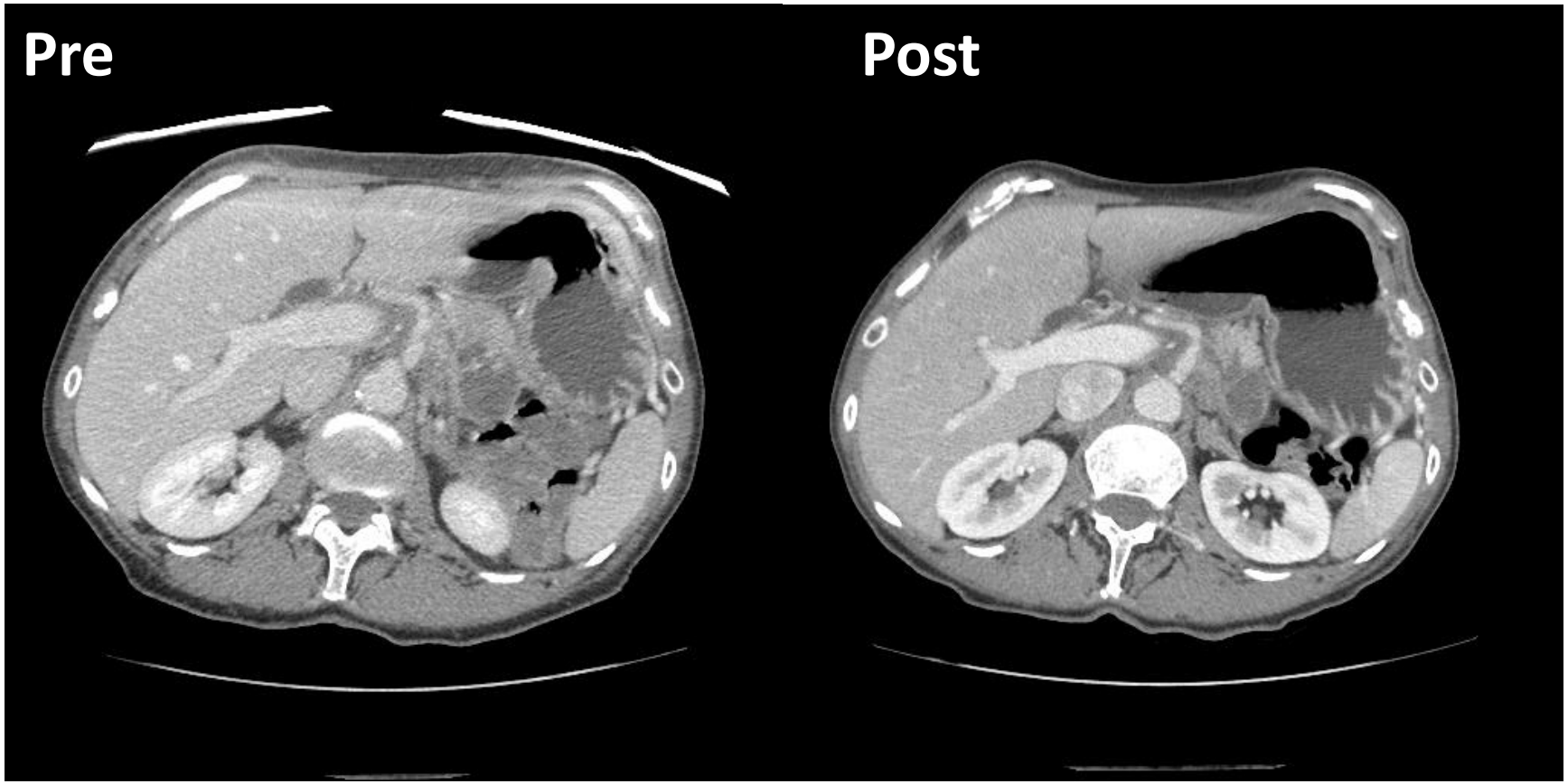
Classification and techniques of en bloc venous reconstruction for pancreaticoduodenectomy

Farzad Alemi[1], Flavio G. Rocha[2], William S. Helton[2], Thomas Biehl[2] & Adnan Alseidi[2]

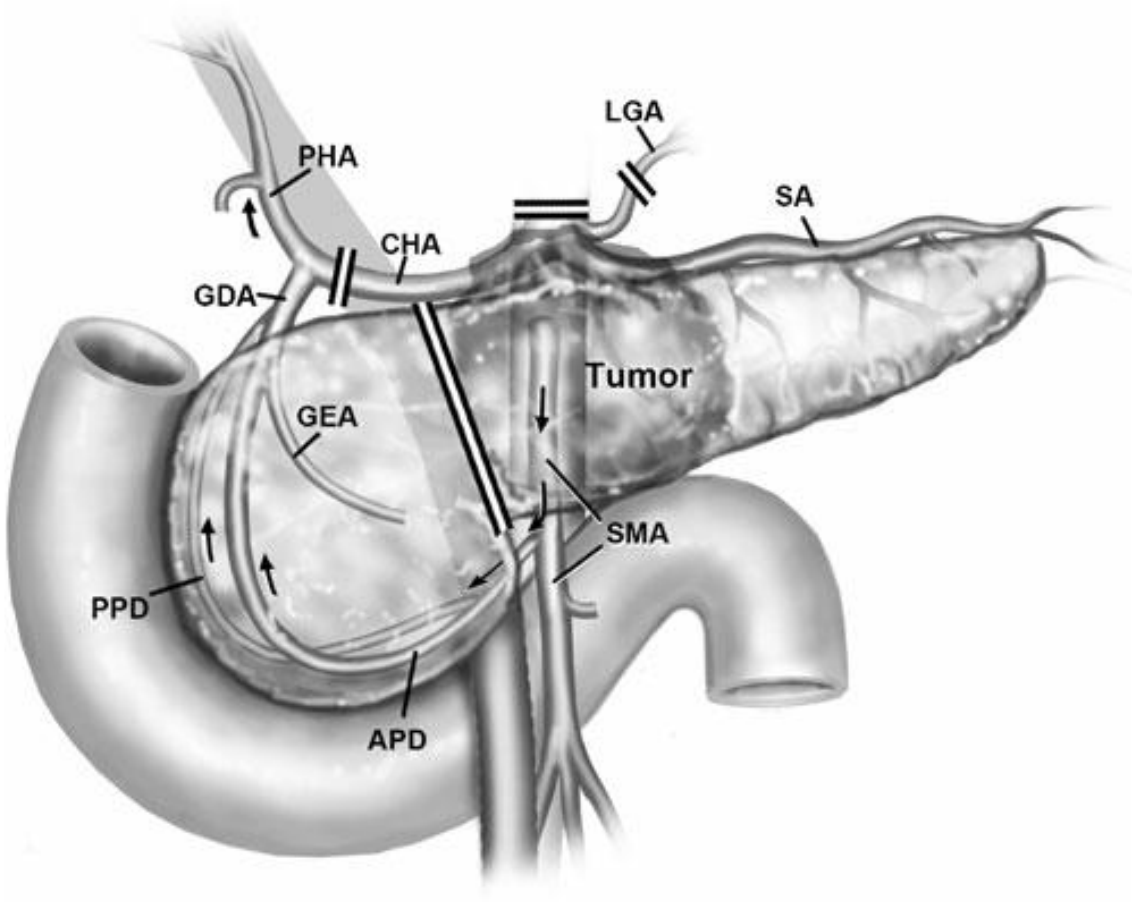
Table 1 Zones of venous involvement

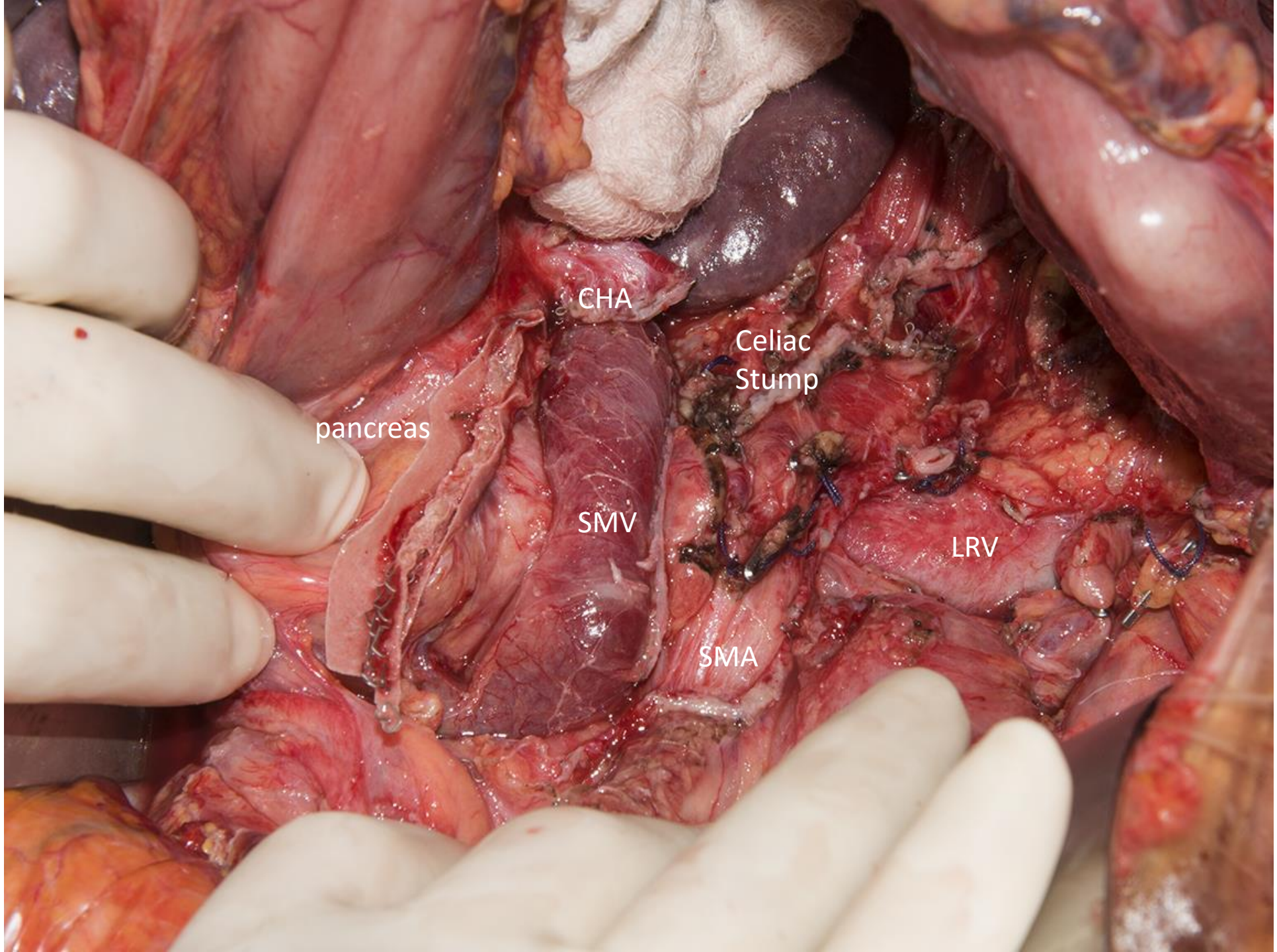
Zone	Venous involvement	Clinical scenario	Preparation	Procedure to perform with en bloc resection	Vascular reconstruction	Backup reconstruction
1	Hepatic Hilum	Hilar cholangioCa	1) Transect liver parenchyma; 2) Lower hilar plate	Liver Resection	1) End-to-end[g] 2) Patch repair[f]	Interposition graft
2	Hepatoduodenal Ligament	Distal cholangioCa Pancreas Head Tumors	1) Mobilize liver 2) Ligate coronary vein	Whipple	End-to-end[g]	Interposition graft
3	SV[a]/PV[b] confluence	1) Pancreas head tumors 2) Pancreas neck tumors 3) Pancreatitis	SMA first approach	WATSA[c]	End-to-end[g]	Interposition graft
3a	Right SV[a]/PV[b]			Whipple	Transverse plication[e]	1) Vein patch[f] 2) End-to-end[g]
3b	Left SV[a]/PV[b]			RAMPS[d]	Vein Patch[f]	
4	Infra-confluence	Pancreas head tumors	1) SMA first 2) Isolate jejunal/ileal branches 3) Liver mobilization	Whipple	1) End-to-end[g] 2) Interposition graft 3) Patch repair[f]	Ligating splenic vein → end-end repair
5	Splenic vein	Pancreas Body and Tail tumors		RAMPS[d]	None	

LAPC with Celiac Axis Involvement

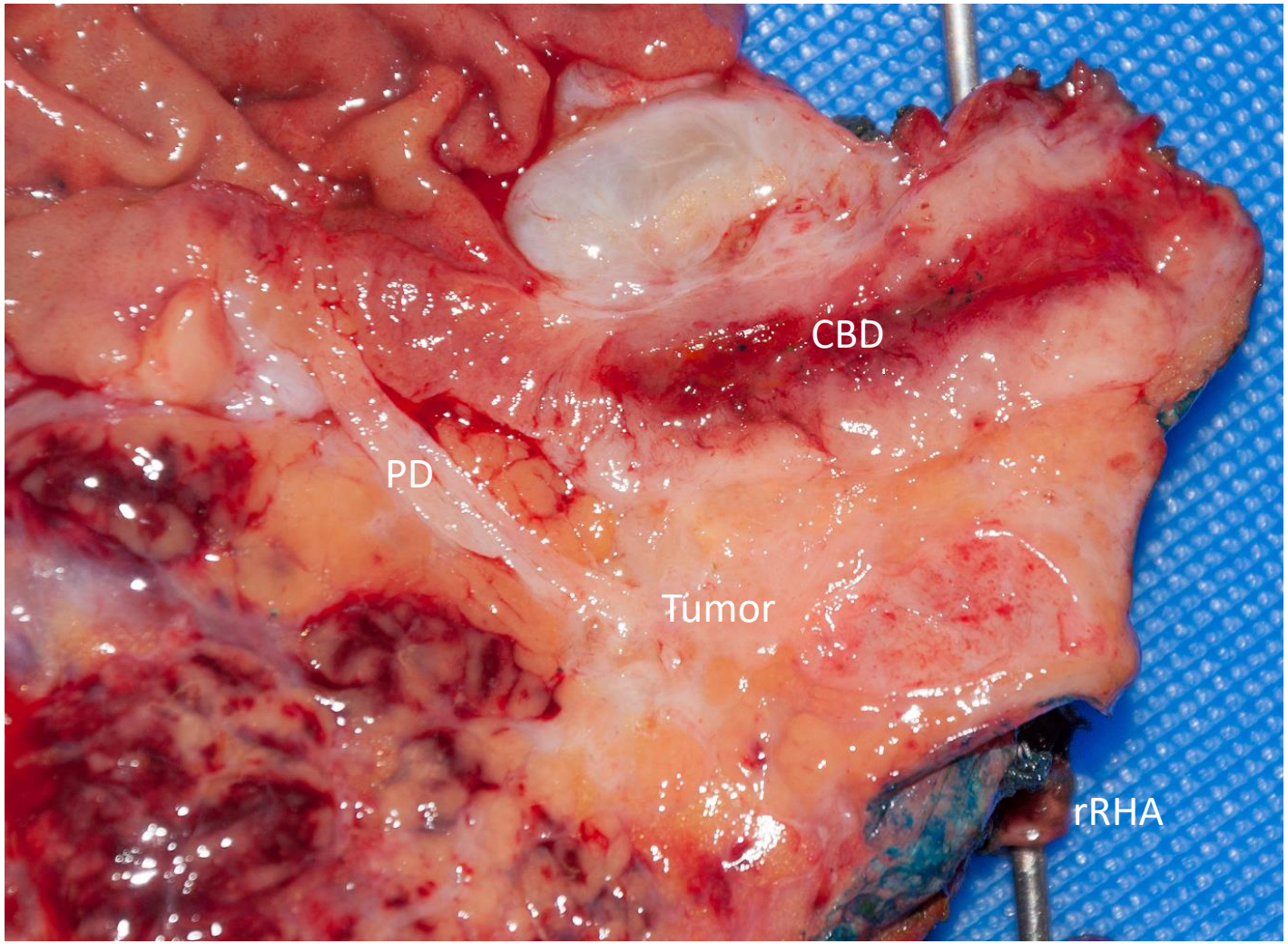


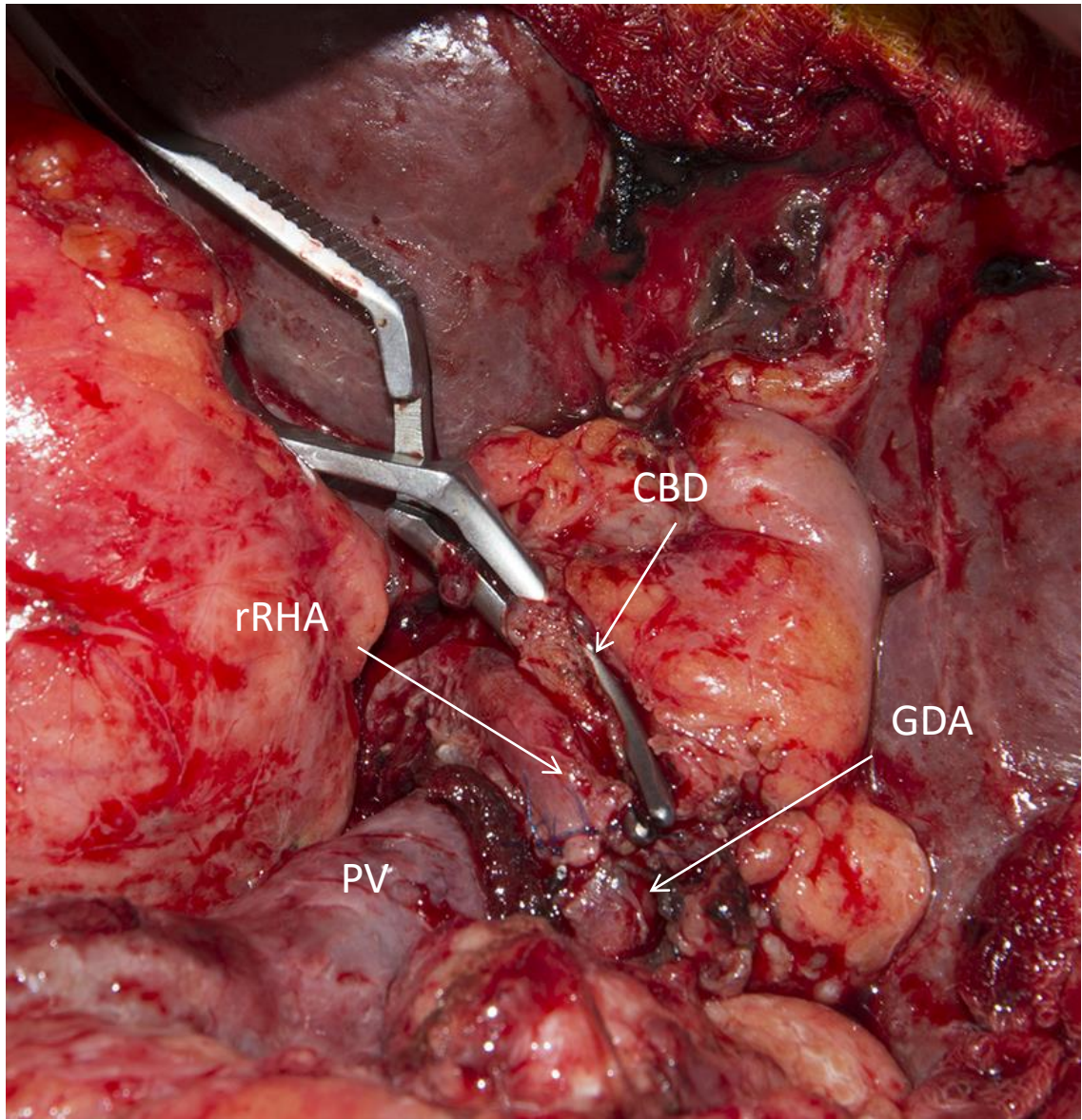
Distal Pancreatectomy with En Bloc Celiac Axis Resection: Appleby Procedure



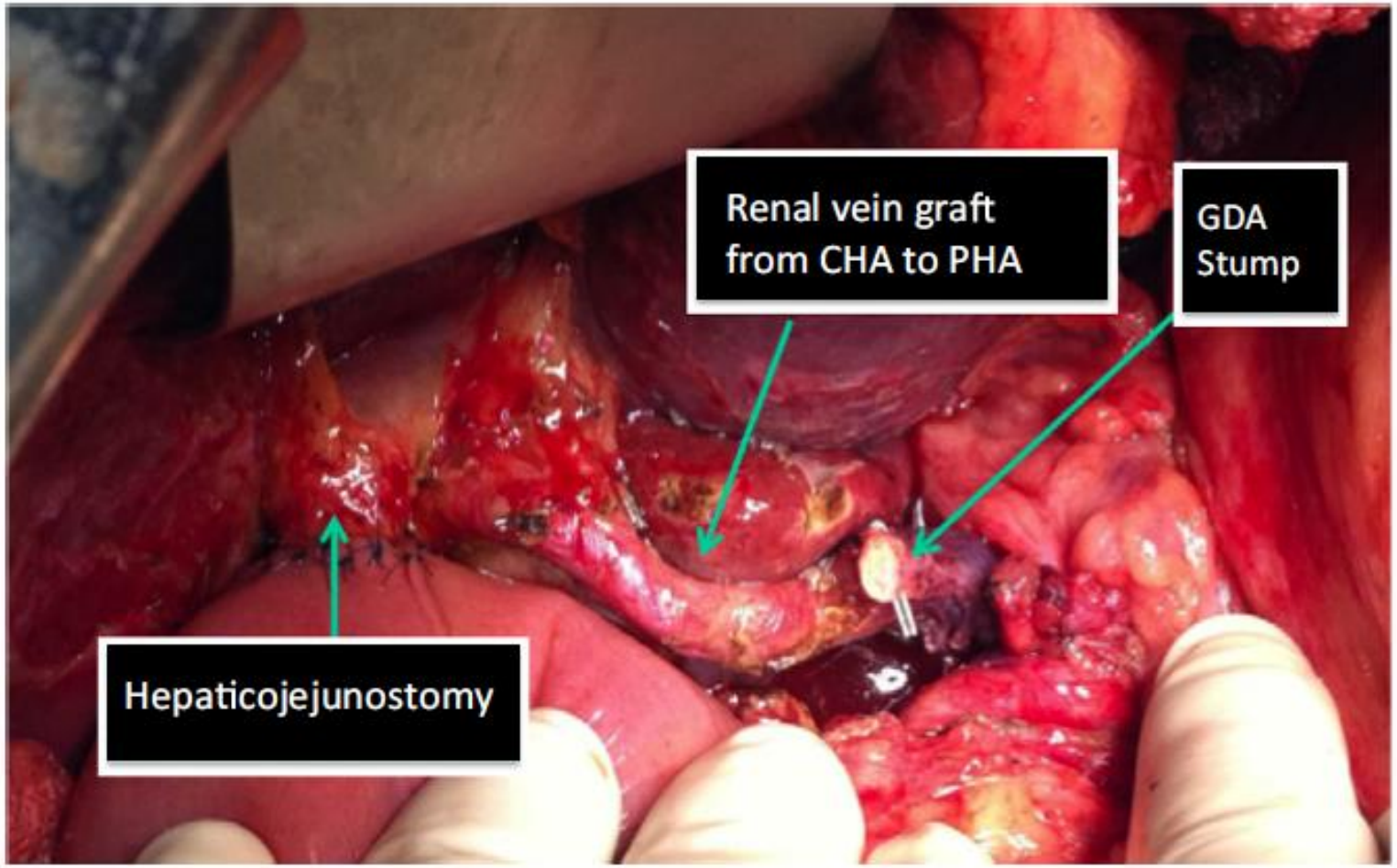

CHA
Celiac
Stump
pancreas
SMV
LRV
SMA

Arterial Reconstruction for Aberrant Anatomy





Short Segment CHA Resection



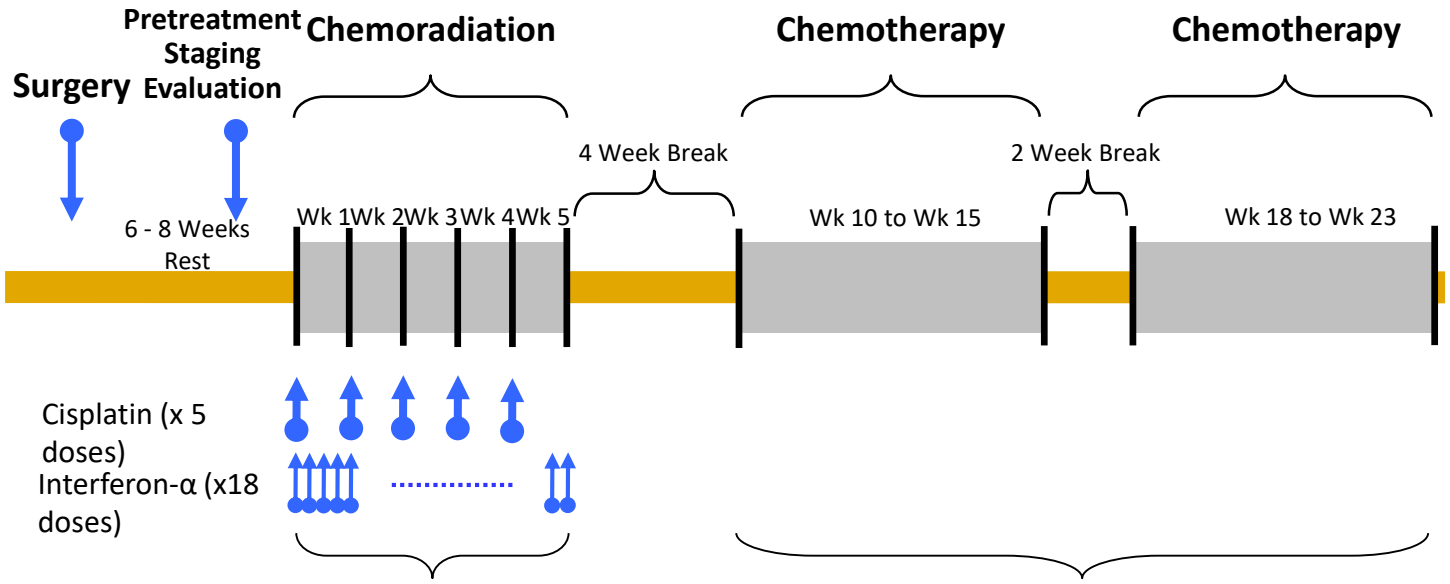
Adjuvant Therapy Trials

Historical Adjuvant Therapy Trials

- Chemotherapy
  - The data **supports** adjuvant chemotherapy
  - CONKOO-001- DFS and OS benefit with gemcitabine
  - ESPAC 1- OS benefit with 5FU/LV
  - ESPAC 3- Gemcitabine and 5FU/LV equivalent OS
  - JASPAC 1- S1 is equal or better than gemcitabine

- Chemoradiation
  - The data is **mixed** for adjuvant chemoradiation (CRT)
  - GITSG- Improved survival when CRT added to surgery
  - EORTC 40891- No difference with the addition of CRT
  - RTOG 9704- No difference when gem added to 5FU-XRT
  - RTOG 0848- Awaiting final CRT results, no benefit to erlotinib with gemcitabine

Treatment Regimen of Adjuvant Interferon-Based Chemoradiation Therapy (IFN-CRT)



EBRT 4,500 to 5,400 cGy (25 fractions for 5 weeks) 5-FU continuous infusion (200 mg/m^2 daily) Cisplatin weekly (30mg/m^2 IV) Interferon-α every other day (3x10^6 units s/c)	5-FU continuous infusion (200 mg/m^2 daily) 6 weeks x 2 course (2 weeks brake)

Interferon-based adjuvant chemoradiation therapy after pancreaticoduodenectomy for pancreatic adenocarcinoma

Vincent J. Picozzi, M.D.[a], Richard A. Kozarek, M.D.[a], L. William Traverso, M.D.[b,*]

[a]*Departments of General Surgery, Medical Oncology, and Gastroenterology, Virginia Mason Medical Center, Seattle, WA, USA*
[b]*Section of General, Vascular, and Thoracic Surgery, 1100 Ninth Ave., C6-GSURG, Seattle, WA 98111, USA*

Manuscript received January 13, 2003; revised manuscript January 23, 2003

Presented at the 89th Annual Meeting of the North Pacific Surgical Association, Seattle, Washington, November 8–9, 2002

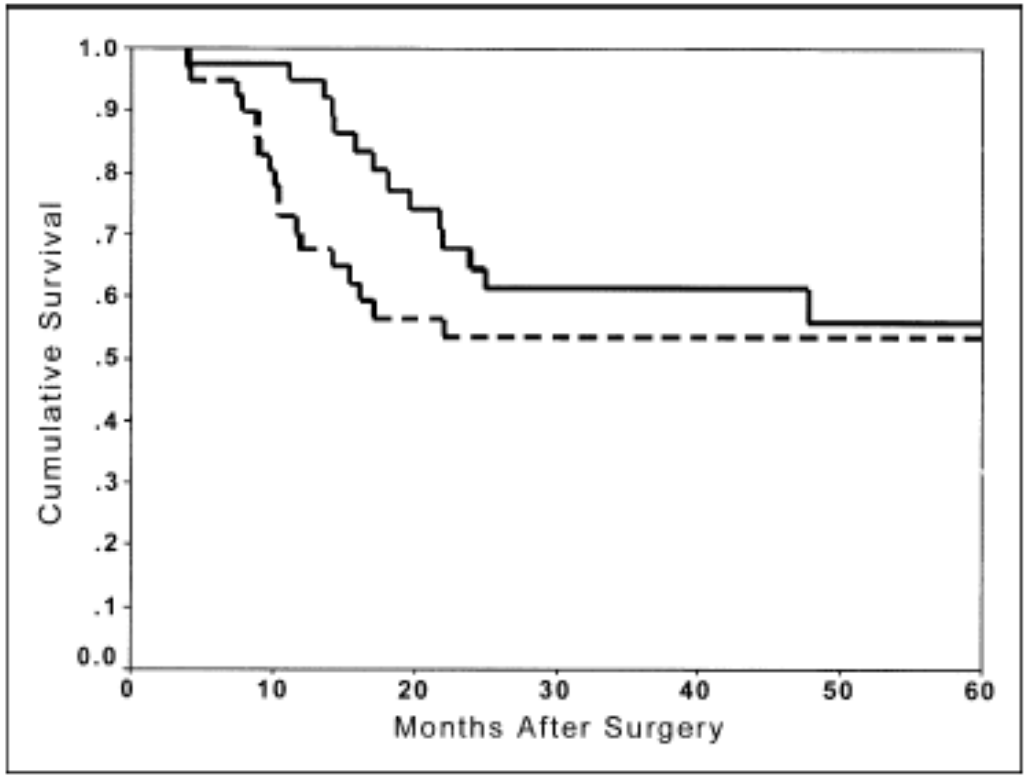


Table 1
Kaplan-Meier survival statistics

Time	Overall survival (95% CI)	Disease-free survival (95% CI)
One year	95% (91%–98%)	67% (60%–74%)
Two years	64% (56%–72%)	52% (44%–60%)
Three years	64% (56%–72%)	52% (44%–60%)
Five years	55% (46%–65%)	52% (44%–60%)
Follow-up (months)		
Mean ± SD	31.9 ± 24.6	29.7 ± 25.9
Median (range)	21.8 (4–86)	16.0 (3.9–86)

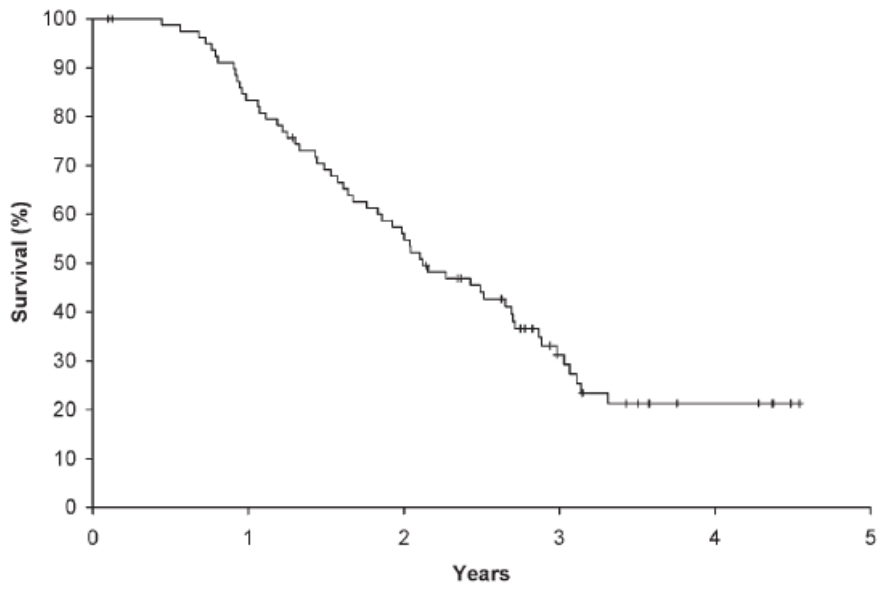
Median survival could not be calculated as 29 of 43 patients (67%) are still alive.

CI = confidence interval.

Multicenter phase II trial of adjuvant therapy for resected pancreatic cancer using cisplatin, 5-fluorouracil, and interferon-alfa-2b–based chemoradiation: ACOSOG Trial Z05031

V. J. Picozzi[1]*, R. A. Abrams[2], P. A. Decker[3], W. Traverso[4], E. M. O'Reilly[5], E. Greeno[6], R. C. Martin[7], L. S. Wilfong[8], M. L. Rothenberg[9], M. C. Posner[10] & P. W. T. Pisters[11] for the American College of Surgeons Oncology Group

Annals of Oncology 22: 348–354, 2011



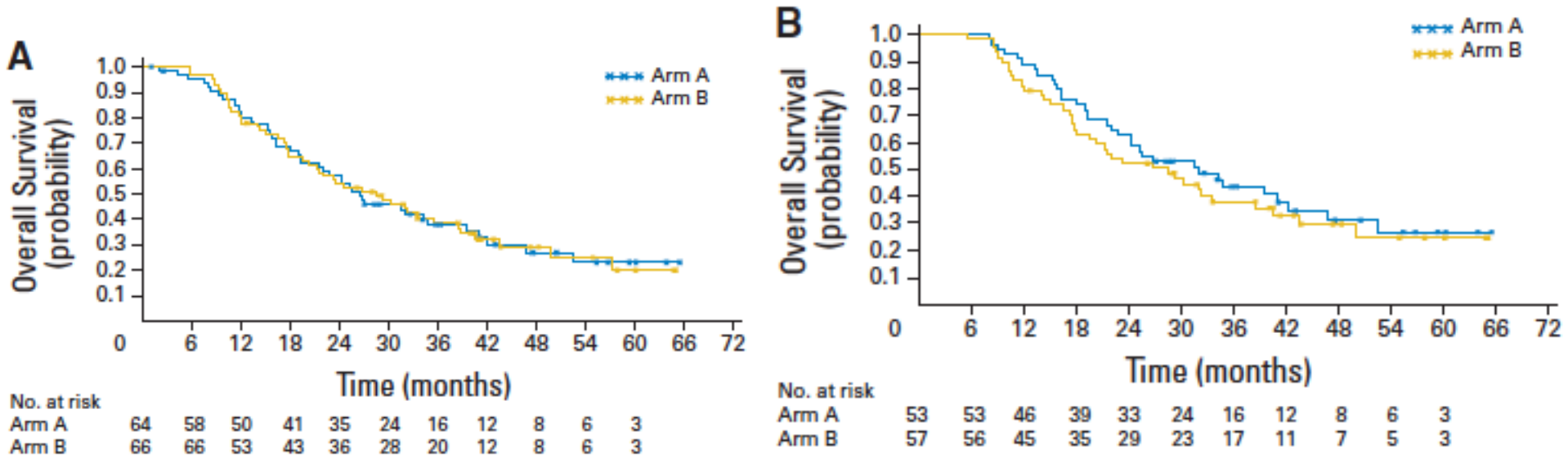
Study	Overall survival		
	Median, months	2 Years, %	5 Years, %
GITSG (chemoradiation) [17]	21	43	19
EORTC (chemoradiation) [2]	17.1	37	20
ESPAC-1 (chemotherapy) [3]	20.1	39	21
RTOG 9704 (gemcitabine) [14]	20.6	31 (3 years)	–
RTOG 9704 (5-FU) [14]	16.7	21 (3 years)	–
CONKO-001 (gemcitabine) [4]	22.8	48	21
ESPAC-3 [5]	23.3	48	–
EORTC/FFCD/GERCOR [18]	24.0	50	–
VMMC[a] [13]	43.7	56	44
Washington, St Louis [19]	25	56	–
ACOSOG Z05031	25.4	59	–

80 pts (95%) experienced ≥ grade 3 toxicity
Trial stopped at 84/88 by DSMB for safety

Open-Label, Multicenter, Randomized Phase III Trial of Adjuvant Chemoradiation Plus Interferon Alfa-2b Versus Fluorouracil and Folinic Acid for Patients With Resected Pancreatic Adenocarcinoma

J Clin Oncol 30:4077-4083. © 2012

Jan Schmidt, Ulrich Abel, Jürgen Debus, Sabine Harig, Katrin Hoffmann, Thomas Herrmann, Detlef Bartsch, Justus Klein, Ulrich Mansmann, Dirk Jäger, Lorenzo Capussotti, Reiner Kunz, and Markus W. Büchler

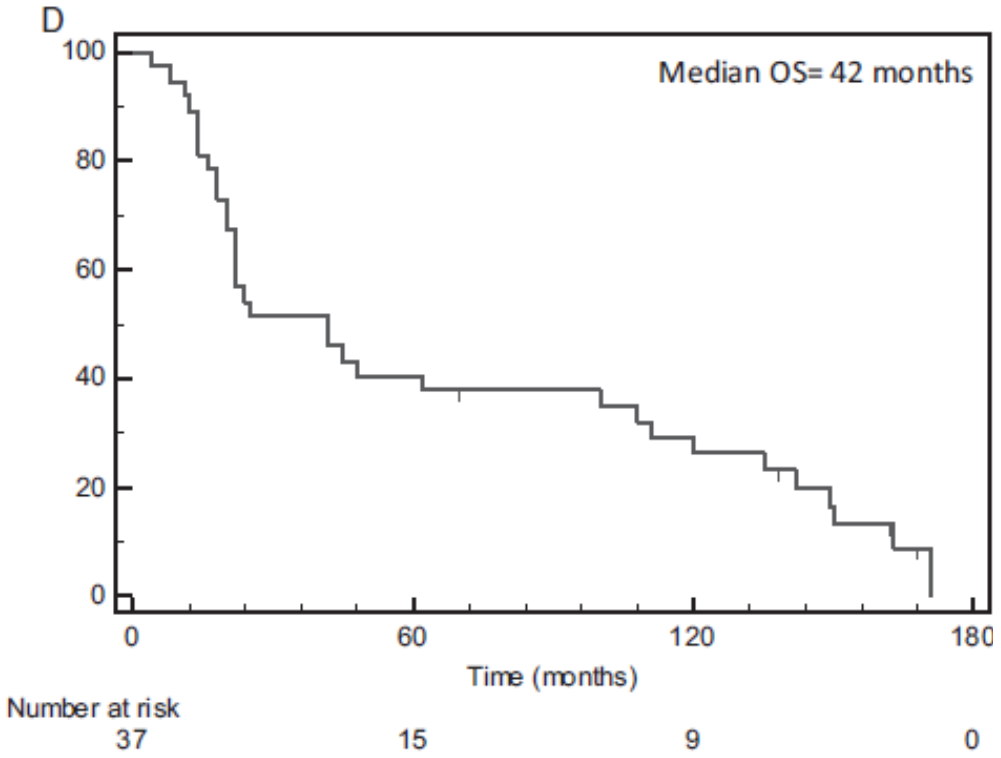


Arm A- IFN-CRT+FU Median OS 32.1 months
Arm B- 5FU and FA Median OS 28.5 months p<0.49

Interferon-based Adjuvant Chemoradiation for Resected Pancreatic Head Cancer

Long-term Follow-up of the Virginia Mason Protocol

Flavio G. Rocha, MD, Yashushi Hashimoto, MD, PhD,† L. William Traverso, MD,‡ Russell Dorer, MD,§ Richard Kozarek, MD,¶ W. Scott Helton, MD,* and Vincent J. Picozzi, MD||*



Ann Surg 2016

43 pts treated from 1995-2003
28 with conventional PDAC
9 with PDAC in IPMN
6 with periampullary tumors

Median follow-up of 45 months
7 still alive and disease-free
9 died of other causes

70% Grade 3 or 4 toxicity
42% required hospitalization

5 yr actual survival 42%
10 yr actual survival 28%

Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial

Lancet 2017; 389: 1011–24

John P Neoptolemos, Daniel H Palmer, Paula Ghaneh, Eftychia E Psarelli, Juan W Valle, Christopher M Halloran, Olusola Faluyi, Derek A O'Reilly, David Cunningham, Jonathan Wadsley, Suzanne Darby, Tim Meyer, Roopinder Gillmore, Alan Anthoney, Pehr Lind, Bengt Glimelius, Stephen Falk, Jakob R Izbicki, Gary William Middleton, Sebastian Cummins, Paul J Ross, Harpreet Wasan, Alec McDonald, Tom Crosby, Yuk Ting Ma, Kinnari Patel, David Sherriff, Rubin Soomal, David Borg, Sharmila Sothi, Pascal Hammel, Thilo Hackert, Richard Jackson, Markus W Büchler, for the European Study Group for Pancreatic Cancer

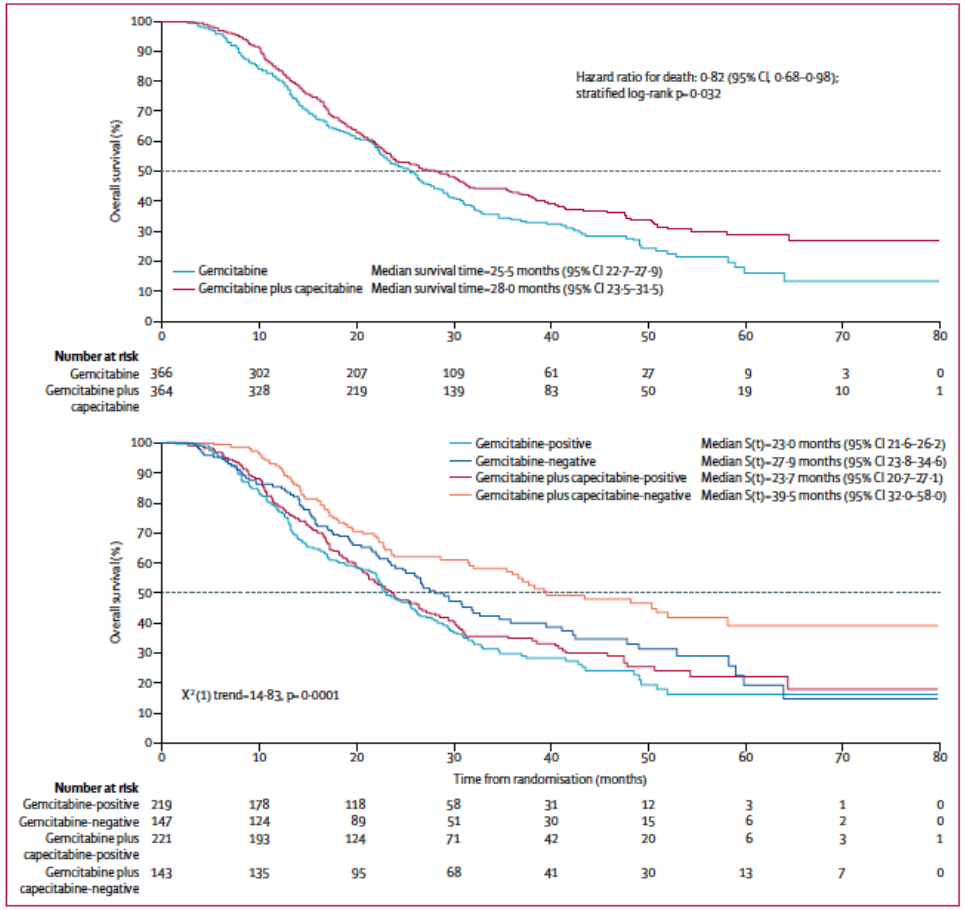


Figure 2: Kaplan Meier plots for overall survival (A) and for overall survival by resection margin status and treatment group (B)

<u>Unselected</u> postoperative population

732 pts in 92 European hospitals

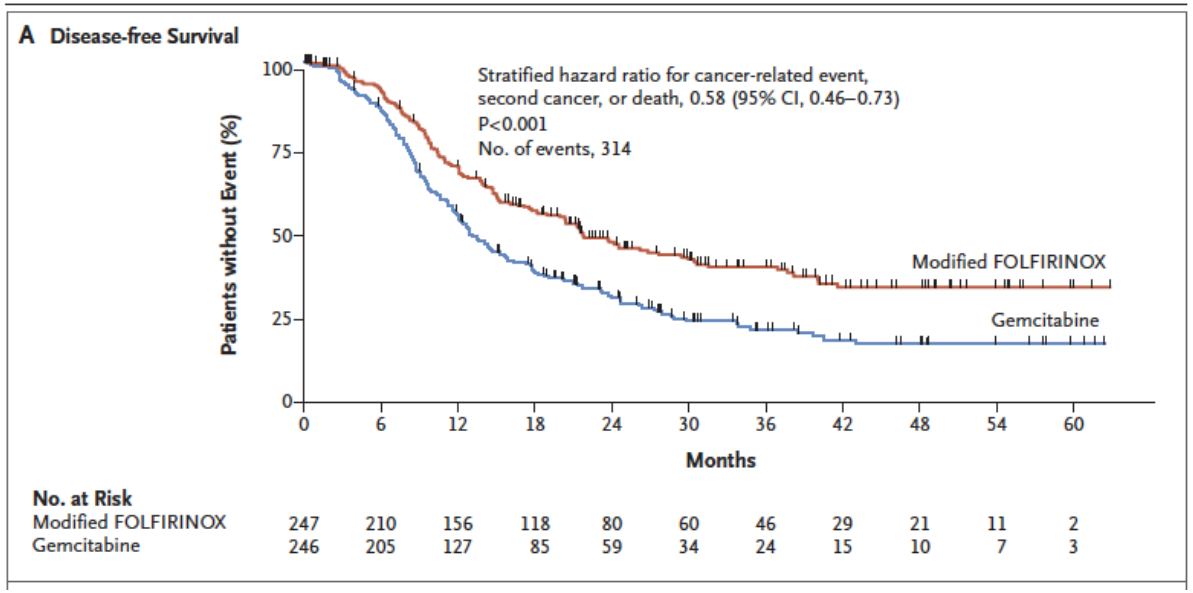
R0 or R1 resections

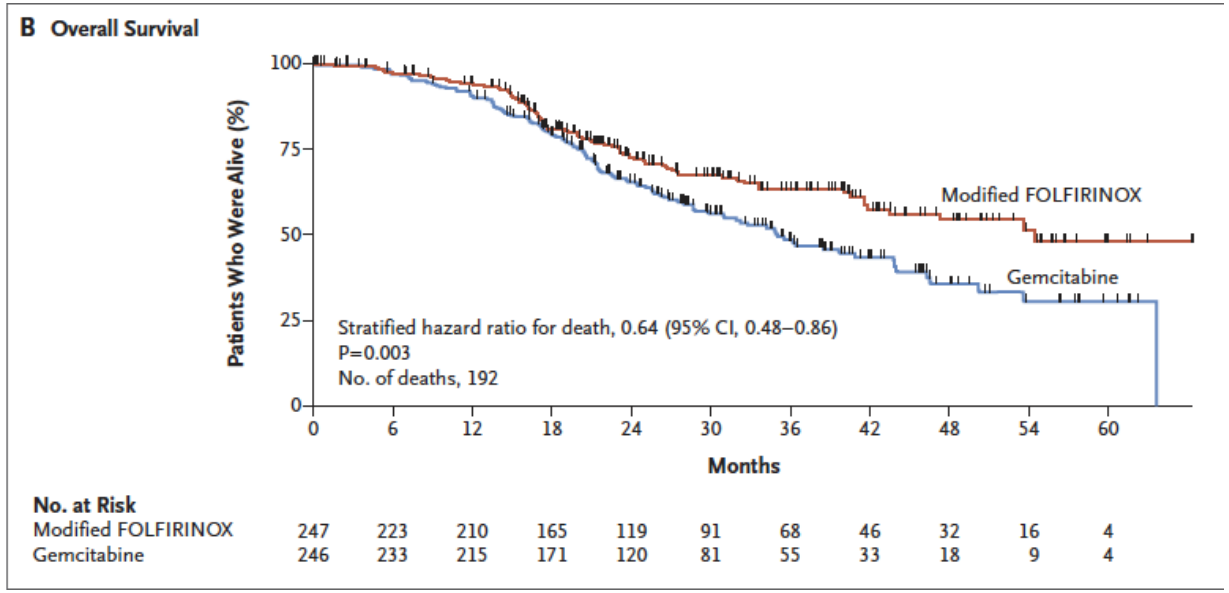
Median OS for gem/cap 28 months vs gem alone 25.5 months

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

N ENGL J MED 379;25 NEJM.ORG DECEMBER 20, 2018

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*





Must have CA 19-9 <180 prior to randomization

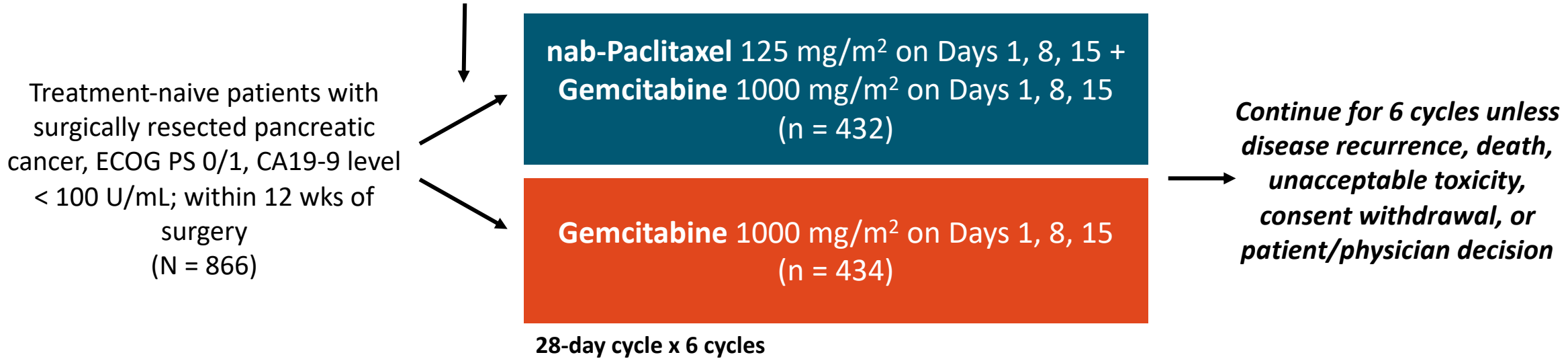
Mean age <u>63 years</u>

Median OS for FOLFIRINOX 54 months vs 35 months with gemcitabine

APACT: Study Design

- Randomized, multicenter, international, open-label phase III trial

Stratified by resection status (R0/R1), lymph node status (LN+/-), geography



- Primary endpoint: DFS by independent review (first adjuvant trial in pancreatic cancer using independently assessed DFS as the primary endpoint)
- Secondary endpoints: OS, safety
- Prespecified sensitivity analysis included investigator-assessed DFS; exploratory endpoints included QoL, tumor and blood biomarker analysis

Tempero. ASCO 2019. Abstr 4000.

Slide credit: clinicaloptions.com

APACT: DFS and OS

	nab-Paclitaxel + Gemcitabine (n = 432)	Gemcitabine (n = 434)	HR (95% CI)	*P* Value
Median DFS by independent review, mos	19.4	18.8	0.88 (0.729-1.063)	.1824
Median DFS by investigator review, mos	16.6	13.7	0.82 (0.694-0.965)	.0168
Median OS,* mos	40.5	36.2	0.82 (0.680-0.996)	.045

- Median treatment duration was 24 wks in both arms; 69% of patients completed 6 cycles
- In prespecified subgroup analysis, nab-paclitaxel + gemcitabine demonstrated DFS benefit (by independent review) in patients with moderately differentiated tumors, lymph node–positive disease, or normal baseline CA19-9 levels and OS benefit in patients with ECOG PS 1, moderately differentiated tumors, lymph node positive–disease, or normal baseline CA19-9 levels

*Interim analysis; OS data 68% mature.

Tempero. ASCO 2019. Abstr 4000.

Slide credit: clinicaloptions.com

Neoadjuvant Therapy Trials

Phase II Neoadjuvant Therapy Trials

Instit.	Era	#	Regimen	R0	Med Surv
FCCC	1996- 03	63	Gem + RT	65%	20 mths
MDACC	1998- 01	86	Gem + RT	74%	34 mths* (64) 22 mths
MDACC	2002- 06	90	Gem+Cis → Gem+RT	83%	31 mths* (52) 17.4 mths
Heinrich	2008	28	Gem + Cis	86%	26 mths

Meszoely, Surg Onc Clin NA, 2004. Evans, JCO, 2008
Varadachary, JCO, 2008. Heinrich, Ann Surg, 2008

JAMA Surgery

Original Investigation

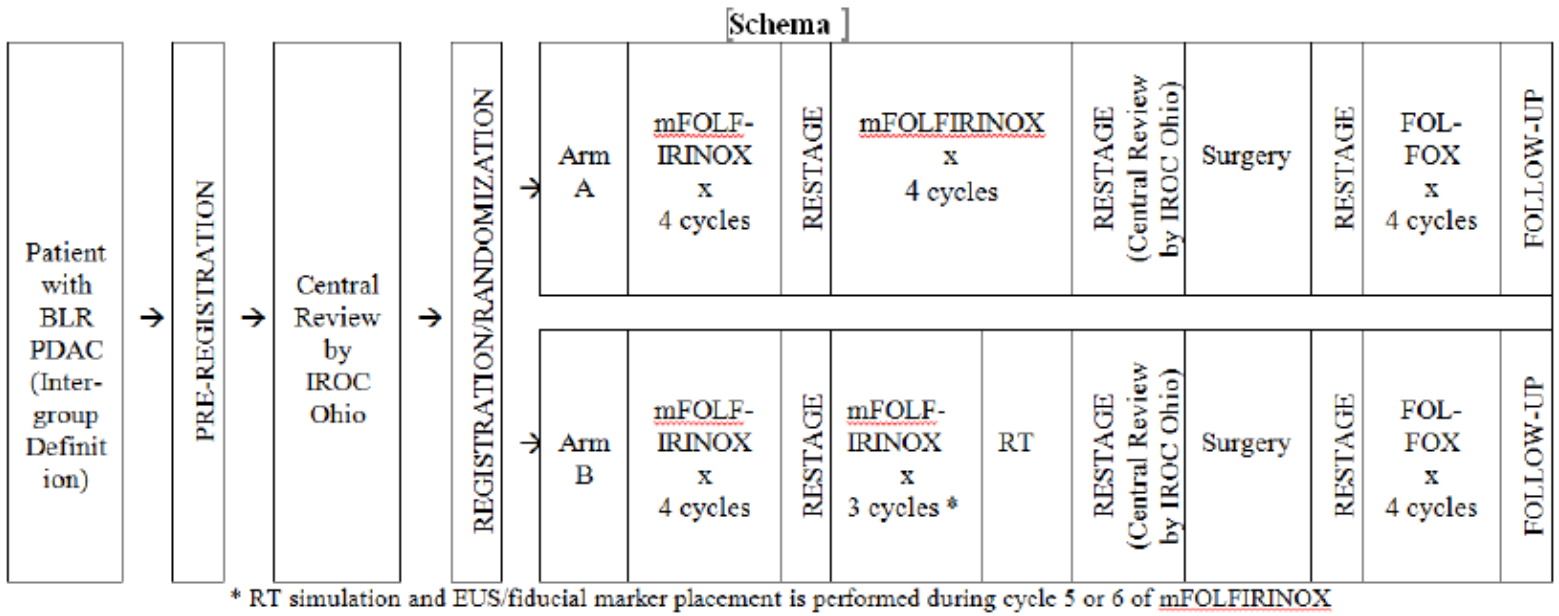
Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer

Alliance for Clinical Trials in Oncology Trial A021101

Matthew H. G. Katz, MD; Qian Shi, PhD; Syed A. Ahmad, MD; Joseph M. Herman, MD; Robert de W. Marsh, MD; Eric Collisson, MD; Lawrence Schwartz, MD; Wendy Frankel, MD; Robert Martin, MD; William Conway, MD; Mark Truty, MD; Hedy Kindler, MD; Andrew M. Lowy, MD; Tanios Bekaii-Saab, MD; Philip Philip, MD, PhD; Mark Talamonti, MD; Dana Cardin, MD; Noelle LoConte, MD; Perry Shen, MD; John P. Hoffman, MD; Alan P. Venook, MD

- Toxicity (Grade III/IV)
  - Chemotherapy (46/5), CRT (38/0), Surg (15/31)
- 22/23 started therapy, 21 completed XRT
  - 2 CR, 4 PR, 15 SD, 1 PD
  - 15 underwent resection (68%), 14 R0 (93%)
  - 80% required vein resection, 7% HA resection
  - 7 (47%) had less than 5% viable tumor in specimen
  - 1 90 day mortality
  - 18 pts alive with median follow-up of 10 months

Pancreas SBRT, A021501 Schema



[13]ARM B closed early due to R0 resection futility

ARM A yielded an 18-month OS rate of 66.4%, median OS duration of 29.8 months

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

Eva Versteijne, MD[1]; Mustafa Suker, MD, PhD[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]; Ferry A.L.M. Eskens, MD, PhD[9]; Sebastiaan Festen, MD, PhD[10]; Jan Willem B. de Groot, MD, PhD[11]; Bas Groot Koerkamp, MD, PhD[2]; Ignace H. de Hingh, MD, PhD[12]; Marjolein Y.V. Homs, MD, PhD[9]; Jeanin E. van Hooft, MD, PhD[13]; Emile D. Kerver, MD[14]; Saskia A.C. Luelmo, MD[15]; Karen J. Neelis, MD, PhD[16]; Joost Nuyttens, MD, PhD[17]; Gabriel M.R.M. Paardekooper, MD[18]; Gijs A. Patijn, MD, PhD[19]; Maurice J.C. van der Sangen, MD, PhD[20]; Judith de Vos-Geelen, MD[21]; Johanna W. Wilmink, MD, PhD[22]; Aeilko H. Zwinderman, PhD[22]; Cornelis J. Punt, MD, PhD[22]; Casper H. van Eijck, MD, PhD[2]; and Geertjan van Tienhoven, MD, PhD[1] for the Dutch Pancreatic Cancer Group

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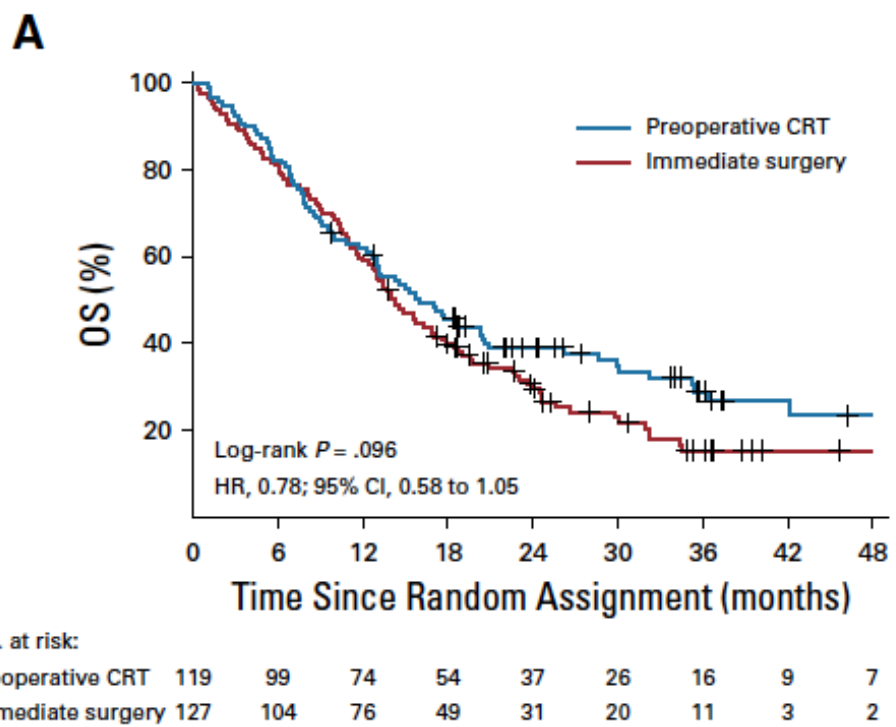


Outcome	Preoperative CRT (n = 119)	Immediate Surgery (n = 127)	HR (95% CI)	P
Primary				
Median OS, months	16.0	14.3	0.78 (0.58 to 1.05)	.0960
Secondary				
Median DFS, months	8.1	7.7	0.73 (0.55 to 0.96)	.0320
Median LFFI, months	NR	13.4	0.56 (0.38 to 0.83)	.0034
Median DMFI, months	17.4	12.5	0.82 (0.58 to 1.14)	.2400
	No. (%)	**No. (%)**	**OR (95% CI)**	
Resection rate	72 of 119 (61)	92 of 127 (72)	0.58 (0.34 to 1.00)	.0580
R0 rate	51 of 72 (71)	37 of 92 (40)	3.61 (1.87 to 6.97)	< .0010
Safety				
Patients with SAEs (all grades)	62 of 119 (52)	52 of 127 (41)	1.57 (0.95 to 2.60)	.0960

- Borderline group
  - Improved disease-free survival (p = 0.013) and locoregional failure-free interval (p = 0.022), and mOS (p = 0.029)
  - No significant difference in distant metastasis-free interval
- No difference in survival for those with resectable disease
  - Exception – those with positive margins

Patients who completed surgery and adjuvant therapy had improved OS compared to those with preoperative chemo

Gemcitabine + XRT not considered standard, modern neoadjuvant regimen

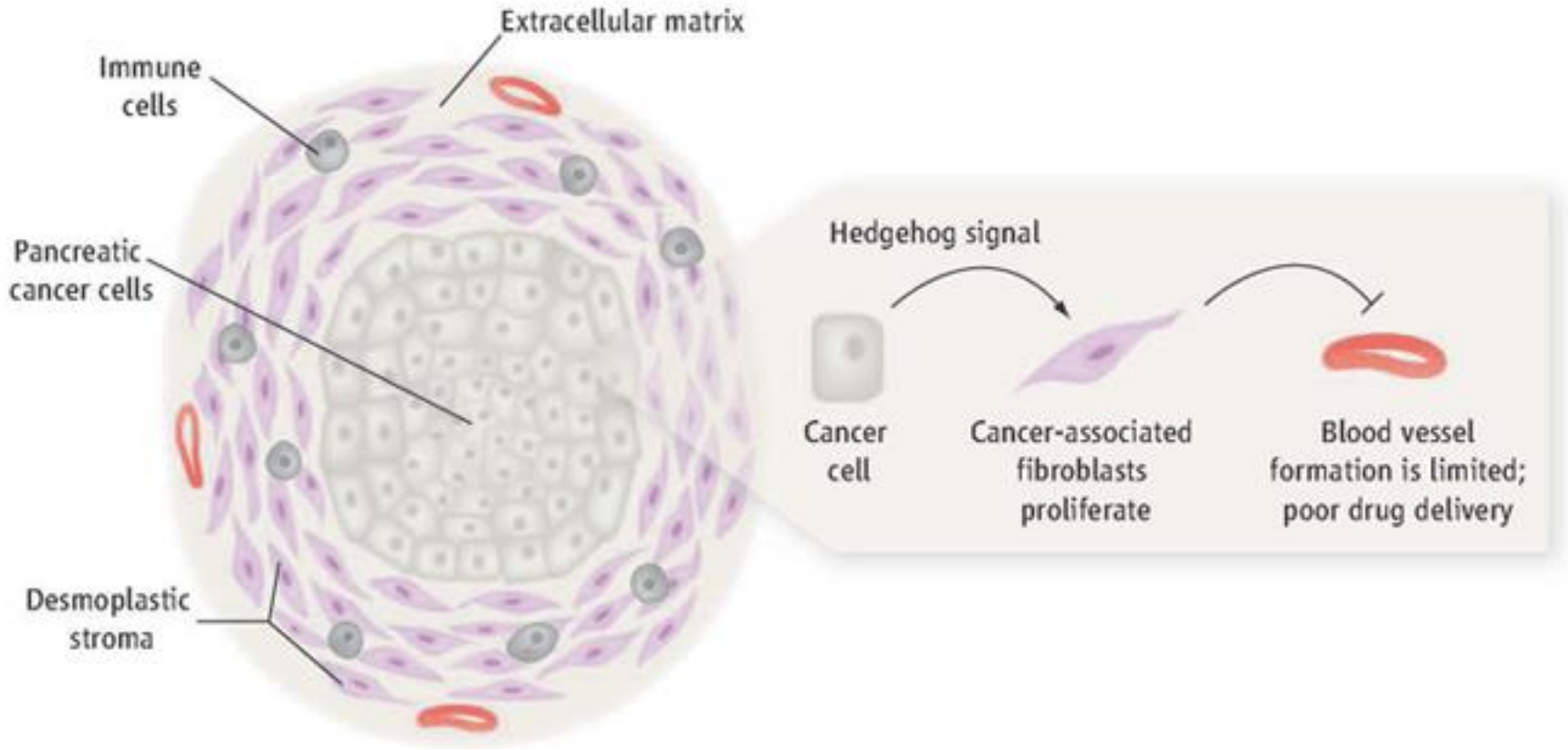
Targeting the Stroma

Anti-CTGF Human Recombinant Monoclonal Antibody Pamrevlumab Combined With Gemcitabine/Nab-Paclitaxel: A Phase 1/2 Randomized Clinical Trial for the Treatment of Locally Advanced Pancreatic Cancer Patients

Vincent Picozzi[1], Flavio G. Rocha[1], Adnan Alseidi[1], Margaret Mandelson[1], Jordan Winter[2], Michael Pishvaian[3], Kabir Mody[4], John Glaspy[5], Timothy Larson[6], Marc Matrana[7], Mairead Carney[8], Ming Zhong[8], Seth Porter[8], Elias Kouchakji[8], Ewa Carrier[8]

[1]Virginia Mason Medical Center, Seattle, WA; [2]Thomas Jefferson Medical Center, Philadelphia, PA; [3]Georgetown Medical Center, Washington, DC; [4]Mayo Clinic Jacksonville, Jacksonville, FL ; [5]UCLA Medical Center, Los Angeles, CA ; [6]Virginia Piper Cancer Institute, Minneapolis, MN; [7]Ochsner Clinic Foundation, New Orleans, LA; [8]FibroGen, Inc. San Francisco, CA

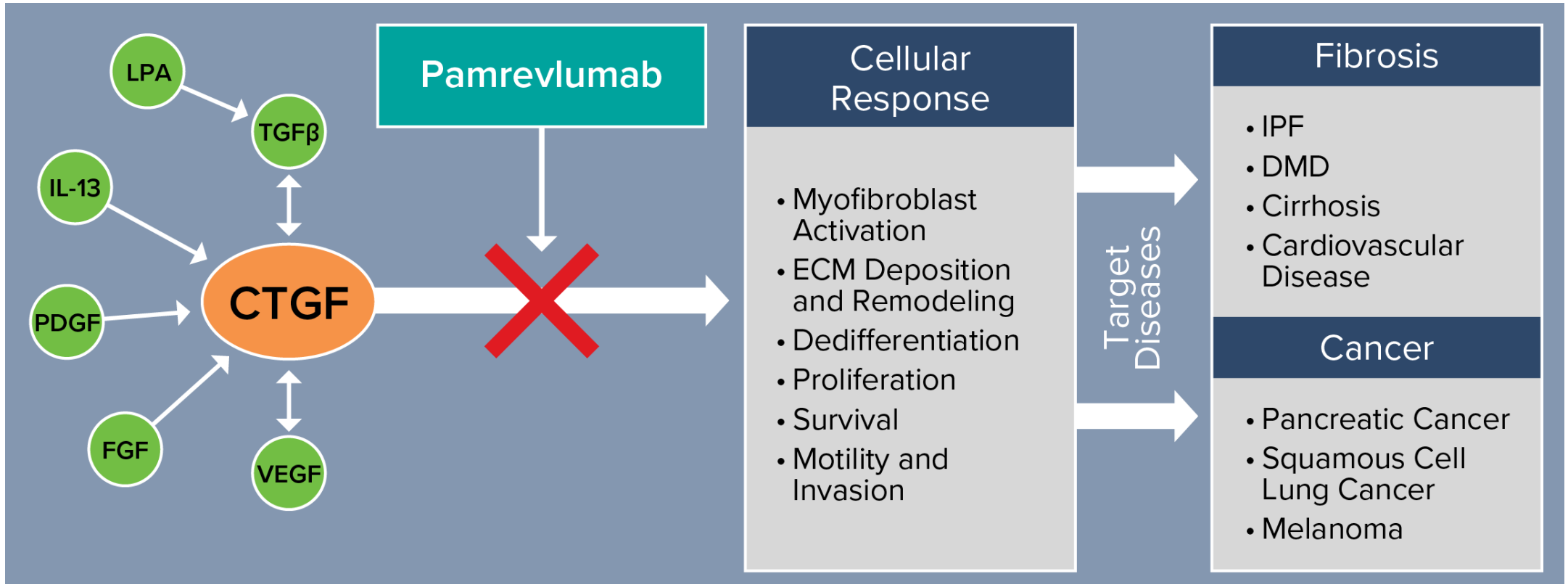
Pancreatic Cancer Microenviroment



Breaching the Cancer Fortress

Peter Olson and Douglas Hanahan
Science 12 Jun 2009:
Vol. 324, Issue 5933, pp. 1400-1401

Role of CTGF in Cancer and Fibrosis

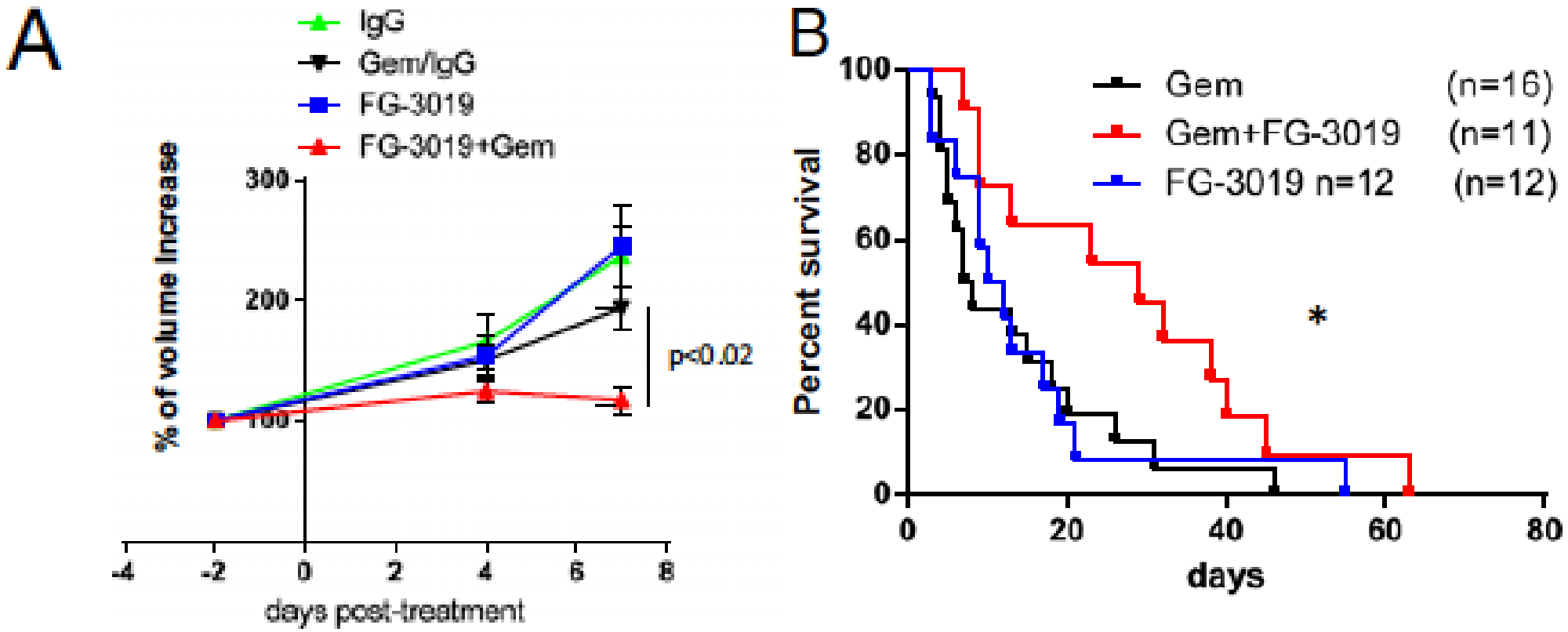


CTGF antagonism with mAb FG-3019 enhances chemotherapy response without increasing drug delivery in murine ductal pancreas cancer

Albrecht Neesse[a,b], Kristopher K. Frese[a], Tashinga E. Bapiro[a,c], Tomoaki Nakagawa[a], Mark D. Sternlicht[d], Todd W. Seeley[d], Christian Pilarsky[e], Duncan I. Jodrell[a,c], Suzanne M. Spong[d], and David A. Tuveson[a,f,1]

PNAS | July 23, 2013 | vol. 110 | no. 30 | 12325–12330

Virginia Mason

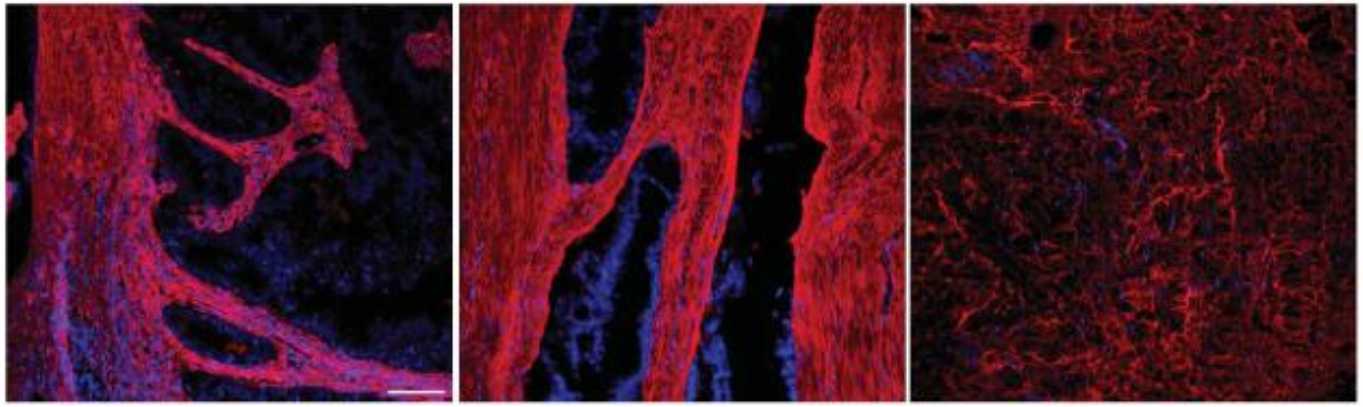


Stromal disrupting effects of nab-paclitaxel in pancreatic cancer

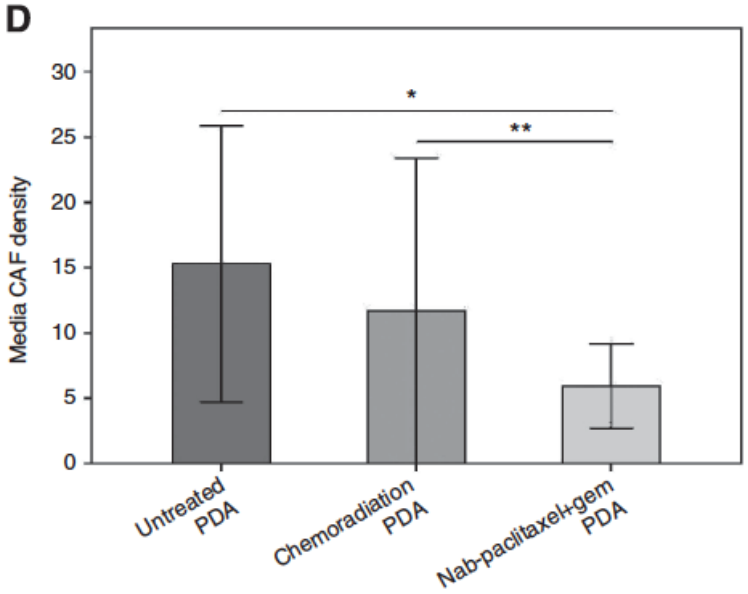
British Journal of Cancer (2013) 109, 926–933

Virginia Mason

R Alvarez[1], M Musteanu[2], E Garcia-Garcia[2], P P Lopez-Casas[2], D Megias[2], C Guerra[2], M Muñoz[2], Y Quijano[1], A Cubillo[1], J Rodriguez-Pascual[1], C Plaza[1], E de Vicente[1], S Prados[1], S Tabernero[1], M Barbacid[2], F Lopez-Rios[1] and M Hidalgo*[,1,2]



Untreated | Chemoradiation | Nab-paclitaxel + gemcitabine



Pamrevlumab in Advanced PDAC

Virginia Mason

-Open label, dose-escalation study in combination with gemcitabine/erlotinib

-75 pts at 7 centers: 15 Stage III, 60 Stage IV

-No SAEs or DLTs occurred with FG-3019

-In per protocol population (n=68): PFS 4.3 mo, OS 9.4 mo

-FG-3019 Cmax and Cmin increased linearly with dose

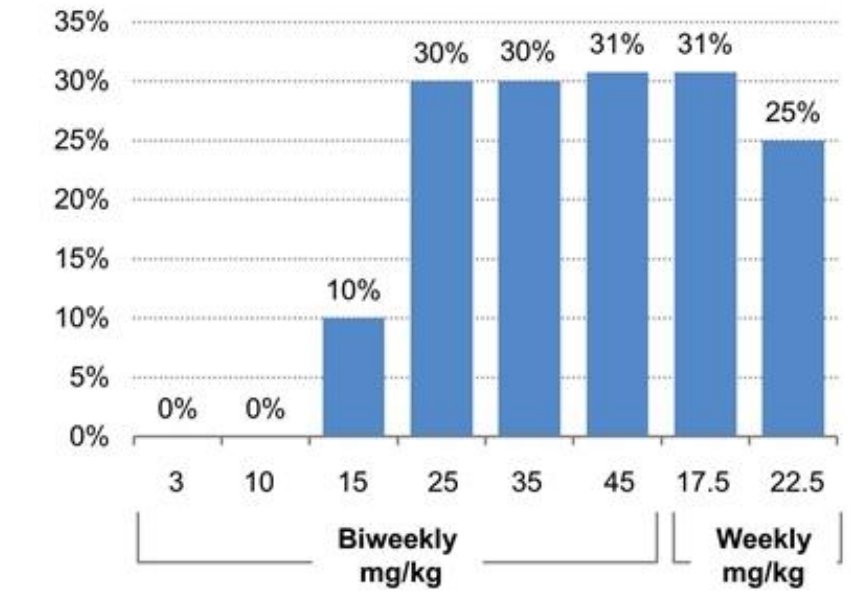
-Outcomes correlated with drug exposure and CTGF expression

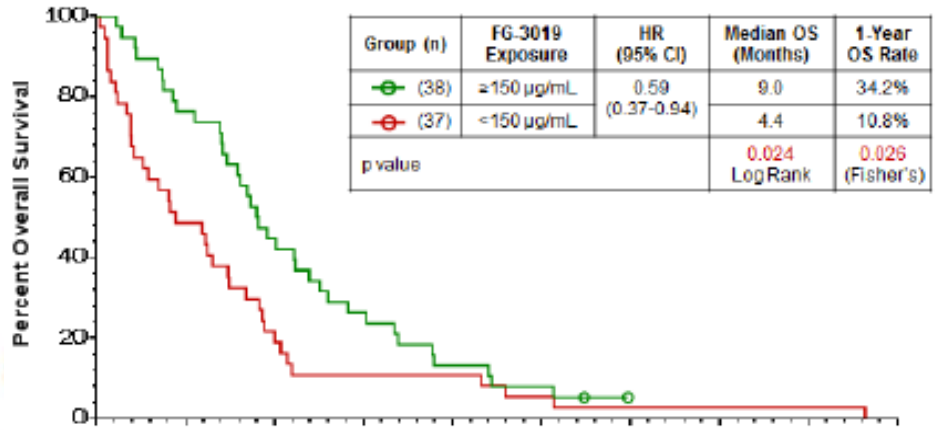
Picozzi et al , J Cancer Clin Trials 2017

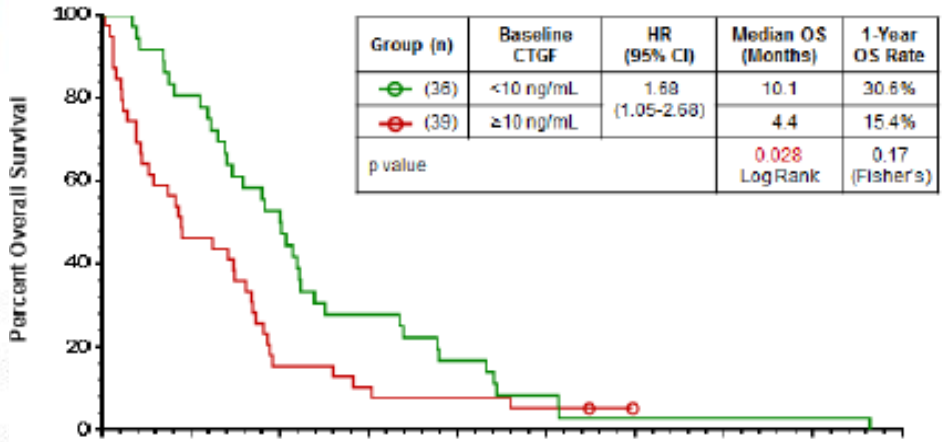
FG-3019 in Advanced PDAC

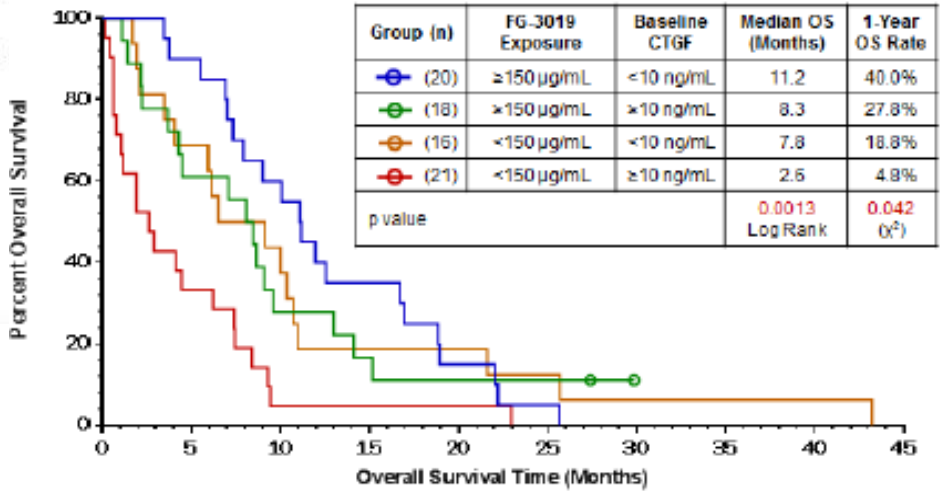
FG-3019 Combined with Gemcitabine

Relationship of 1-Year Survival to Dose



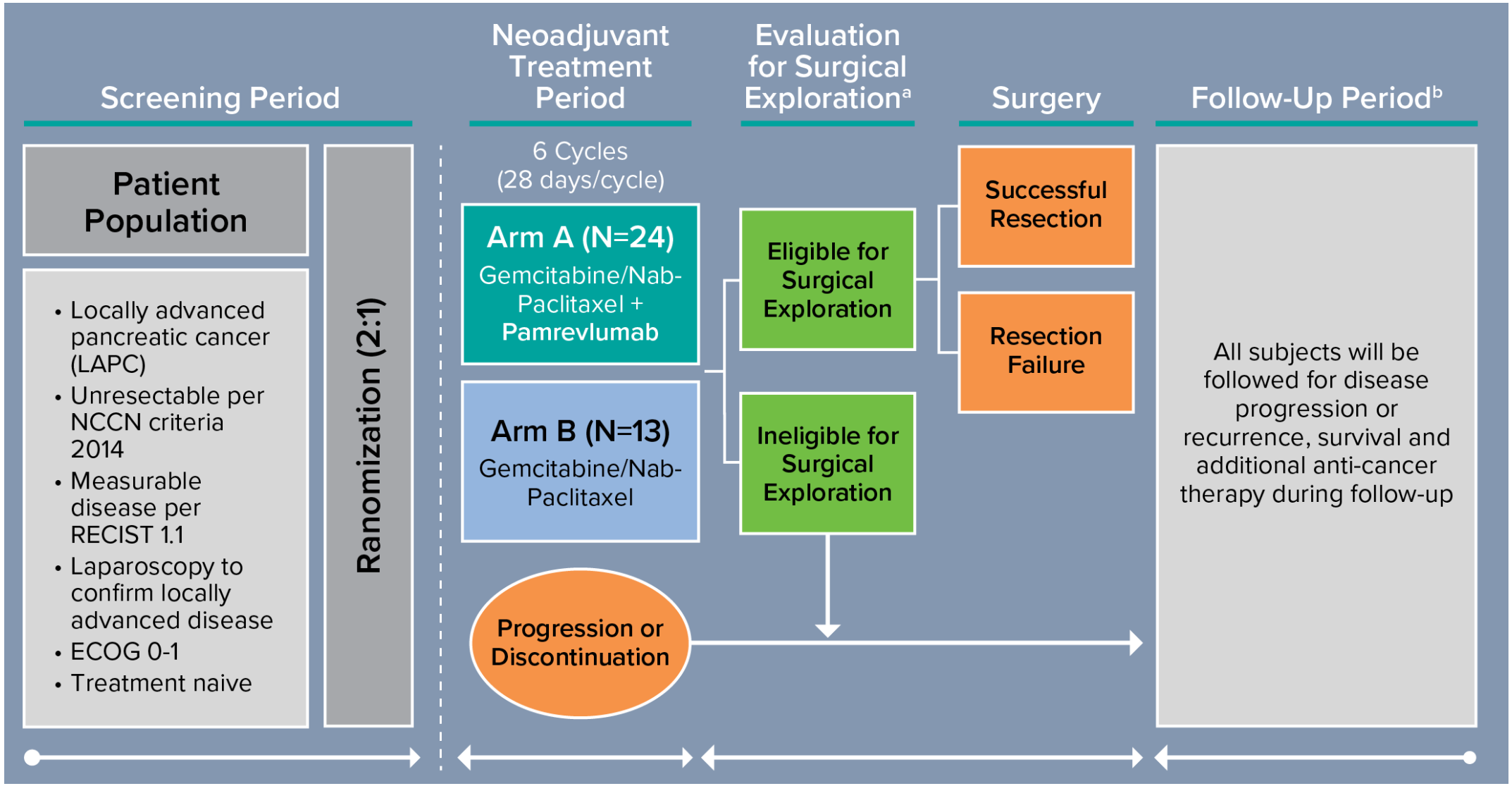




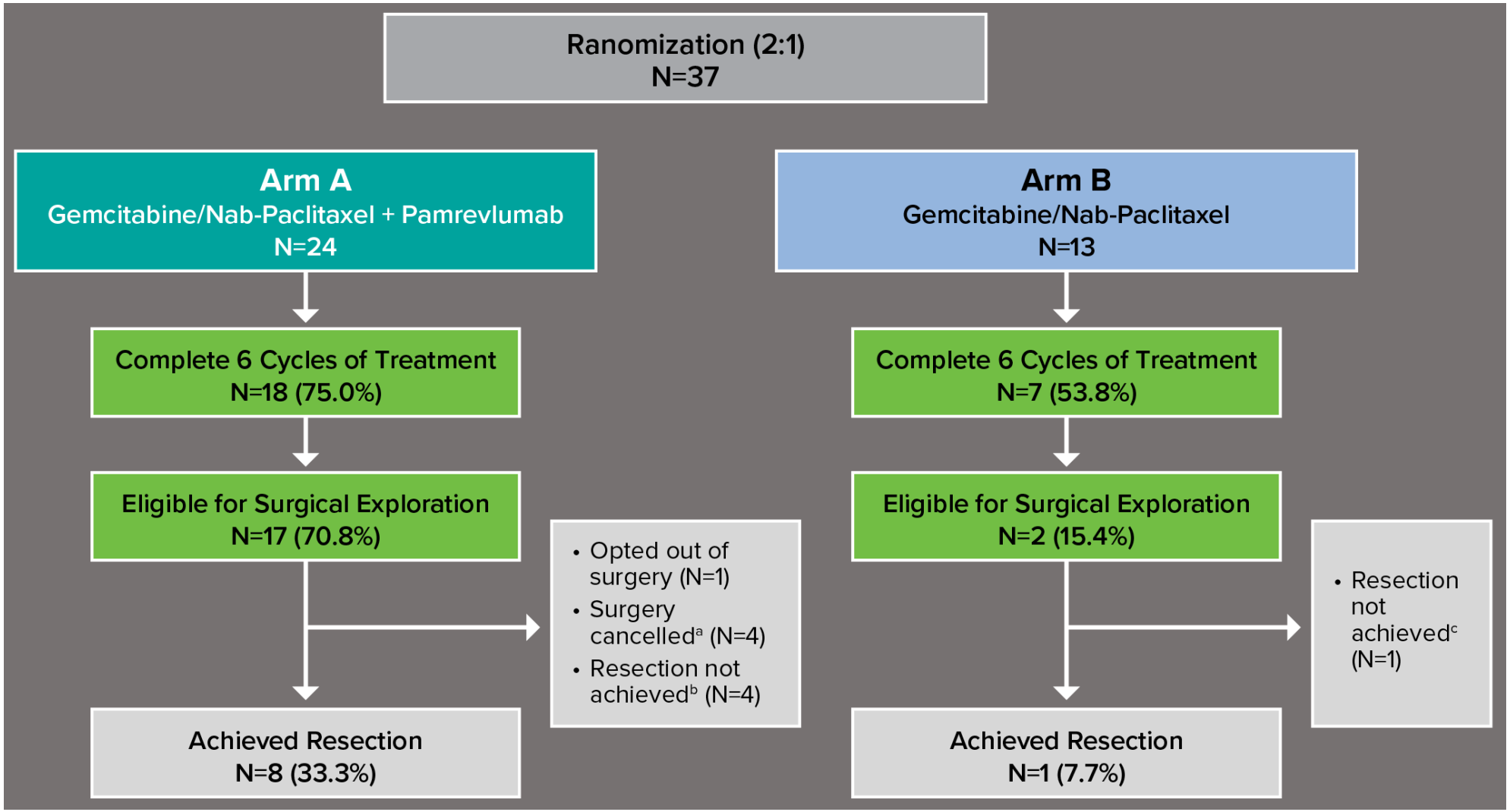


Picozzi, J Cancer Clin Trials 2017

Study Schema



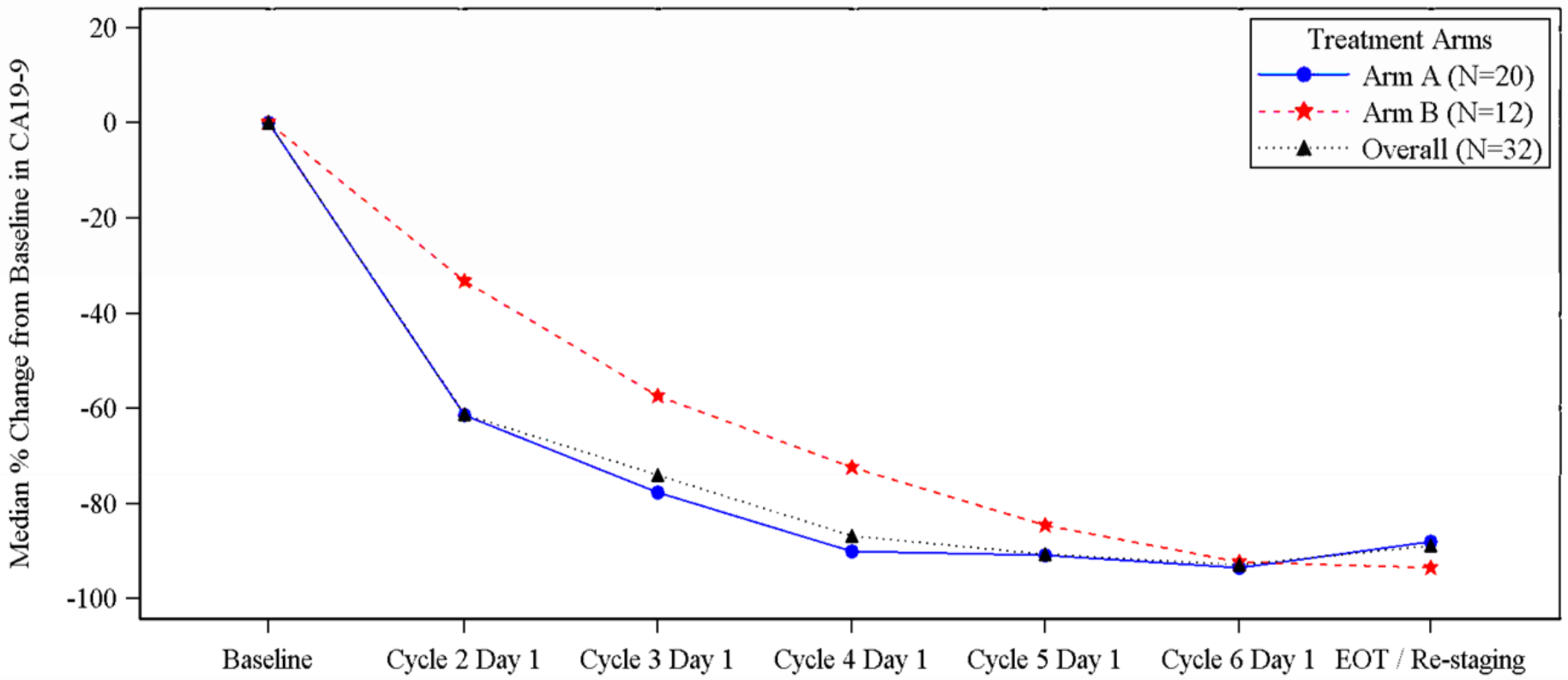
Results



a. In Arm A, four of the eligible subjects had their surgeries canceled (1 = portal vein thrombosis, 3 = medical issues precluding surgery)
b. In Arm A, four eligible subjects underwent surgery, but resection was not achieved (3 = metastatic disease discovered, 1 = extensive SMA encasement)
c. In Arm B, one eligible subject underwent surgery, but resection was not achieved (1 = extensive vascular encasement)

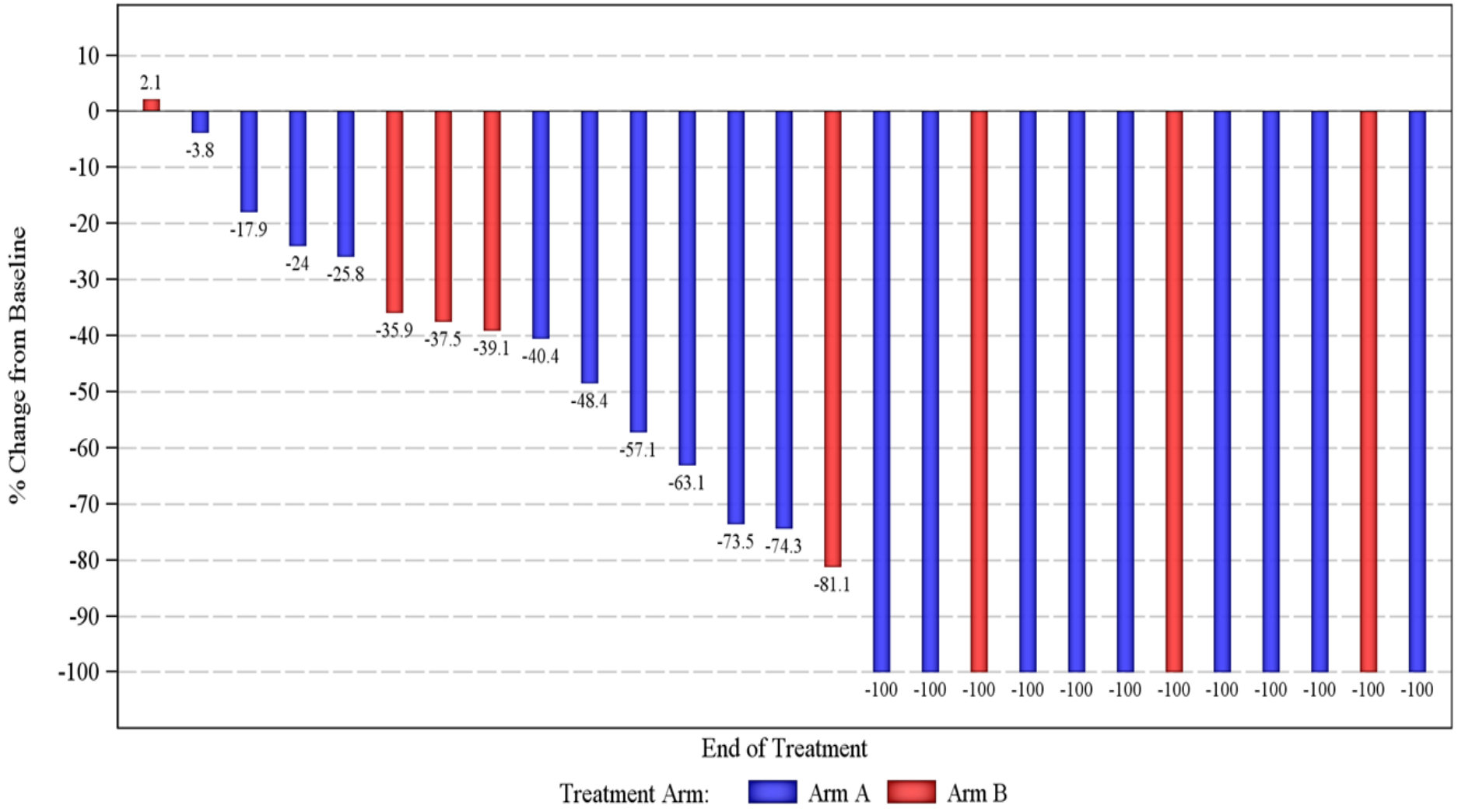
Picozzi, Rocha et al, ESMO J 2020

Median CA19-9 % Change from Baseline



Arm/Median:						
Arm A	-61.4	-77.7	-90.0	-90.7	-93.4	-88.0
Arm B	-33.2	-57.3	-72.3	-84.4	-92.3	-93.4
Overall	-61.2	-74.0	-86.8	-90.7	-92.9	-88.8

PET SUV_{max} % Change: Baseline to EOT



Summary of resected subjects

Virginia Mason

Site-Subject ID	Treatment Arm	Response to Treatment[a]	NCCN Baseline	NCCN End of Treatment	Resection Status
1001-1001	A	1,2,3	Unresectable (celiac, hepatic, artery)	Unresectable (celiac, hepatic, artery)	R0
1001-1004	A	1,2	Unresectable (SMA, SMV)	Unresectable (SMA, SMV)	R1
1001-1005	A	1,2	Unresectable (celiac)	Unresectable (celiac)	R0
1001-1009	A	2,4	Unresectable (celiac)	Borderline resectable	R0
1001-1015	A	1,3	Unresectable (SMV)	Unresectable (SMV)	R1
1001-1017	A	1,2	Unresectable (SMA)	Unresectable (SMA)	R1
1008-8001	A	1,2	Unresectable (SMA,SMV,celiac)	Unresectable (celiac)	R1
1008-8005	A	2	Unresectable (SMA)	Unresectable (SMA)	R0
1001-1008	B	1,2	Unresectable (celiac)	Unresectable (celiac)	R0

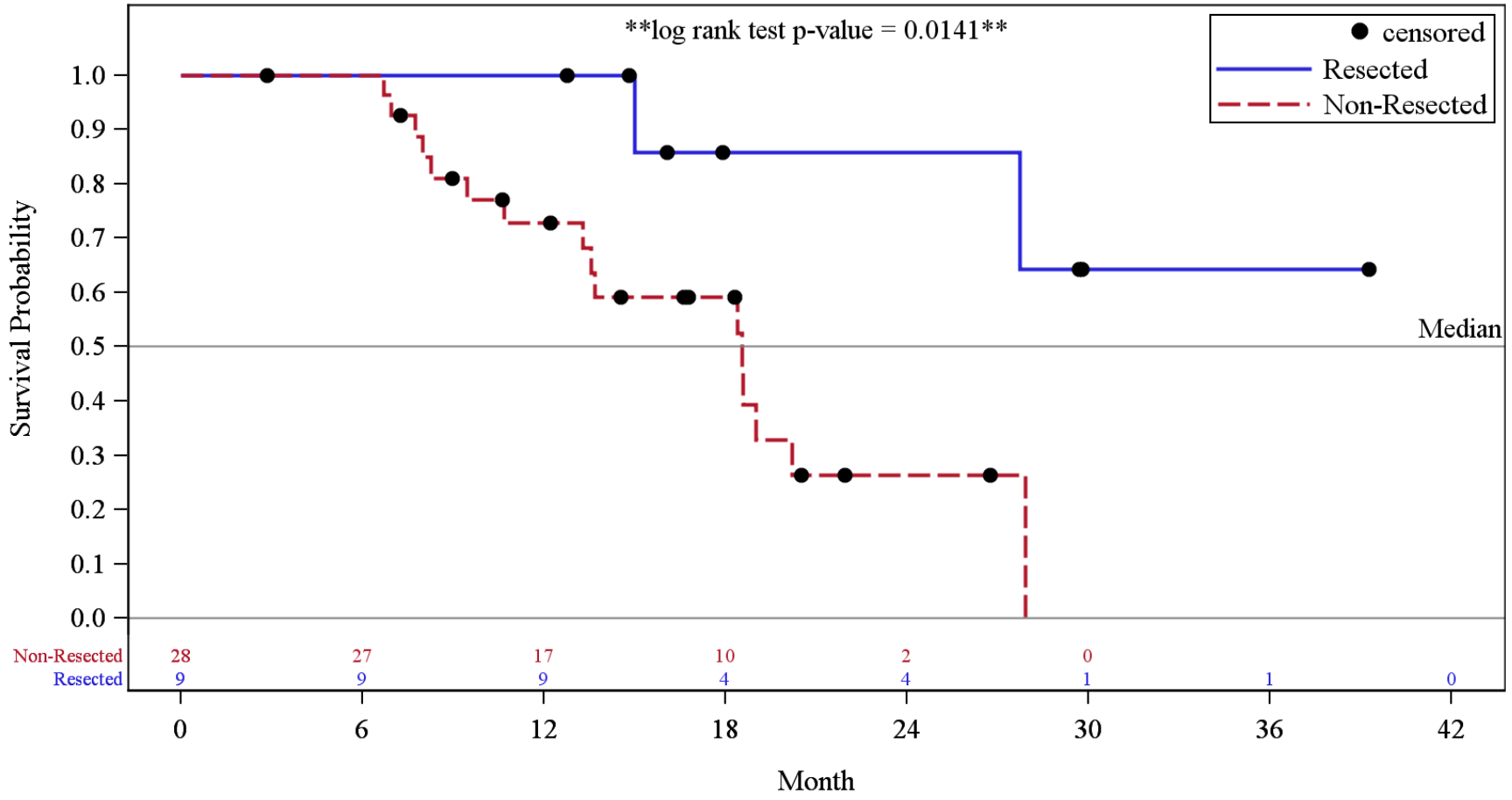
[a]1=CA19-9 decline ≥ 50% at EOT, 2=PET SUVmax decline ≥ 30% at EOT, 3=PR or CR per RECIST at EOT, 4=resectable or borderline resectable per NCCN at EOT

Surgical safety

- Surgical complications included:
  - Blood loss (median estimate of 500 mL for the 14 pts)
  - Ischemic gastritis and ulceration and right lower lung lobe collapse (reported for 1 patient each)
  - 2 clinically significant pancreatic leaks, 1 in each arm
  - One gastric perforation in single resected patient in arm B
  - Readmissions 4/12 (33%) in arm A and 1/2 (50%) in arm B
  - No wound complications or superficial site infections

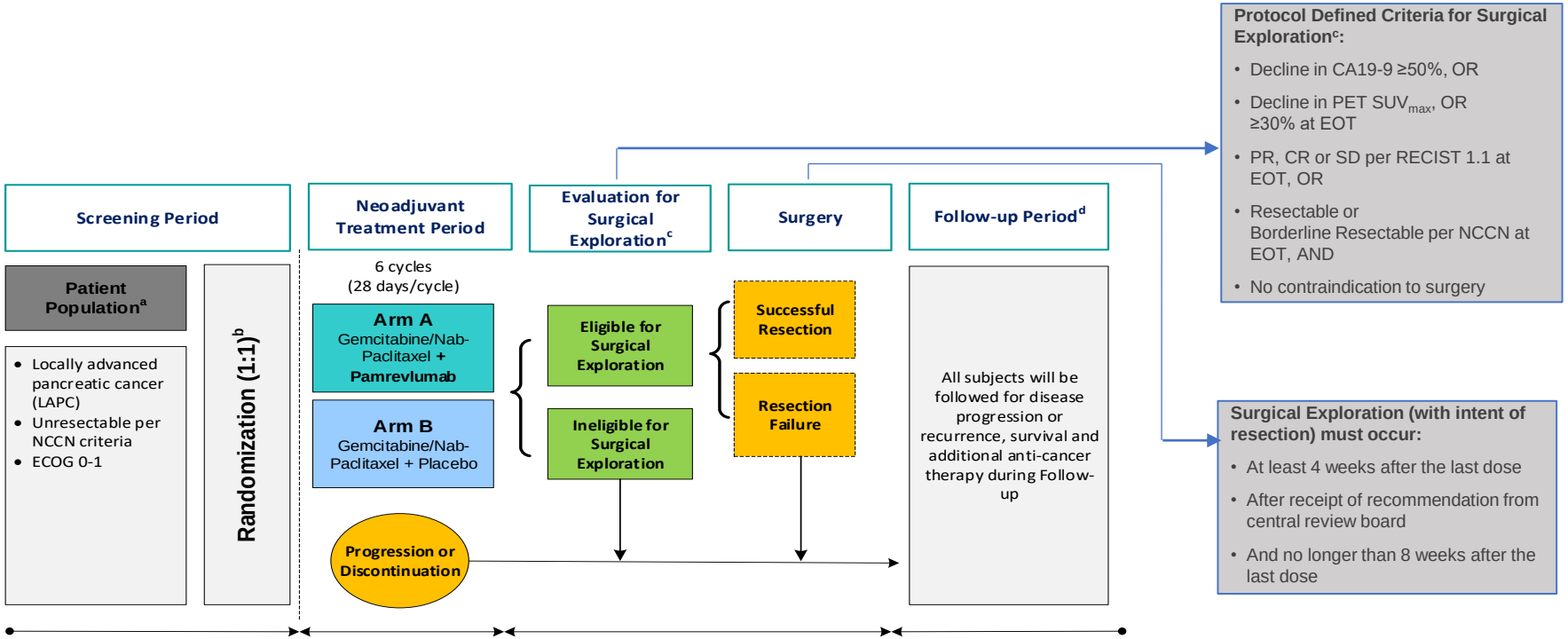
- There were no re-operations and no 30 or 90-day surgical mortality.

Overall Survival by Resected Status (ITT)



	N	Event	Censored	Median(95%CI)
Non-Resected	28	16 (57.1%)	12 (42.9%)	18.56 (13.27, 20.21)
Resected	9	2 (22.2%)	7 (77.8%)	NE (15.01, NE)

Phase III LAPIS Study Schema



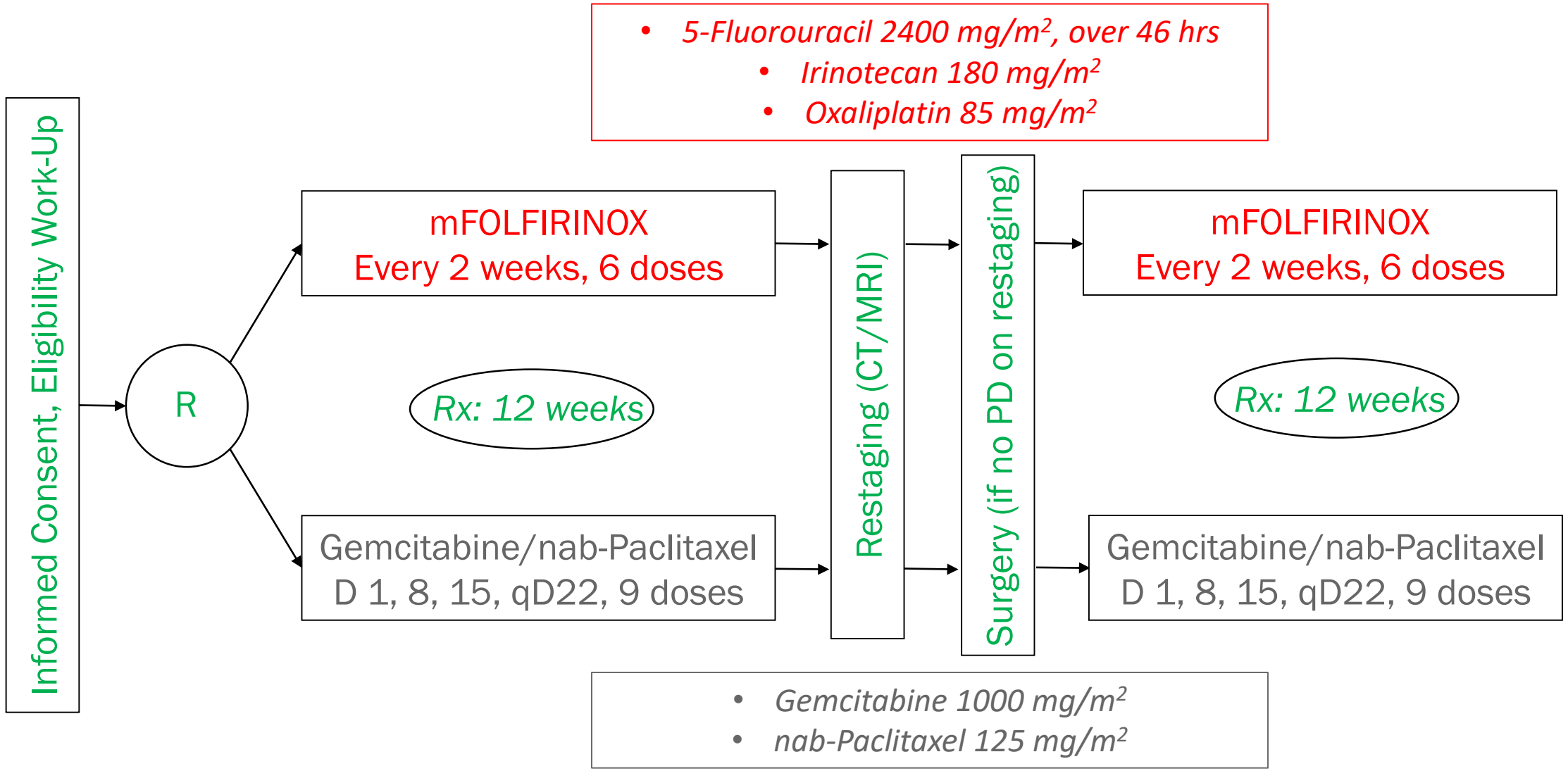
[a]Central review team (including radiologists and surgeons) will confirm subjects have locally advanced unresectable disease prior to enrollment.
[b]Subjects will be stratified at randomization according to the following factors; SMA encasement (> or ≤ 180 degrees), unreconstructible disease and geographic region.
[c]Subjects must meet at least ONE of the four protocol-defined criteria AND have no contraindication to surgery. A central review team (including radiologists, surgeons and oncologists) will determine whether a subject is eligible for surgical exploration per protocol.
[d]Second-Line Treatment may be administered as per the investigator/institutional SOC.

Multi-center trial with 256 patients at 40-60 sites

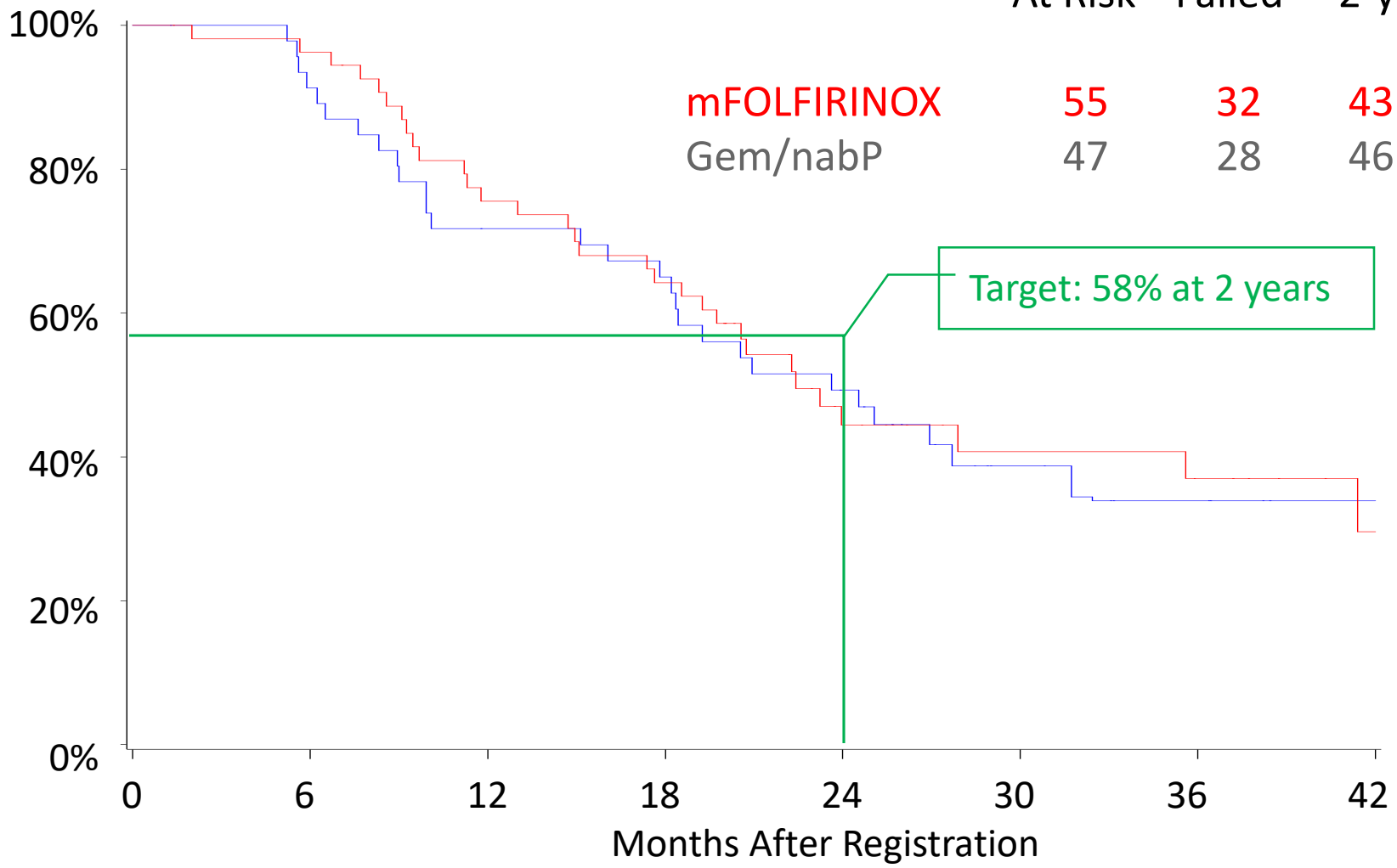
Strict surgical eligibility quality control with central imaging review of LAPC and criteria for resection

Perioperative Therapy

SWOG 1505 Study Schema



Primary Endpoint: Two-year OS



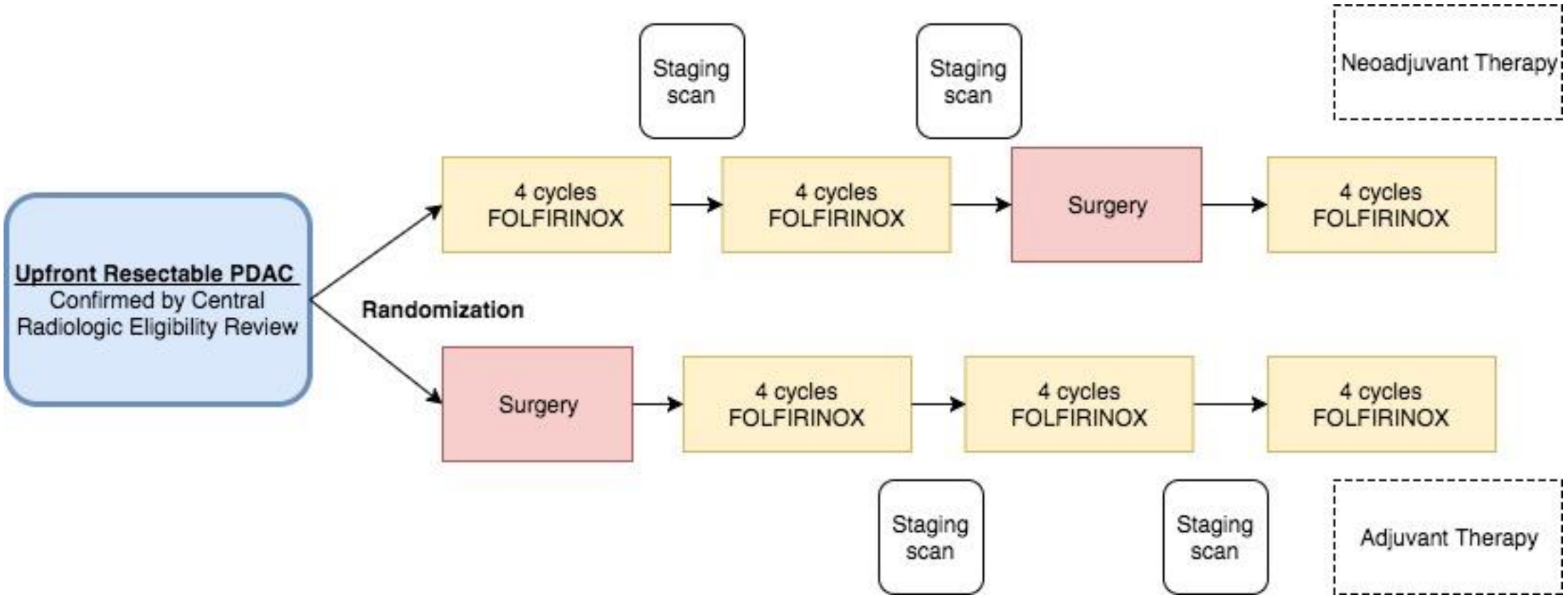
	At Risk	Failed	2-yr OS	mOS
mFOLFIRINOX	55	32	43.1%	22.4 mths
Gem/nabP	47	28	46.9%	23.6 mths

Secondary Endpoints

In Patients Undergoing Resection	mFOLFIRINOX (N=55)	Gem/nabP (N=47)
R0 Resection	34 (62%)	28 (60%)
Complete or Major Pathologic Response	10 (18%)	14 (30%)
Disease-Free Survival after Resection	10.9 mths	14.2 mths

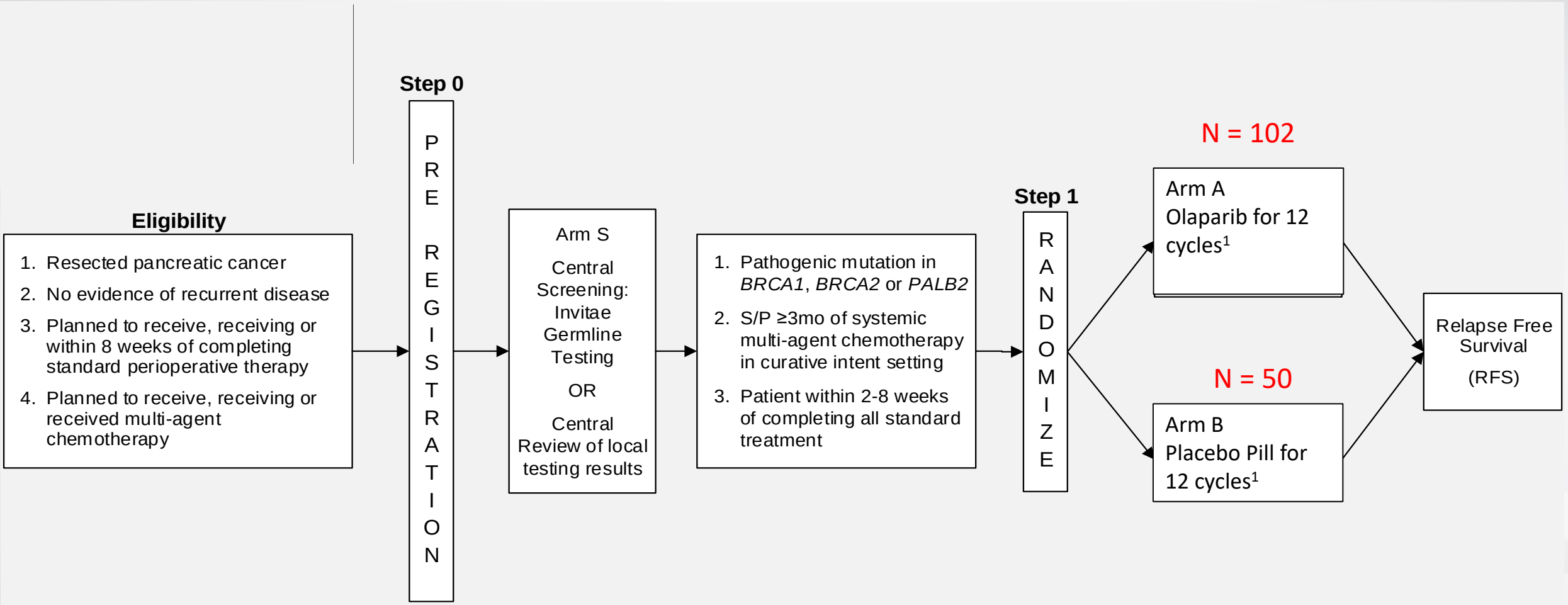
Tissue and radiology correlative studies ongoing

Alliance 021806: Neoadjuvant (Perioperative) vs. Adjuvant Therapy for Resectable Pancreatic Cancer



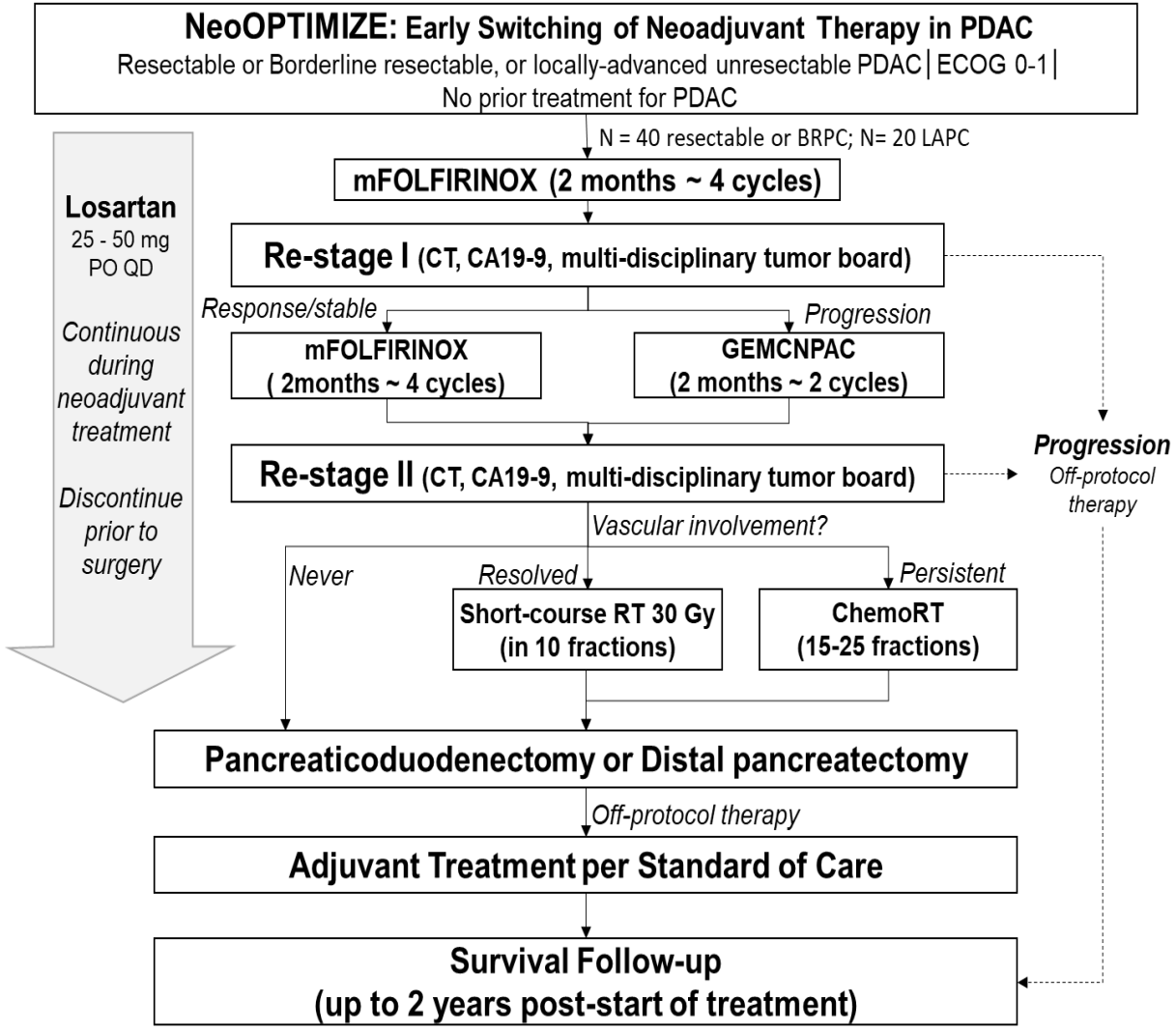
Future Directions

APOLLO (EA2192) Study Schema



[1] One cycle = 4 weeks

NeoOptimize Trial



OHSU KNIGHT CANCER Institute

Table 1. Guidelines for mFOLFIRINOX to GA Switching
Continued mFOLFIRINOX at Re-Stage I will be based on the following considerations*:
1. If the participant is considered to have a radiographic response (per radiology clinical report), then they will proceed to receive an additional 2 months of mFOLFIRINOX (approximately 4 cycles). This treatment response may be considered independent of any possible increases in serum CA19-9 levels, or 1. In the absence of radiographic disease progression (per radiology clinical report), participants may continue to receive an additional 2 months of mFOLFIRINOX (approximately 4 cycles) if: a. serum CA19-9 levels have decreased ≥ 25% (from baseline), or a. serum CA19-9 levels remain unchanged (from baseline), or a. serum CA19-9 levels have increased <30% (from baseline)
Switch to GA at Re-stage I will be guided by the following considerations*:
1. Participants should be switched to receive up to 2 months of preoperative GA (approximately 2 cycles) if there is evidence of radiographic disease progression (per radiology clinical report), or 1. In the absence of radiographic disease progression (per radiology clinical report), participants may be switched to receive 2 months of preoperative GA (approximately 4 cycles) if serum CA19-9 levels have increased ≥30% (from baseline), 1. Participants responding to FOLFIRINOX but, per assessment of treating physician, are unlikely to physically tolerate additional courses, will also proceed to having treatment switched to GA.
*The decision to continue or switch therapy at Re-Stage I is at the discretion of the treating physician in consultation with the multi-disciplinary tumor board. There is no protocol deviation if the above algorithm is not explicitly followed. Reasons for alternate treatment decisions that are consistent with the general guidelines of the neoadjuvant treatment should be recorded.

NCT04539808 Lopez (PI)

Goals for treatment of PDAC

1) Identify earlier stage disease
    - Screen at risk and underserved populations
    - Timely diagnosis and multidisciplinary evaluation

2) Provide highest quality surgical and medical care
    - Expand candidate pool for curative therapy
    - Reduce operative morbidity, enhance recovery and deliver chemotherapy/XRT with minimal toxicity

3) Novel therapeutics
    - Develop more effective locoregional/systemic regimens
    - Test thru clinical trials for all stages of disease

Thank You

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