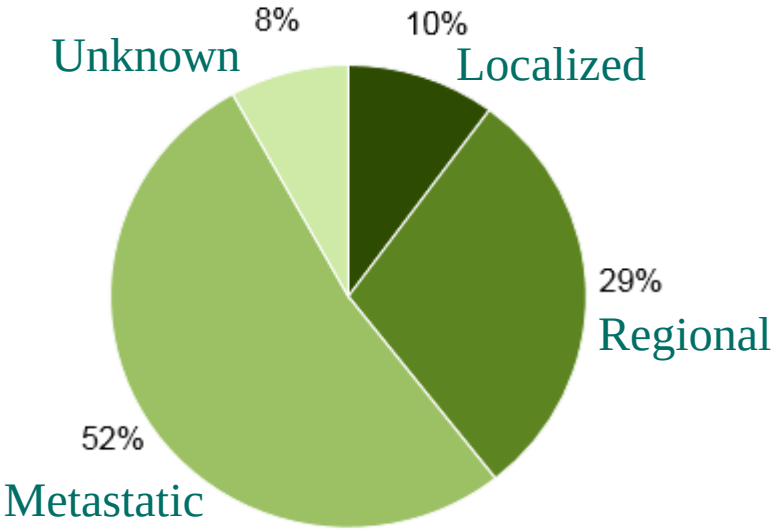
TREATMENT SEQUENCING IN PANCREATIC CANCER

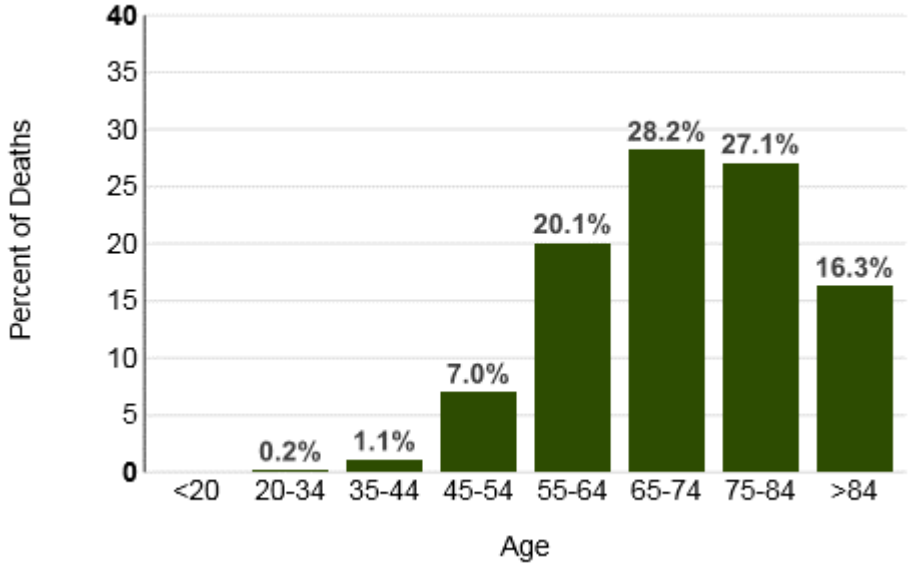
Ben George, MD
Associate Professor of Medicine
Division of Hematology and Oncology
Director, Phase I Clinical Trials Program
Medical Director, Cancer Precision Medicine Practice Integration
Genomic Sciences and Precision Medicine Center,
Medical College of Wisconsin,
Milwaukee, Wisconsin

DISCLOSURES

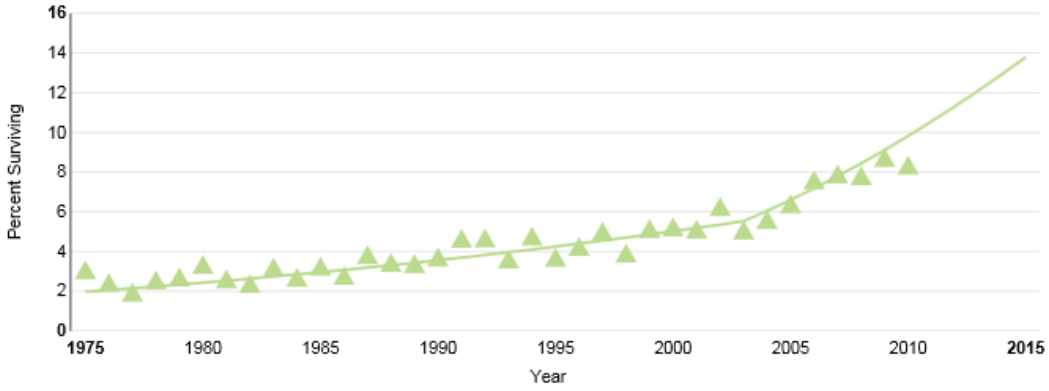
- Consultant: Celgene, Cook Medical, Merrimack, Foundation Medicine, Ipsen, Bristol Myers Squibb, Exelixis, Terumo Interventional Systems, Taiho Oncology, Eisai
- Honoraria: Celgene, Cook Medical, Merrimack, Foundation Medicine, Ipsen, Bristol Myers Squibb, Exelixis, Terumo Interventional Systems, New Link Genetics, Taiho Oncology, Eisai
- Research Support: B.Braun CeGaT (I), Celgene (Inst), Foundation Medicine (Inst), Roche/Genentech (Inst), Hoffman La-Roche (Inst), Taiho Oncology (Inst), Boehringer Ingelheim (Inst)

PANCREATIC CANCER – SEER DATA

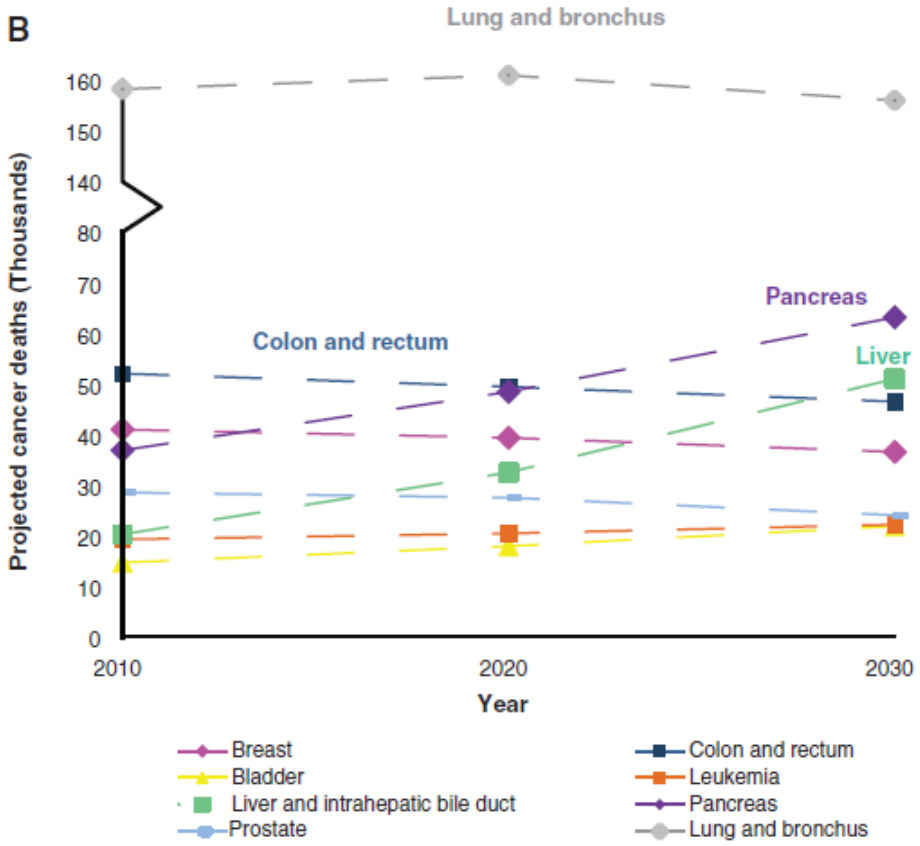




5-year Survival
Observed and Modeled



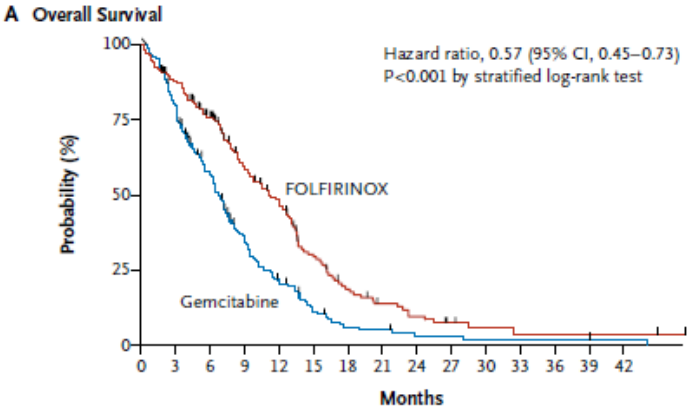
PANCREATIC CANCER –BURDEN OF DISEASE



CHEMOTHERAPY HAS MADE INCREMENTAL ADVANCES

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

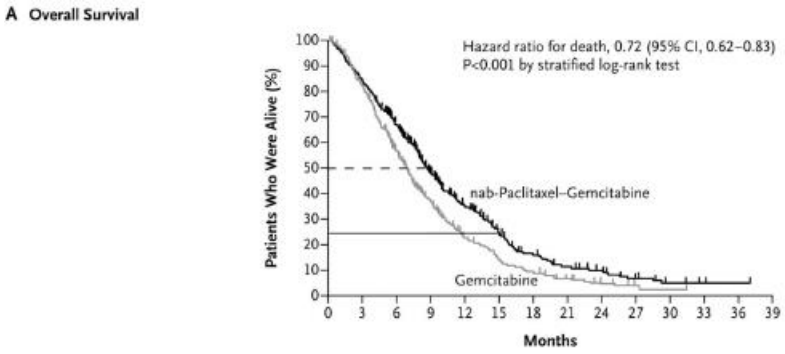
Thierry Conroy, M.D., Françoise Desseigne, M.D., Marc Ychou, M.D., Ph.D., Olivier Bouché, M.D., Ph.D., Rosine Guimbaud, M.D., Ph.D., Yves Bécouarn, M.D., Antoine Adenis, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Sophie Gourgou-Bourgade, M.Sc., Christelle de la Fouchardière, M.D., Jaafar Bennouna, M.D., Ph.D., Jean-Baptiste Bachet, M.D., Faiza Khemissa-Akouz, M.D., Denis Péré-Vergé, M.D., Catherine Delbaldo, M.D., Eric Assenat, M.D., Ph.D., Bruno Chauffert, M.D., Ph.D., Pierre Michel, M.D., Ph.D., Christine Montoto-Grillot, M.Chem., and Michel Ducreux, M.D., Ph.D., for the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup*



N ENGL J MED 364;19 NEJM.ORG MAY 12, 2011

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

Daniel D. Von Hoff, M.D., Thomas Ervin, M.D., Francis P. Arena, M.D., E. Gabriela Chiorean, M.D., Jeffrey Infante, M.D., Malcolm Moore, M.D., Thomas Seay, M.D., Sergei A. Tjulandin, M.D., Wen Wee Ma, M.D., Mansoor N. Saleh, M.D., Marion Harris, M.D., Michele Reni, M.D., Scot Dowden, M.D., Daniel Laheru, M.D., Nathan Bahary, M.D., Ramesh K. Ramanathan, M.D., Josep Tabernero, M.D., Manuel Hidalgo, M.D., Ph.D., David Goldstein, M.D., Eric Van Cutsem, M.D., Xinyu Wei, Ph.D., Jose Iglesias, M.D., and **Markus F. Renschler, M.D.**



N Engl J Med. 2013 October 31; 369(18): 1691–1703.

TNM STAGING IN PANCREATIC CANCER

Definitions	
Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to pancreas, ≤2 cm in greatest dimension
T2	Tumor limited to pancreas, >2 cm in greatest dimension
T3	Tumor extends beyond pancreas but no involvement of celiac axis or superior mesenteric artery
T4	Tumor involves celiac axis or superior mesenteric artery
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

1. American Joint Committee on Cancer. Pancreatic Cancer Staging, 7th edition; 2010. https://cancerstaging.org/references-tools/quickreferences/Documents/PancreasSmall.pdf. Accessed October 4, 2017
2. Chun YS, Pawlik TM, and Vauthey JN, Ann Surg Oncol. 2017; Epub ahead of print

SELECTED ADJUVANT CHEMOTHERAPY TRIALS

Trial	N	Primary Endpoint	Randomization	R0 status (%)	Node Positive (%)	Local Recurrence Rate (%)	DFS	OS (months)
ESPAC-1	473	OS	Bolus 5-FU vs. Observation	81%	53%	-	-	19.7 vs. 14.0 (HR -0.66; 95% CI 0.52-0.83, p = 0.005)
CONKO-001	368	DFS	Gemcitabine vs. Observation	82.3%	74.4%	34% vs. 41%	13.4 vs. 6.7 (HR-0.55; 95% CI 0.44-0.69; p <0.001)	22.8 vs. 20.2 (HR-0.76; 95% CI 0.61-0.95; p = 0.01)
JSAP-02	119	OS	Gemcitabine vs. Observation	84%	69%	23% vs. 32%	11.4 vs 5.0 (HR-0.6; 95% CI 0.40-0.89; p = 0.01)	22.3 vs. 18.4 (HR-0.77; 95% CI 0.51-1.14; p = 0.19)
ESPAC-3	1088	OS	Gemcitabine vs. Bolus 5-FU/LV	65%	72%	-	14.3 vs. 14.1 (HR-0.96; 95% CI 0.84-1.10; p = 0.53)	23.6 vs. 23.0 (HR- 0.94; 95% CI 0.81-1.08; *P* = .39)
ESPAC-4	732	OS	Gemcitabine + Capecitabine vs. Gemcitabine	40%	80%	46% vs. 53%	-	28.0 vs 25.5 (HR-0·82; 95% CI 0·68–0·98, p=0·032)

George and Ritch, Chapter 9: Neoadjuvant versus Adjuvant Therapy in Localized Pancreatic Cancer, Management of Localized Pancreatic Cancer, Springer Nature Publishers, in press

SELECTED ADJUVANT CHEMORADIATION TRIALS

Trial	N	Primary Endpoint	Randomization	R0 (%)	N1 (%)	RT Dose/ Chemo	Chemotherapy	LR (%)	DFS (months)	OS (months)
GITSG	43	OS & DFS	CCRT → Bolus 5-FU vs. Observation	-	28%	40Gy/5-FU	Bolus 5-FU	-	11 vs 9	20 vs 11
EORTC	218	OS	CCRT vs. Observation	81%	47%	40 Gy/5-FU	-	15% vs. 15%	17.4 vs. 16	24.5 vs. 19.0 p = 0.208
ESPAC-1	353	OS	CCRT Vs. Observation	82.4%	55.6%	20 Gy/5-FU	Bolus 5-FU	-	-	15.5 vs. 16.1 (HR-1.18; 95% CI 0.90-1.55; p=0.24)
RTOG-9704	451	OS	Gemcitabine vs. 5-FU	41.7%	66.3%	50.4 Gy/5-FU	Gemcitabine vs. 5-FU	25% vs. 30%		20.5 vs 16.9(pancreatic head tumors (HR - 0.82; 95% CI 0.65-1.03; *p*= .09)

George and Ritch, Chapter 9: Neoadjuvant versus Adjuvant Therapy in Localized Pancreatic Cancer, Management of Localized Pancreatic Cancer, Springer Nature Publishers, in press

PRODIGE 24/CCTG PA.6, an Unicancer GI trial: a multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas.

T. Conroy, P. Hammel, M. Hebbar, M. Ben Abdelghani, A.C. Wei, J-L. Raoul, L. Choné, E. François, P. Artru, J. Biagi, T. Lecomte, E. Assenat, R. Faroux, M. Ychou, J. Volet, A. Sauvanet, C. Jouffroy, P. Rat, F. Castan, J-B. Bachet, for the CCTG and the UNICANCER-GI /PRODIGE Group

Institut de Cancérologie de Lorraine, Nancy; Hôpital Beaujon, Clichy; Hôpital Huriez, Lille; Centre Paul Strauss, Strasbourg; Princess Margaret Hospital, Toronto; Institut Paoli-Calmettes, Marseille; University hospital, Nancy; Centre Antoine-Lacassagne, Nice; Hôpital Jean-Mermoz, Lyon; Kingston General Hospital, Kingston; Hôpital Trousseau, Tours; University Hospital, Montpellier; CHD Vendée, La Roche-sur-Yon; Institut du Cancer de Montpellier, Montpellier; Centre Hospitalier Universitaire, Dijon; Hôpital Pitié-Salpétrière, Paris; Canadian Cancer Trials Group, Kingston, Canada; R&D UNICANCER, Paris; France

PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Thierry Conroy

PRODIGE 24/CCTG PA.6 trial: study design

NCT01526135

- R0 or R1 resected pancreatic cancer
- postoperative CT-scan mandatory
- CA19-9 level < 180 U/mL within 12 weeks after surgery

Stratification:
- center
- resection margin (R0 vs R1)
- CA19-9 level (≤ 90 vs 91-179 U/mL)
- pN0 (< 12 vs ≥ 12 examined nodes) vs pN1

RANDOMIZE

1:1

mFolfirinox

Oxaliplatin 85 mg/m², Leucovorin 400 mg/m²,
Irinotecan 180 mg/m²*, all at D1
Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours
Every 2 weeks; 12 cycles
**Reduced to 150 mg/m² after patient 162*

Gemcitabine

1000 mg/m², qw 3/4 *weeks;*
6 cycles

for both arms:
- 6 months of chemotherapy
- CT scans: every 3 months

Key Inclusion Criteria

- Histologically confirmed resected pancreatic ductal adenocarcinoma
- Macroscopically complete resection (R0 or R1 resection)
- Patients able to receive chemotherapy within 12 weeks after resection
- ECOG performance status 0 or 1
- Patients aged from 18 to 79 years
- No prior radiotherapy or chemotherapy
- Adequate hematologic/blood chemistry levels
- Patient information and written informed consent

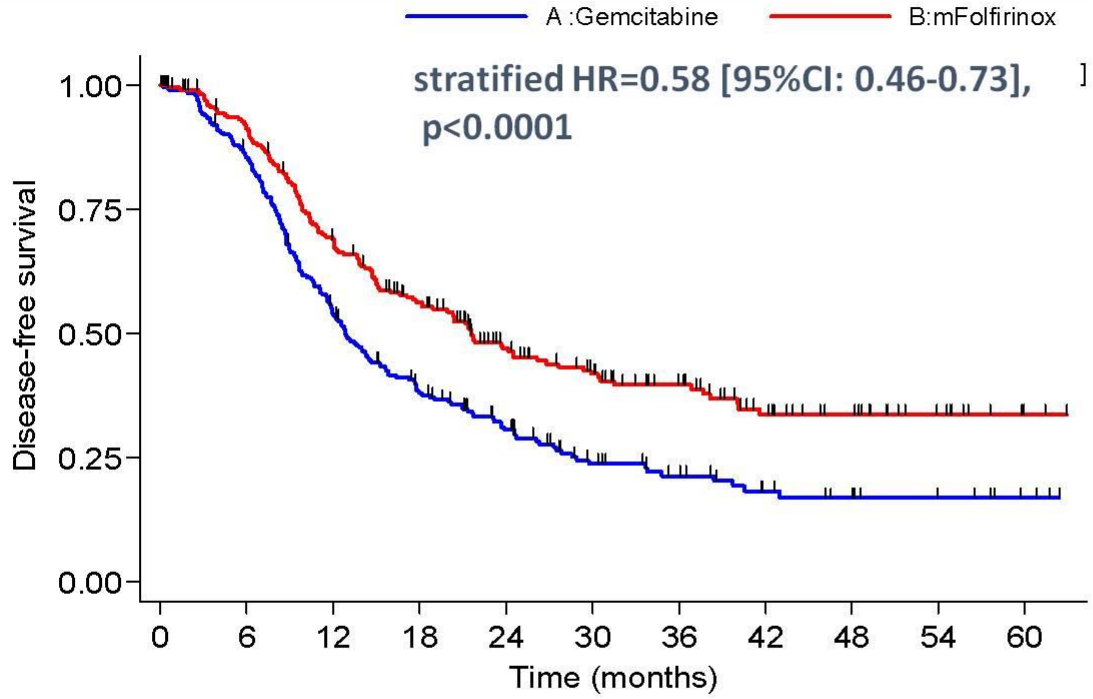
Key Exclusion Criteria

- Metastatic disease, or macroscopic incomplete tumor removal (R2 resection)
- Postoperative CA 19-9 ≥ 180 U/ml assessed within 21 days of randomization
- Symptomatic heart failure or coronary heart disease
- Major comorbidity, active infection, history of HIV or uncontrolled diabetes
- Inflammatory bowel disease, or occlusion or sub-occlusion of the intestine or severe postoperative uncontrolled diarrhea
- Concomitant occurrence of another cancer, or significant history of cancer

Endpoints

- **Primary: Disease-Free Survival (DFS)**
- **Secondary:**
  - Toxicity (NCI-CTC version 4.0 grading)
  - Overall survival (OS)
  - Cancer specific survival (SS)
  - Metastasis-free survival (MFS)

Disease-Free Survival



Number at risk

A:Gemcitabine	246	205	127	85	59	34	24	15	10	7	3
B:mFolfirinox	247	210	156	118	80	60	46	29	21	11	2

No DFS events: 314

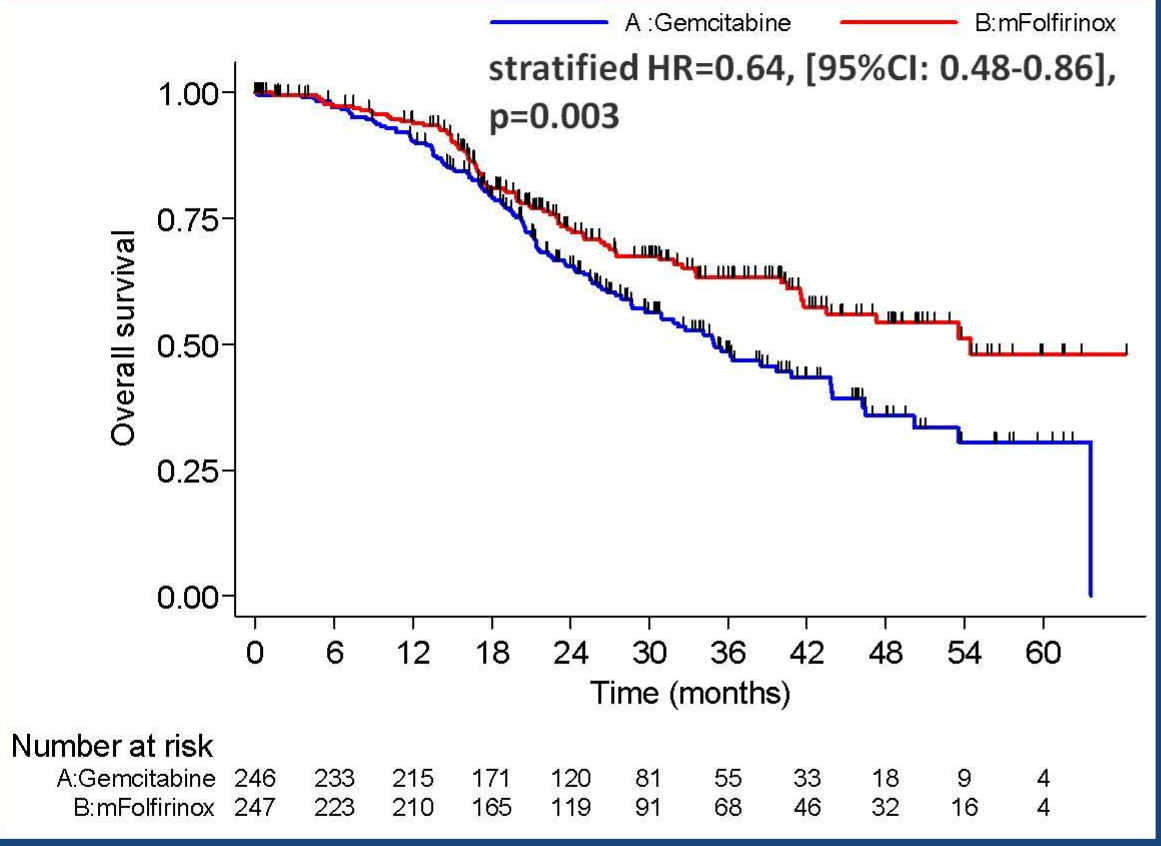
Median DFS:

- **21.6 mths [95%CI: 17.7-27.6] with mFolfirinox**
- **12.8 mths [95%CI: 11.7-15.2] with Gemcitabine**

3-year DFS:

- **39.7% [95%CI: 32.8-46.6] with mFolfirinox**
- **21.4% [95%CI: 15.8-27.5] with Gemcitabine**

Overall Survival



Median overall survival:

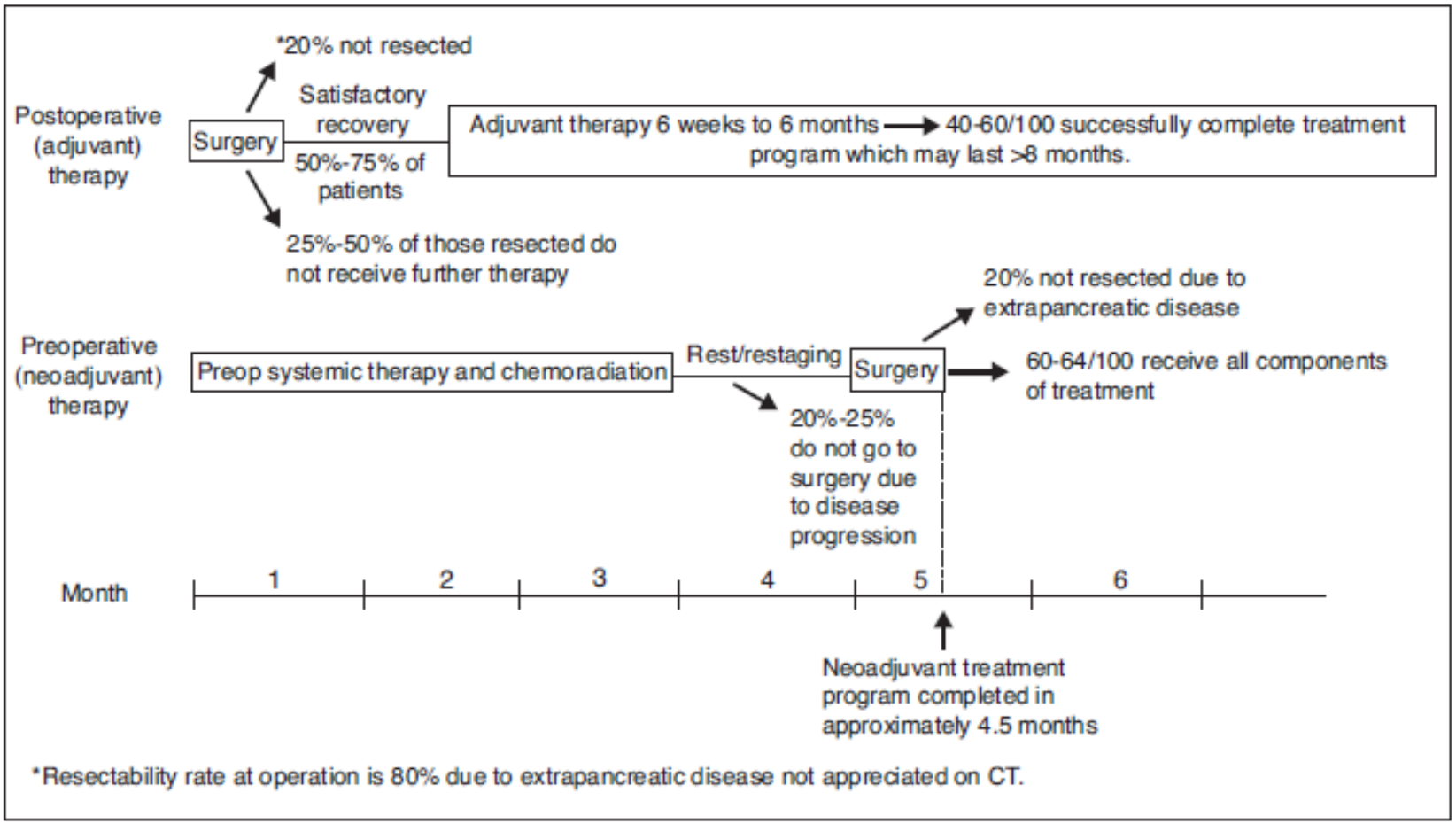
- **54.4 months** [95%CI: 41.8-NR] **with mFolfirinox**
- **35.0 months** [95%CI: 28.7-43.9] **with Gemcitabine**

3-year overall survival:

No OS events=192

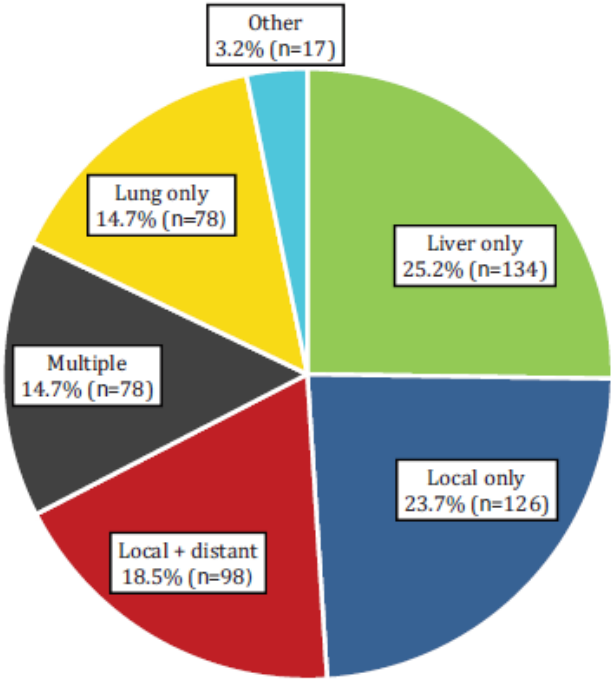
- **63.4% (mFolfirinox) vs 48.6 % (Gem)**

CHALLENGES IN DELIVERING ADJUVANT THERAPY

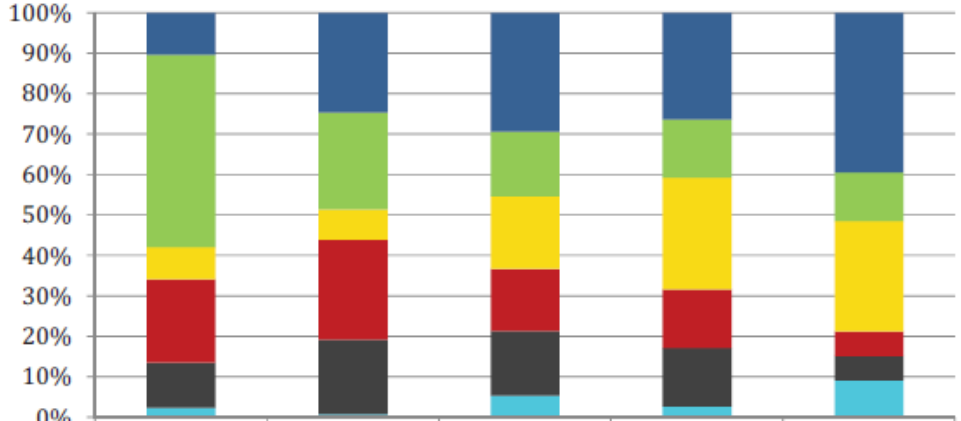


Wayne, Abdalla, Wolff et al, The Oncologist, 2002

RECURRENCE PATTERNS AFTER SURGERY



A



	0-6 months (n=126)	6-12 months (n=146)	12-24 months (n=150)	24-48 months (n=76)	>48 months (n=33)
Local only	10.3%	24.7%	29.3%	26.3%	39.4%
Liver only	47.6%	24.0%	16.0%	14.5%	12.1%
Lung only	7.9%	7.5%	18.0%	27.6%	27.3%
Local + distant	20.6%	24.7%	15.3%	14.5%	6.1%
Multiple	11.1%	18.5%	16.0%	14.5%	6.1%
Other	2.4%	0.7%	5.3%	2.6%	9.1%

Groot, Rezaee, Wu et al, Ann Surg 2018

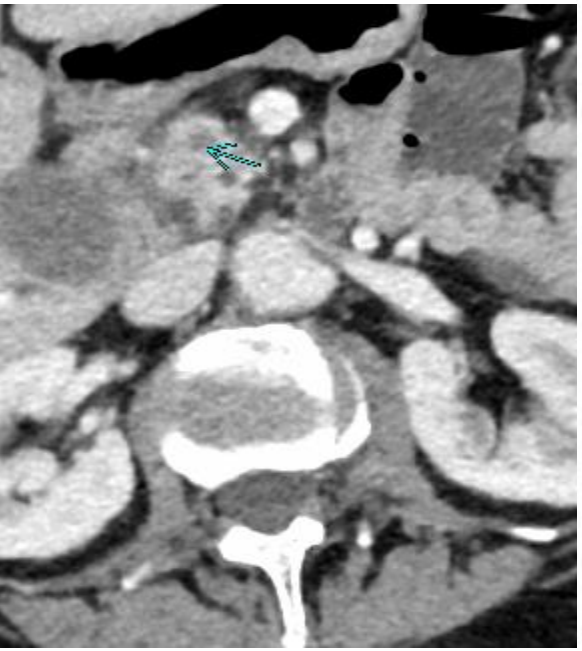
RECURRENCE PATTERNS AFTER SURGERY

TABLE 1. Demographics, Clinicopathological, and Treatment Characteristics of 692 Included Patients

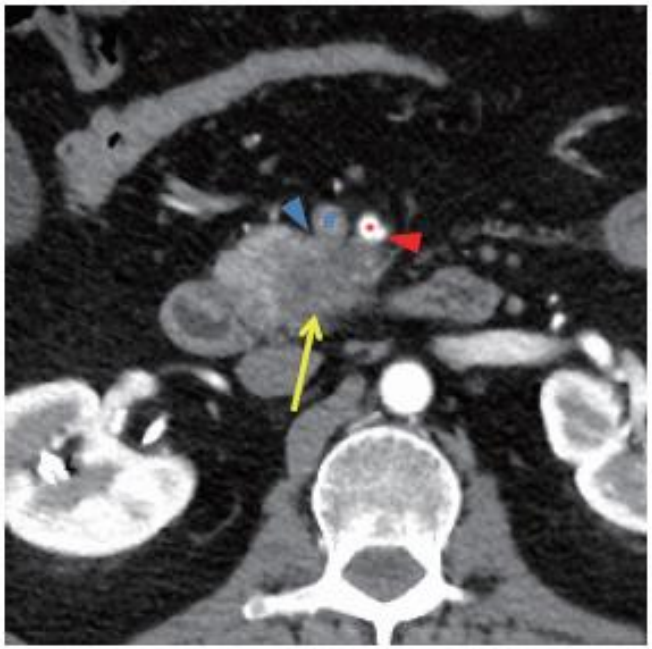
Variable	All Patients (n = 692)
Resection margin, n (%)	
R0	451 (65.2%)
R1	241 (34.8%)
Tumor differentiation, n (%)	
Well-moderate	445 (64.3%)
Poor	247 (35.7%)
Tumor size, mean cm (SD)	3.1 (1.5)
T-stage, n (%)	
1–2	155 (22.4%)
3–4	537 (77.6%)
Positive lymph nodes, n (%)	525 (75.9%)
Lymph node ratio, n (%)	
LNR ≤0.2	460 (66.5%)
LNR >0.2	232 (33.5%)
Perineural invasion, n (%)	622 (89.9%)
Perivascular invasion, n (%)	404 (58.4%)
AJCC stage, n (%)	
≤2A	156 (22.5%)
≥2B	536 (77.5%)
Adjuvant treatment	
None	226 (32.7%)
Chemotherapy	142 (20.5%)
Chemoradiotherapy	324 (46.8%)

CLINICAL STAGING OF PANCREATIC CANCER

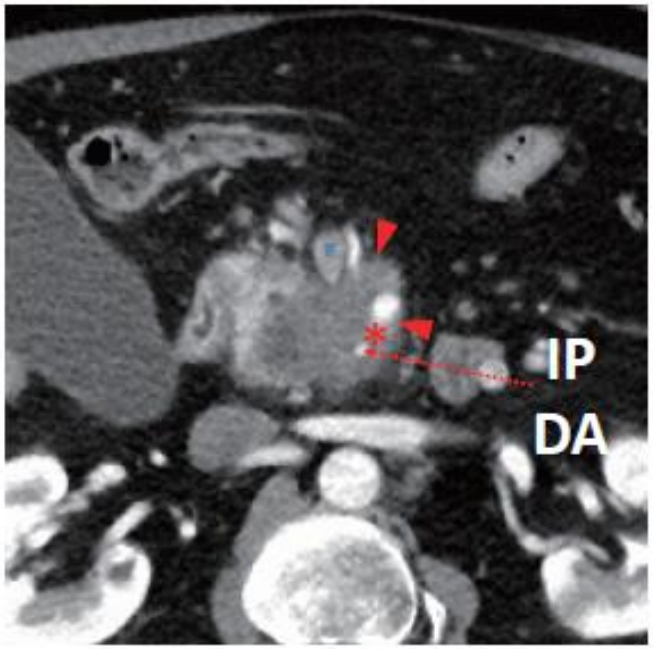
CLINICAL STAGING OF PANCREATIC CANCER



Resectable



Borderline Resectable



Locally Advanced

Fathi, Christians, George, et. al, J. Gastrointest Oncol, 2015

CLINICAL STAGING OF PANCREATIC CANCER

Stage	MCW	NCCN 2015
Resectable		
SMA, Celiac	No abutment	No abutment
Hepatic Artery	No abutment	No abutment
SMV-PV	≤50 % narrowing of SMV, PV, or SMV-PV	No tumor contact or ≤180° contact without vein contour irregularity
Borderline resectable		
SMA	≤180° (abutment)	≤180° (abutment)
Celiac	≤180° (abutment)	≤180° (abutment) >180° without involvement of the aorta and amenable to celiac resection (HA-GDA not involved)*
Hepatic Artery	Abutment or short segment encasement**	Contact without extension to celiac or HA bifurcation**
SMV-PV	>50 % narrowing of SMV, PV, SMV/PV or short segment occlusion**	Contact >180° or contour irregularity or thrombosis and reconstruction possible (suitable proximal and distal targets)**
Other	CT scan findings suspicious but not diagnostic of metastatic disease	
Locally advanced		*Unresectable*
SMA, Celiac	>180° (encasement)	>180° (encasement)
SMV-PV	Occlusion without option for reconstruction	Unreconstructable SMV/PV

SMA superior mesenteric artery; *SMV* superior mesenteric vein; *PV* portal vein; *SMV-PV* superior mesenteric-portal vein; *HA-GDA* hepatic artery-gastroduodenal artery; *NA* not applicable

* Also considered locally advanced, refer to NCCN guidelines

** Amenable to reconstruction

Evans, George and Tsai, Ann Surg Oncol, 2015

ADVANTAGES OF NEOADJUVANT THERAPY

Table 2 Potential advantages of neoadjuvant therapy
Benefits of neoadjuvant therapy
The ability to deliver systemic therapy to all patients
Identification of patients with aggressive tumor biology (manifested as disease progression) at the time of post-treatment, preoperative restaging who thereby avoid the toxicity of surgery
Increased efficacy of radiation therapy; free radical production in a well oxygenated environment
Decreased radiation induced toxicity to adjacent normal tissue as the radiated field is resected at the time of pancreatectomy
Decreased rate of positive resection margins; SMA margin in particular
Decreased rate of pancreatic fistula formation
Potential for the downstaging of borderline resectable tumors to facilitate surgical resection
Disadvantages of neoadjuvant therapy
Potential for complications from pre-treatment endoscopic procedures
Biliary stent related morbidity; stent occlusion during neoadjuvant therapy
Disease progression obviating resectability; loss of a "window" of resectability which may occur (rarely) in the borderline resectable patient
Physicians have to work together during the preoperative phase; discrete handoff from surgeon to medical oncologist to radiation oncologist is not possible in the neoadjuvant setting (as occurs with adjuvant therapy)

Fathi, Christians, George, et. al, J. Gastrointest Oncol, 2015

SELECTED NEOADJUVANT TRIALS IN RESECTABLE PDAC

Author	N	Neoadjuvant Regimen	Resected (%)	R0 (%)	Survival
Evans DB, 1992 [39]	28	CCRT (5-FU)	61%	82%	-
Staley, 1996 [40]	39	CCRT (5-FU)	100%	54%	19 months
Pisters PW, 1998 [41]	35	CCRT(5-FU) + EB-IORT	74%	88%	3-yr survival-23%
Hoffman JP, 1998 [42]	53	CCRT (5-FU and Mitomycin)	45%	71%	9.7 months
White RR, 2001 [43]	53	CCRT (5-FU)	53%	72%	-
Pisters PW, 2002 [44]	35	CCRT (Paclitaxel) + EB-IORT	57%	68%	3-yr survival-28%
Moutardier V, 2004 [45]	61	CCRT (5-FU and Cisplatin)	65%	92.5%	13 months
Talamonti MS, 2006 [46]	20	CCRT (Gemcitabine)	85%	94%	26 months for resected patients
Palmer DH, 2007 [47]	50	Gemcitabine vs. Gemcitabine +Cisplatin	Gemcitabine - 38% Gemcitabine + Cisplatin -70%	Gemcitabine -75% Gemcitabine + Cisplatin -75%	1-yr survival Gemcitabine -42% Gemcitabine + Cisplatin -62%
Heinrich S, 2008 [48]	28	Gemcitabine + Cisplatin	93%	80%	26.5months
Evans DB, 2008 [23]	86	CCRT (Gemcitabine)	74%	89%	34 months (resected patients)
Varadachary, GR, 2008 [24]	90	Gemcitabine +Cisplatin → CCRT (Gemcitabine)	66%	96%	31 months (resected patients)
Le Scodan R, 2009 [49]	41	CCRT (5-FU and Cisplatin)	63%	81%	2-yr survival-32%
O'Reilly, EM, 2014 [50]	38	Gemcitabine +Oxaliplatin	71%	74%	27.2months
Christians, KK, 2016 [31]	69	Chemotherapy (various) and Chemoradiation	87%	97%	31.5 months

George and Ritch, Chapter 9: Neoadjuvant versus Adjuvant Therapy in Localized Pancreatic Cancer, Management of Localized Pancreatic Cancer, Springer Nature Publishers, in press

SELECTED NEOADJUVANT TRIALS IN PATIENTS WITH BORDERLINE RESECTABLE PDAC

Author	N	Neoadjuvant Regimen	Number Resected (%)	R0 Resection (%)	Survival
Kim S, 2016 [51]	26	FOLFIRINOX (n = 26) then RT (n = 4)	26 (100)	22 (92)	Median survival not reached at median follow-up 27.6 months
Katz M, 2016 [52]	22	FOLFIRINOX then CRT	15 (68)	14 (93)	Median 21.7 months
Takahashi H, 2013 [53]	80	Gem-RT	43 (54)	42 (98)	5-year: 34 percent
Kim E, 2013 [54]	39	GEMOX-RT	24 (62)	NR	Median 18.4 months
Kang C, 2012 [55]	32	Gem with or without Cis-RT	32 (100)	28 (88)	NR
Barugola G, 2012 [56]	27	Various	27 (100)	NR	NR
Stokes J, 2011 [57]	40	Cape-RT	16 (40)	12 (75)	NR
Chun Y, 2010 [58]	74	Various	74 (100)	44 (60	Median 21 months
McClaine R, 2010 [59]	29	Various	12 (41)	8 (75)	NR

George and Ritch, Chapter 9: Neoadjuvant versus Adjuvant Therapy in Localized Pancreatic Cancer, Management of Localized Pancreatic Cancer, Springer Nature Publishers, in press

The Oncologist®

Neoadjuvant FOLFIRINOX for Borderline Resectable Pancreas Cancer: A New Treatment Paradigm?

Kathleen K. Christians,[a] Susan Tsai,[a] Anna Mahmoud,[a] Paul Ritch,[b] James P. Thomas,[b] Lauren Wiebe,[b] Tracy Kelly,[c] Beth Erickson,[c] Huamin Wang,[d] Douglas B. Evans,[a] Ben George[b]

[a]Department of Surgery, Division of Surgical Oncology, [b]Department of Medicine, Division of Medical Oncology, and [c]Department of Radiation Oncology, Pancreatic Cancer Program, Medical College of Wisconsin, Milwaukee, Wisconsin, USA; [d]Department of Pathology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Survival of patients with resectable pancreatic cancer who received neoadjuvant therapy

Kathleen K. Christians, MD,[a] Jonathan W. Heimler,[a] Ben George, MD,[b] Paul S. Ritch, MD,[b] Beth A. Erickson, MD,[c] Fabian Johnston, MD,[a] Parag P. Tolat, MD,[d] William D. Foley, MD,[d] Douglas B. Evans, MD,[a] *and* Susan Tsai, MD, MS,[a] *Milwaukee, WI*

Pancreas

Use of neoadjuvant therapy in patients 75 years of age and older with pancreatic cancer

John T. Miura, MD,[a] Ashley N. Krepline, BS,[a] Ben George, MD,[b] Paul S. Ritch, MD,[b] Beth A. Erickson, MD,[c] Fabian M. Johnston, MD, MHS,[a] Kiyoko Oshima, MD,[d] Kathleen K. Christians, MD,[a] Douglas B. Evans, MD,[a] *and* Susan Tsai, MD, MHS,[a] *Milwaukee, WI*

DOI:10.1111/hpb.12448 HPB

ORIGINAL ARTICLE

Pre-treatment carbohydrate antigen 19-9 does not predict the response to neoadjuvant therapy in patients with localized pancreatic cancer

Mohammed Aldakkak[1], Kathleen K. Christians[1], Ashley N. Krepline[1], Ben George[2], Paul S. Ritch[2], Beth A. Erickson[3], Fabian M. Johnston[1], Douglas B. Evans[1] & Susan Tsai[1]

[1]Departments of Surgery, [2]Departments of Medicine, and [3]Departments of Radiation Oncology, Pancreatic Cancer Program, The Medical College of Wisconsin, Milwaukee, WI, USA

J Gastrointest Surg (2014) 18:2016–2025
DOI 10.1007/s11605-014-2635-9

ORIGINAL ARTICLE

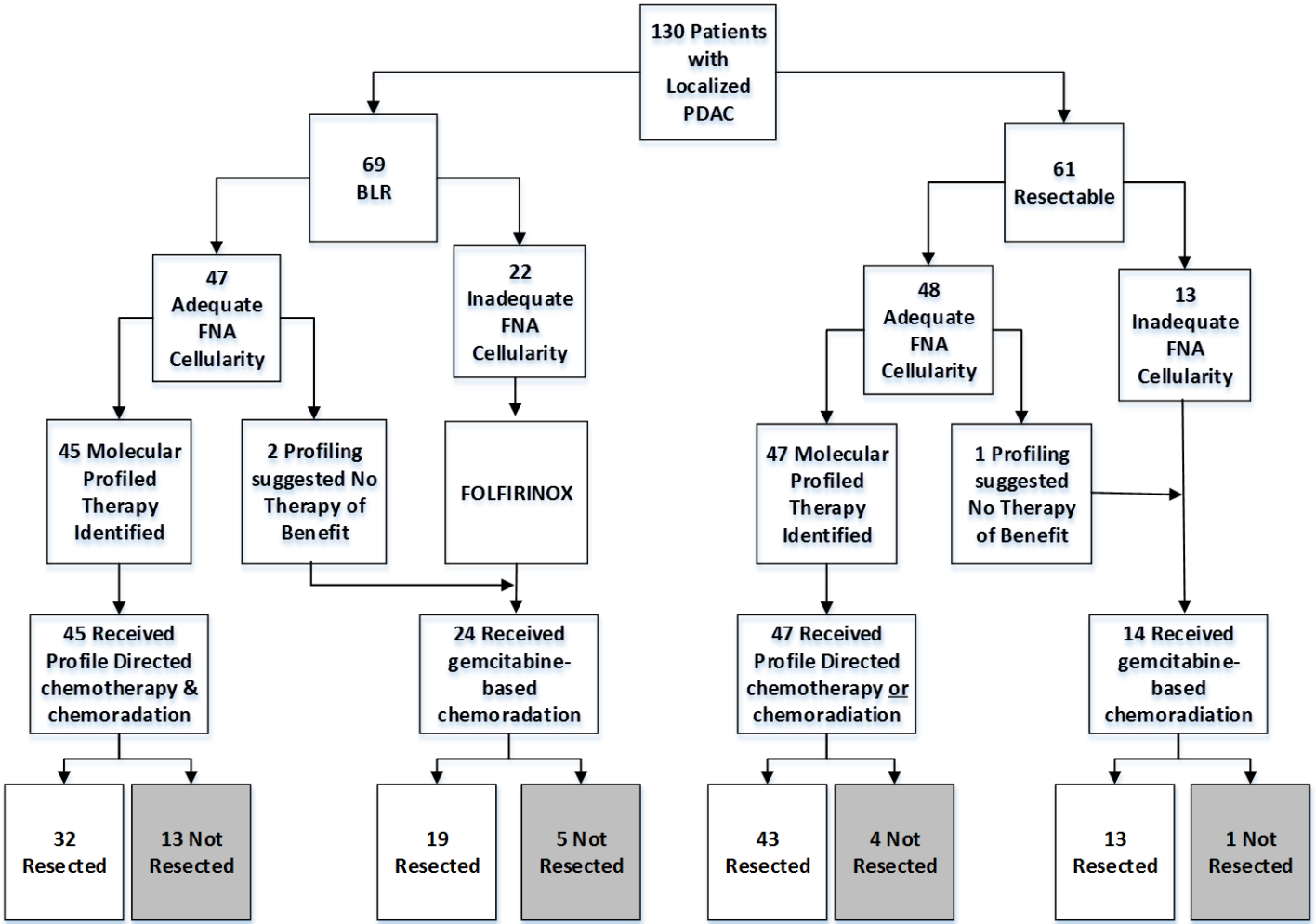
Patency Rates of Portal Vein/Superior Mesenteric Vein Reconstruction After Pancreatectomy for Pancreatic Cancer

A. N. Krepline • K. K. Christians • K. Duelge • A. Mahmoud • P. Ritch • B. George • B. A. Erickson • W. D. Foley • E. J. Quebbeman • K. K. Turaga • F. M. Johnston • T. C. Gamblin • D. B. Evans • S. Tsai

Arterial resection at the time of pancreatectomy for cancer

Kathleen K. Christians, MD,[a] Charles H. C. Pilgrim, MD, PhD,[a] Susan Tsai, MD, MS,[a] Paul Ritch, MD,[b] Ben George, MD,[b] Beth Erickson, MD,[c] Parag Tolat, MD,[d] *and* Douglas B. Evans, MD,[a] *Milwaukee, WI*

A PHASE II CLINICAL TRIAL OF MOLECULAR PROFILE DRIVEN NEOADJUVANT THERAPY FOR LOCALIZED PANCREATIC CANCER



Tsai, Christians, George et. al, Annals of Surgery, 2018

PATIENT CHARACTERISTICS

Table 1: Baseline Characteristics of the Patients (n=130)				
Characteristic	Total n=130	Resectable n=61	BLR n= 69	p-value
Age in years, median (IQR)	65 (14)	66 (16)	65 (12)	0.80
Gender (Female), n (%)	74 (57)	36 (59)	38 (55)	0.72
Charlson Comorbidity Index, median (IQR)	5 (2)	5 (2)	5 (1)	0.85
Pre-treatment CA19-9, U/mL median (IQR)¥	245 (490)	237 (476)	258 (389)	0.50
Hemoglobin A1c at diagnosis, median (IQR)	5.9 (1.6)	5.9 (1.4)	5.9 (1.7)	0.89
Tumor size by CT in cm, median (IQR)	2.9 (1.7)	2.4 (1.2)	3.3 (1.1)	<0.001
FNA cellularity adequate for profiling, n (%)	95 (73)	48 (78)	47 (68)	0.17
Molecular Profiled Therapy Delivered, n (%)	92 (71)	47 (77)	45 (65)	0.14
Received all care at MCW, n (%)	62 (48)	27 (44)	35 (51)	0.49
Neoadjuvant Chemotherapy , n (%)				
FOLFIRINOX	52 (40)	16 (26)	36 (52)	0.02
FOLFIRI	26 (20)	16 (26)	10 (14)	
Gemcitabine/Nab-paclitaxel	16 (12)	7 (11)	9 (13)	
Capecitabine/Nab-paclitaxel	15 (11)	3 (5)	12 (17)	
Neoadjuvant Chemoradiation, n (%)	83 (64)	19 (31)	64 (93)	<0.001
Preoperative CA19-9, U/mL, median (IQR)	46 (105)	43 (122)	49 (102)	0.60
Normal Preoperative CA19-9, n (%)Δ	73 (57)	34 (56)	39 (57)	0.78
Completed neoadjuvant therapy and surgery, n (%)	107 (82)	56 (92)	51 (74)	0.008

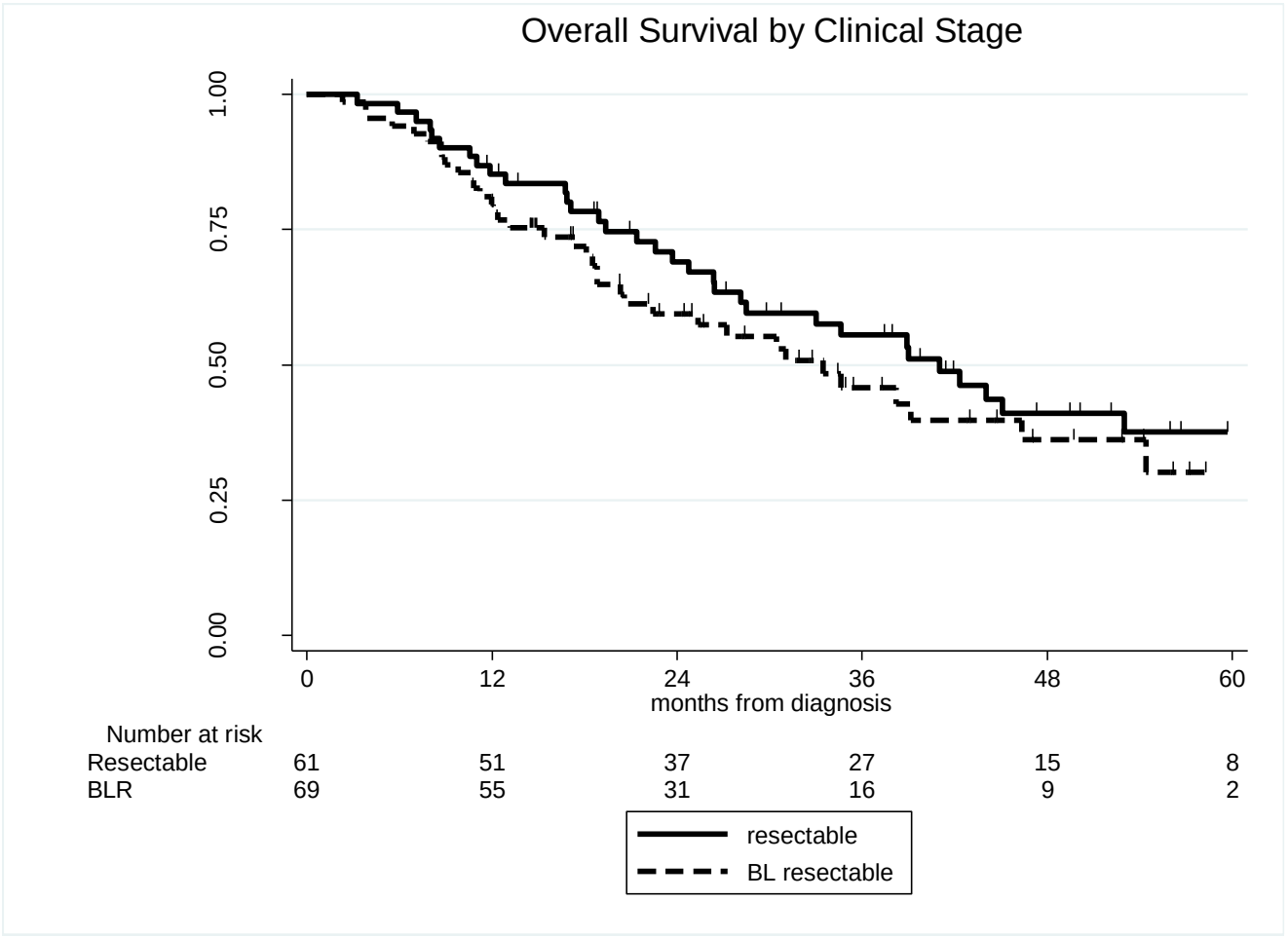
Tsai, Christians, George et. al, Annals of Surgery, 2018

CLINICOPATHOLOGIC CHARACTERISTICS

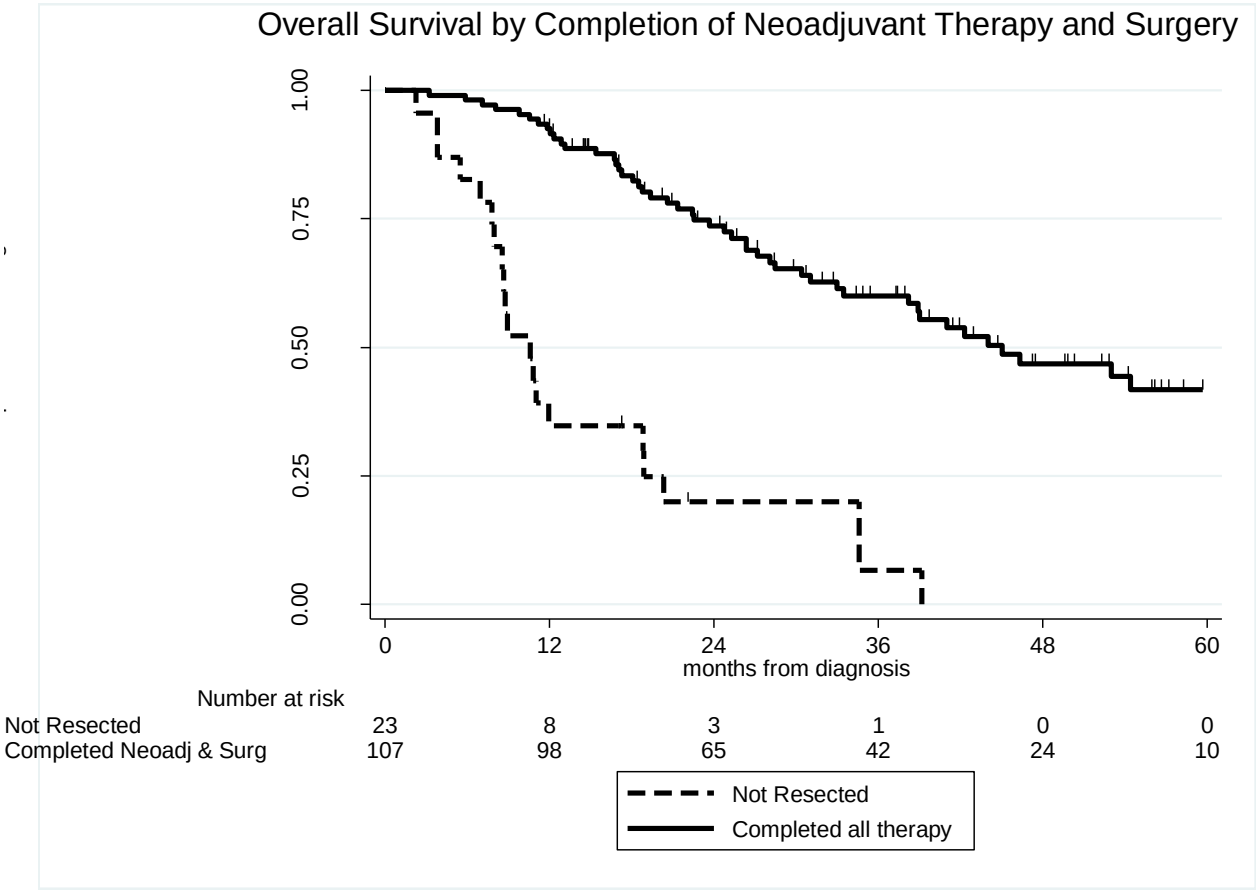
Table 2. Clinicopathologic Characteristics of Resected Patients (n = 107)				
Variable(s)	Total n=107	Resectable n=56	BLR n=51	p-value
T Stage, n (%)				0.49
T0	2 (0)	1 (2)	1 (2)	
T1	10 (9)	5 (9)	5 (10)	
T2	14 (13)	10(18)	4 (8)	
T3	81 (78)	40 (71)	41 (80)	
N Stage, n (%)				0.50
N0	53 (50)	26 (46)	27 (53)	
N1	54 (50)	30 (54)	24 (47)	
Pathologic tumor size, cm, median (IQR)	2.5 (1.3)	2.5 (1.6)	2.5 (1.3)	0.65
Histologic Grade, n (%)$^{\Delta}$				0.23
Well diff	81 (80)	45 (85)	36 (75)	
Moderate or Mod-poor diff	20 (20)	8 (15)	12 (25)	
Pathologic Response, n (%)				0.63
CR or near CR	19 (18)	9 (16)	10 (20)	
PR or no response	86 (82)	46 (84)	40 (80)	
Perineural Invasion, n (%)	82 (76)	44 (79)	38 (75)	0.49
Lymphovascular Invasion, n (%)	36 (34)	20 (36)	16 (31)	0.59
Positive Margin, n (%)	20 (19)	8 (14)	12 (23)	0.22
Elevated Postoperative CA19-9, n (%)	25 (23)	12 (21)	13 (25)	0.62
Adjuvant Therapy, n (%)	93 (87)	50 (89)	43 (84)	0.45

$^{\Delta}$101 patients had histologic grade reported

Tsai, Christians, George et. al, Annals of Surgery, 2018



Tsai, Christians, George et. al, Annals of Surgery, 2018



Tsai, Christians, George et. al, Annals of Surgery, 2018

RESPONSE TO NEOADJUVANT THERAPY

Method of assessment	Responder	Stable disease	Nonresponder
Patient performance status (to include pain assessment)	Improved	Not worse	Worse
Imaging of the primary tumor (CT/MRI/PET, etc.)	Improved or no progression	No progression	Local or distant progression on cross-sectional imaging
Biomarker Profile (including CA19-9* and other emerging biomarkers)	Suggests treatment response (for example, a normalization of CA19-9, other biomarkers being developed)	Not worse	Suggests progressive disease
How to use the above information	All three required to be a "Responder"	All three required to be considered as having "Stable Disease"	Any of the three would define a "Nonresponder"**

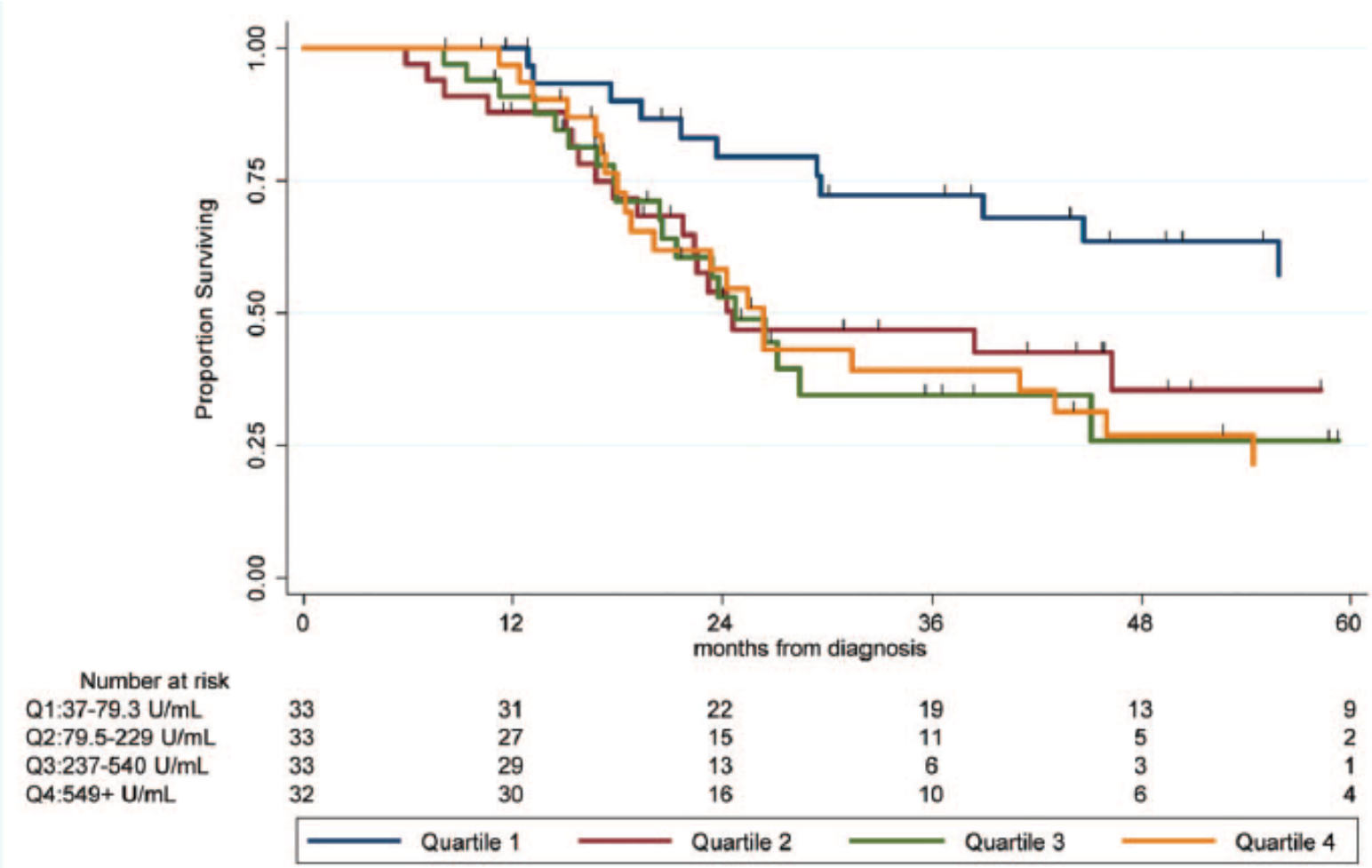
* CA19-9 must be measured when the serum bilirubin has normalized and such biomarkers should be assessed before treatment is initiated and at each re-staging evaluation

** Assuming clinical symptoms leading to a decline in performance status are not medically correctable

Evans, George and Tsai, Ann Surg Oncol, 2015

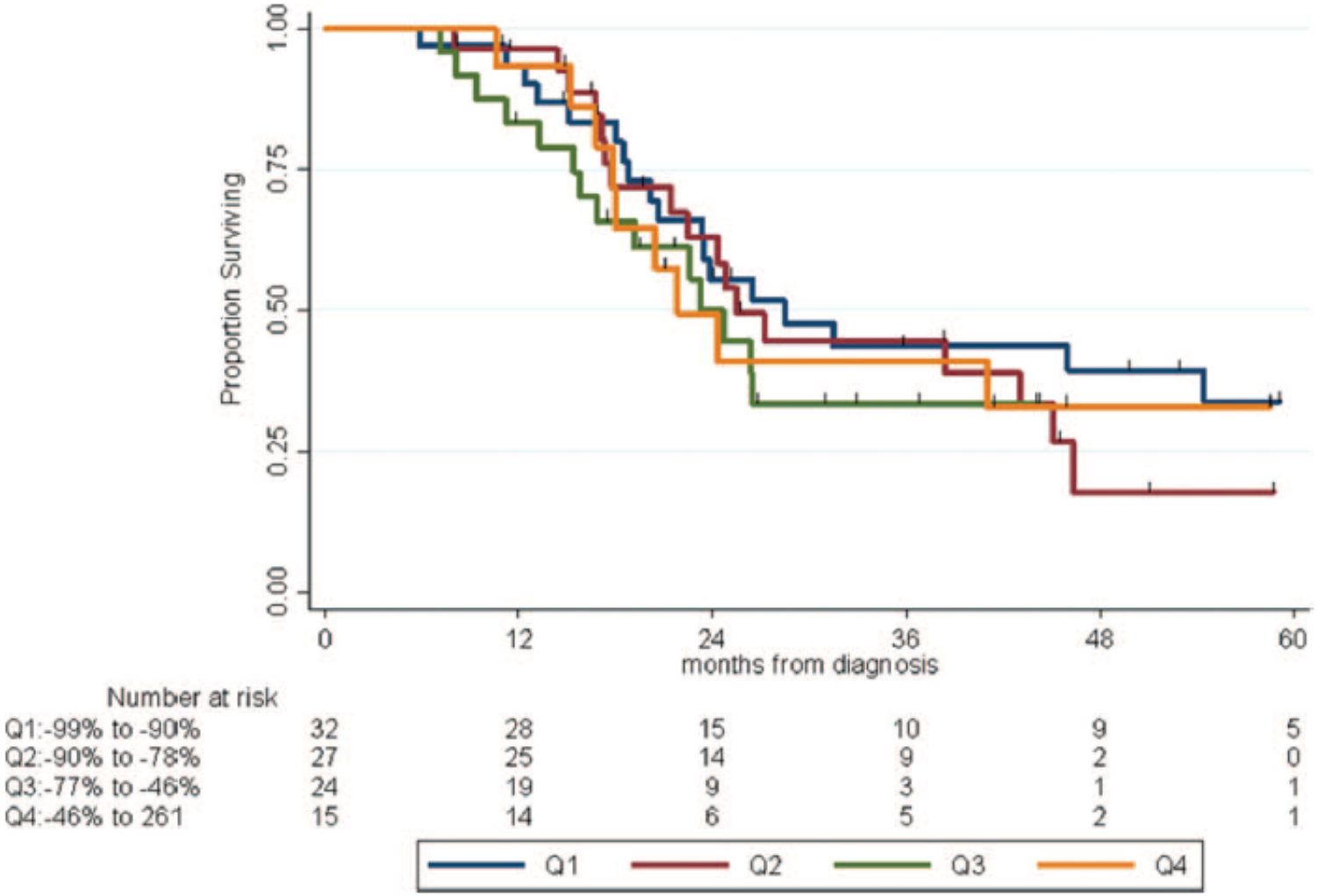
ROLE OF CA 19-9

CA 19-9 AT DIAGNOSIS



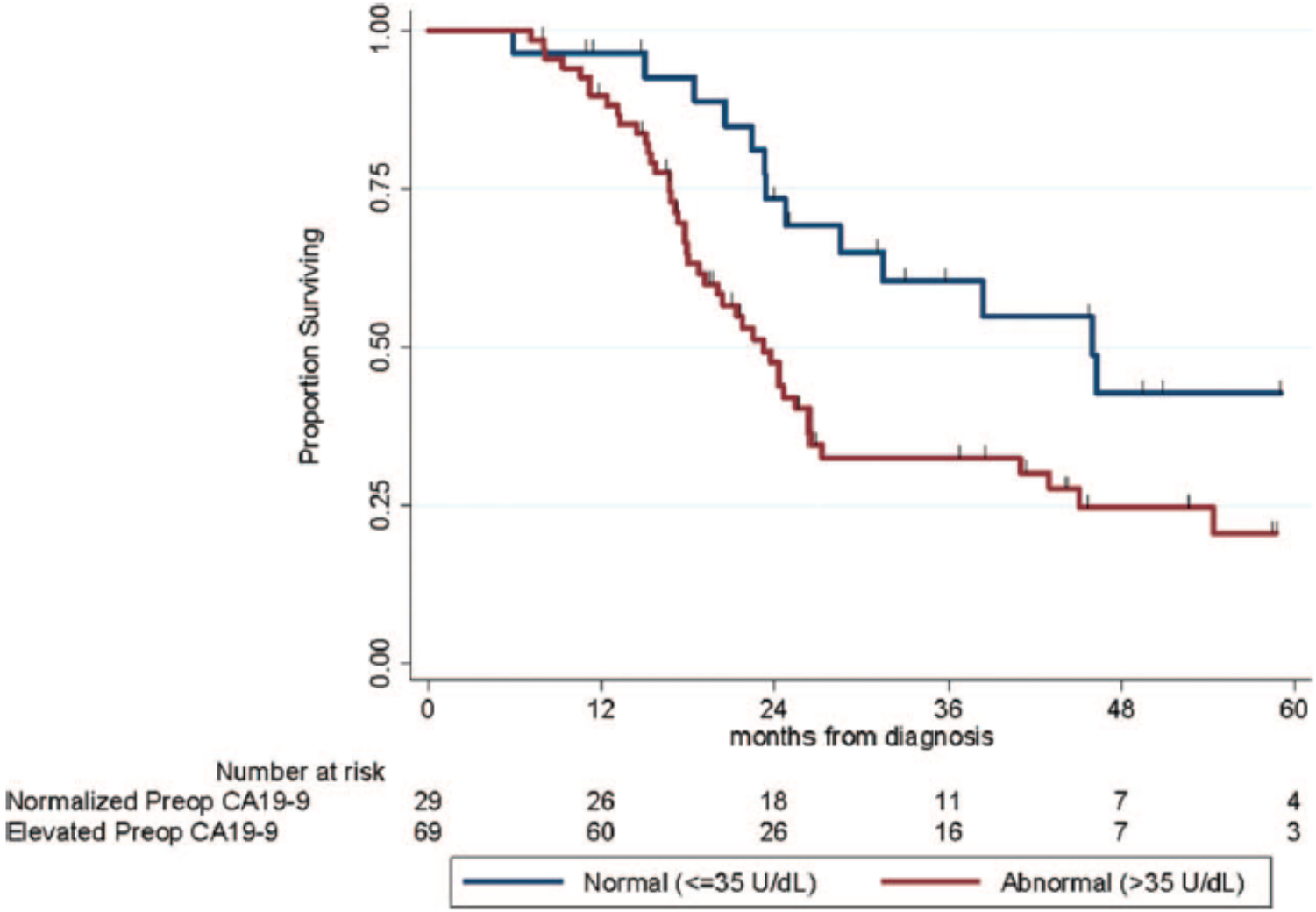
Tsai, George, Wittman et. al, Annals of Surgery, 2018

OS BY Δ CA 19-9 AFTER NEOADJUVANT THERAPY



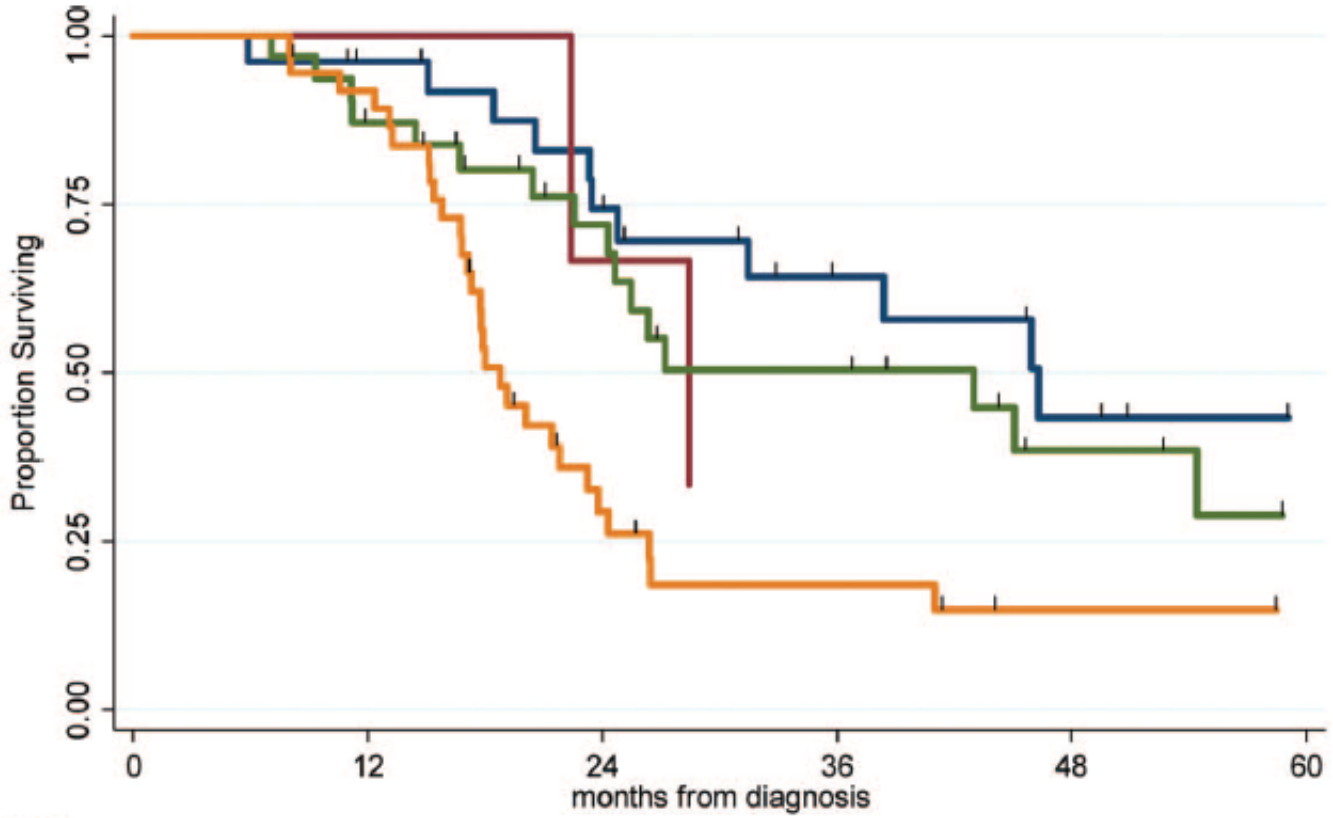
Tsai, George, Wittman et. al, Annals of Surgery 2018

OS BY PRE-OP CA 19-9 (NORMAL VS ELEVATED)



Tsai, George, Wittman et. Annals of Surgery 2018

OVERALL SURVIVAL BY PERIOPERATIVE CA 19-9 STATUS

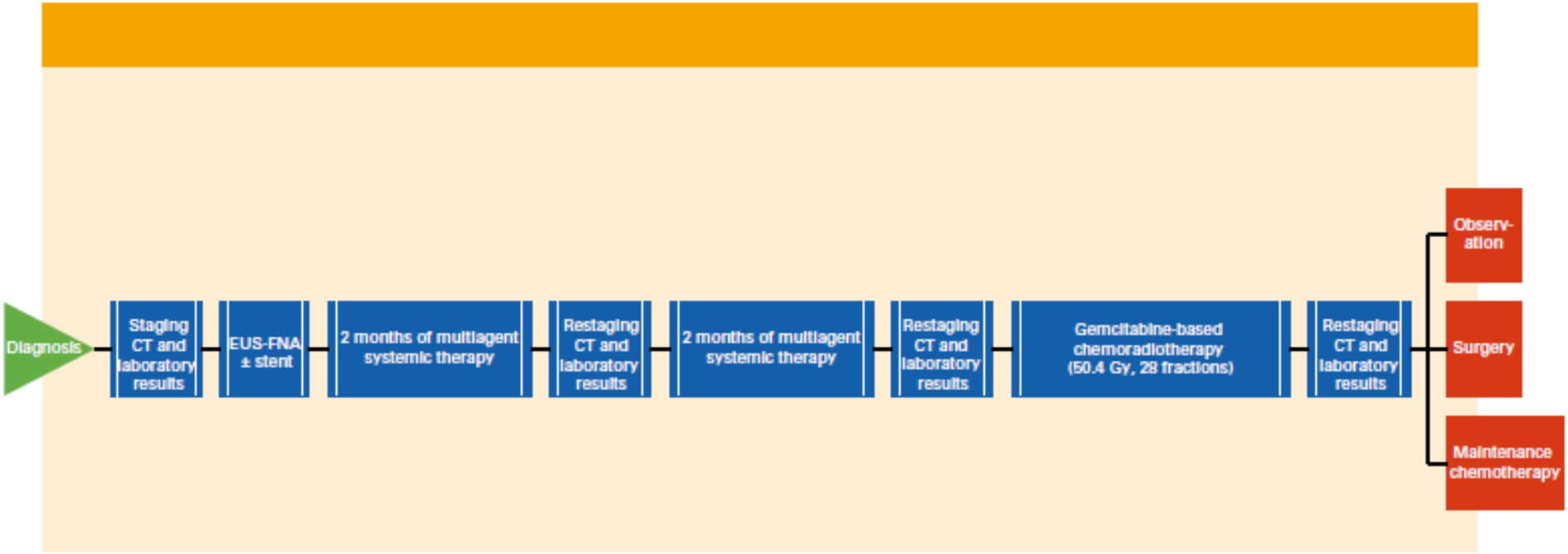


Number at risk						
normal/normal	26	23	16	10	6	3
normal/elevated	3	3	2	1	1	1
elevated/normal	32	26	17	11	5	2
elevated/elevated	37	34	9	5	2	1

Normal/Normal Normal/Elevated Elevated/Normal Elevated/Elevated

Tsai, George, Wittman et. al, Annals of Surgery, 2018

TREATMENT SEQUENCING IN LOCALIZED PANCREATIC CANCER



Tsai, Christians, Ritch et. al, JOP, 2016

Neoadjuvant Versus Adjuvant – Chemoradiation

N = 110 BRPC Planned
N = 57 BRPC Enrolled

XRT 45Gy in 25 and 9Gy in 5 fractions
Gem 400mg/m2

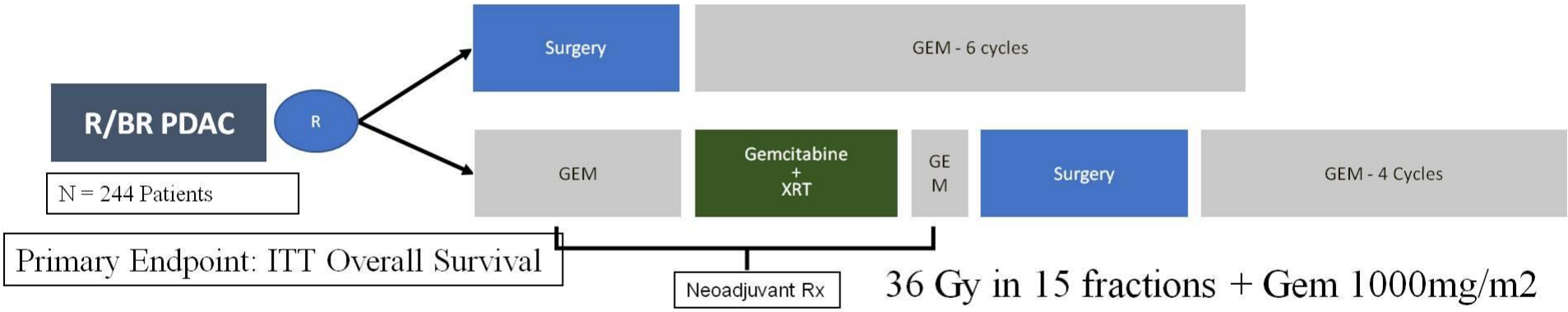
Primary Endpoint = 2-Yr Survival

	Neoadjuvant CRT	Adjuvant CRT	
2 year survival - ITT	**40%**	26%	p = 0.004
Median OS (months) – ITT	**21**	12	HR 1.97; p = 0.028
R0 Resection Rate - ITT	**51%**	26%	p = 0.004
R0 Resection Rate - Resected	**82%**	33%	p = 0.010
Positive Lymph Nodes	**29%**	83%	p = 0.004

Jang, J-Y et al, Annals of Surgery 2018

Slide Courtesy: Cristina Ferrone

Preoperative Radiochemotherapy Versus Immediate Surgery For (Borderline) Resectable Pancreatic Cancer: (PREOPANC)

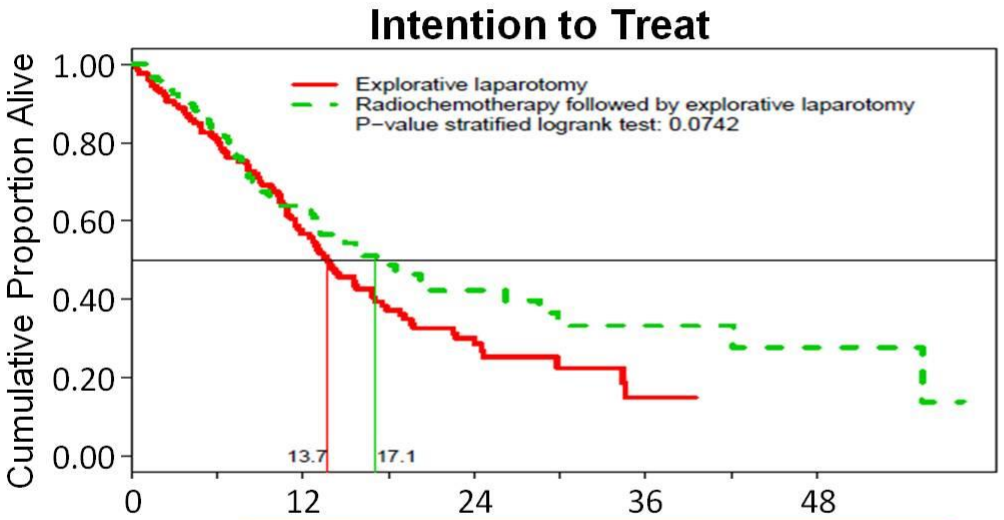


	Immediate Surgery N=127	Neoadjuvant CRT N=119	P-value
Resection Rate (%)	72%	62%	.065
R0 Resection Rate PP (%)	31%	63%	<.001
Serious Adverse Events(%)	39	46	<.28

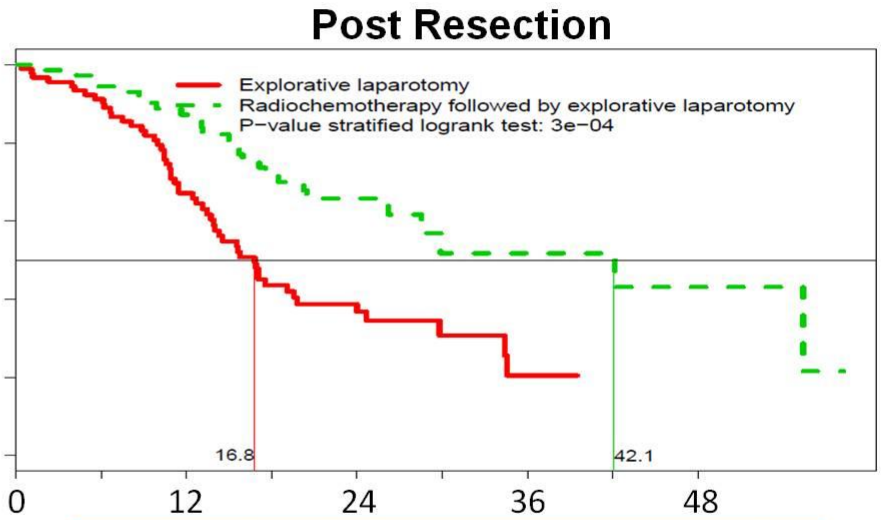
Van Tienhoven G, et al. ASCO 2018

Slide Courtesy: Cristina Ferrone

Overall Survival Analyses



Median:13.7 vs 17.1 Mos. HR 0.74; p=0.074

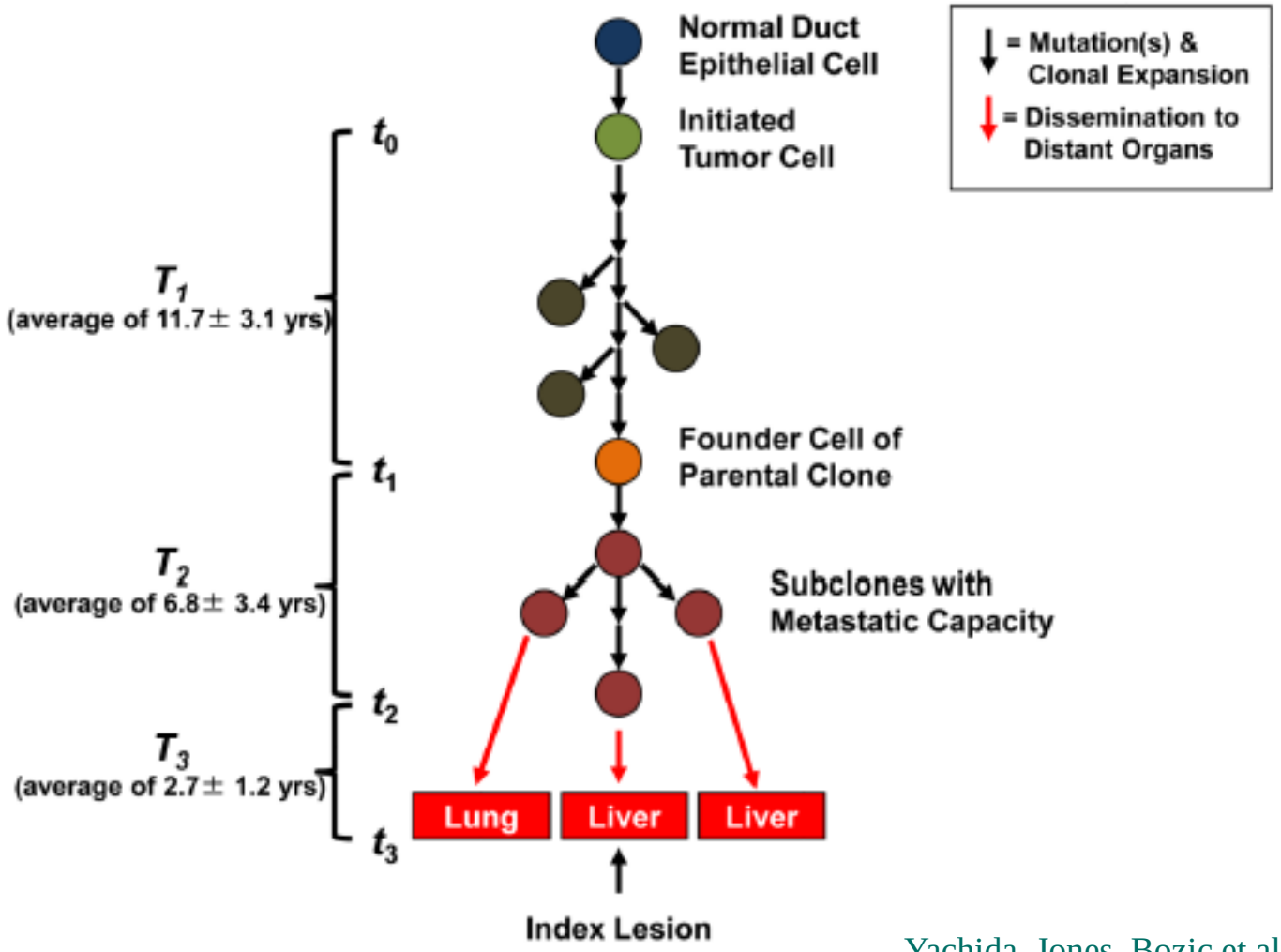


Median Survival 16.8 vs 29.9 Months, p = 0.001

Slide Courtesy: Cristina Ferrone

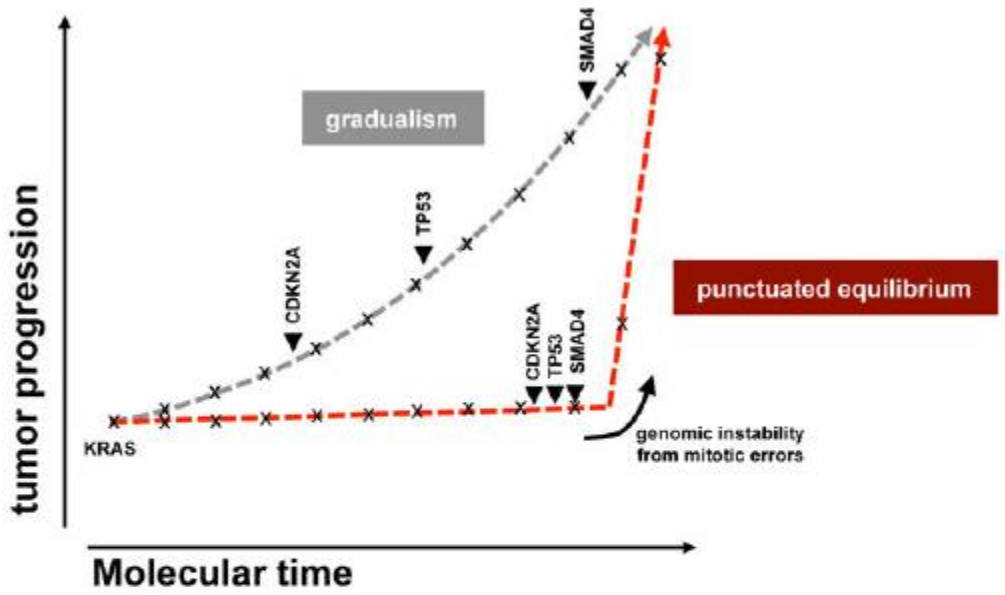
CHALLENGES

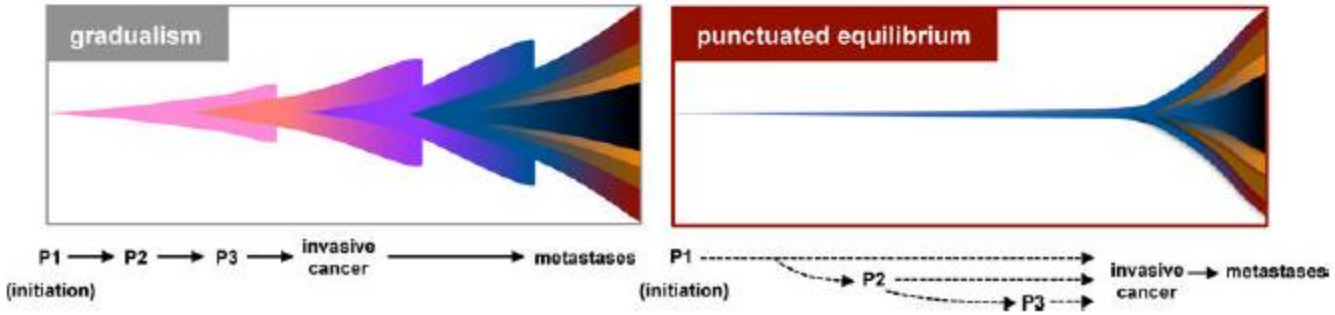
EVOLUTION OF PANCREATIC CANCER



Yachida, Jones, Bozic et al, Nature, 2010

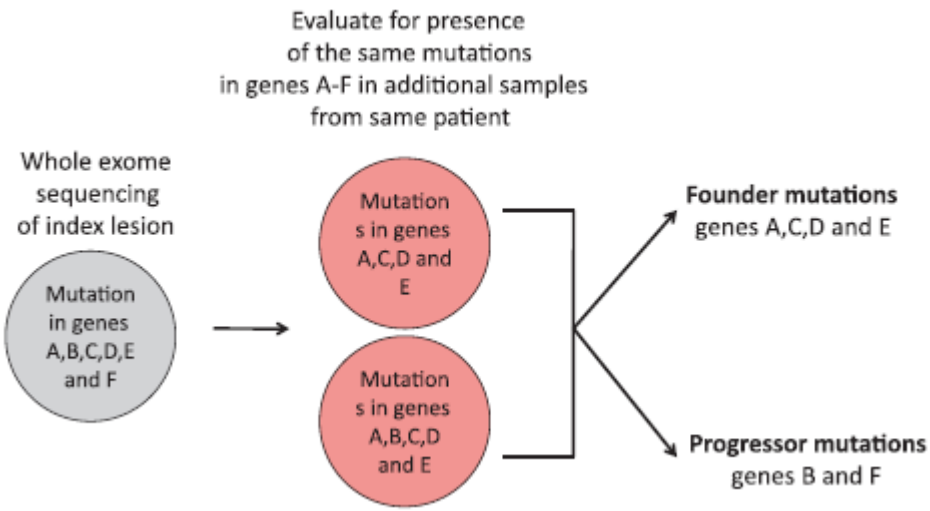
EVOLUTION OF PANCREATIC CANCER

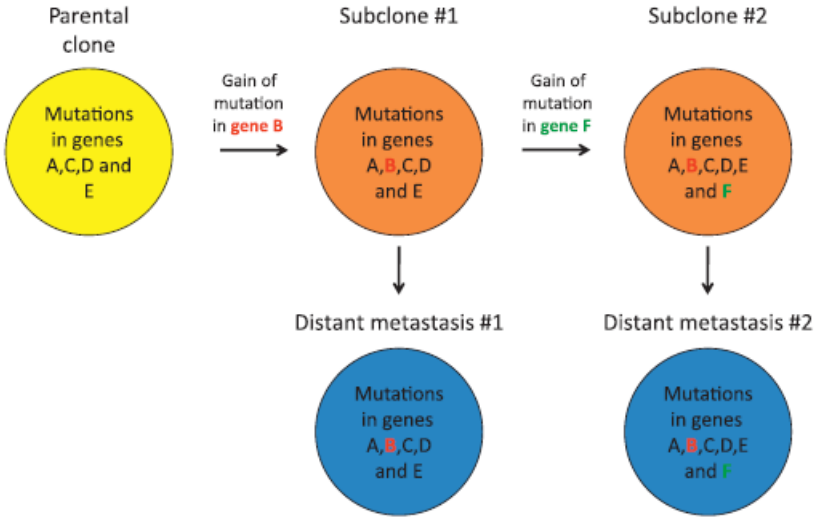




Notta, Chan-Seng-Yue, Lemire et al, Nature 2016

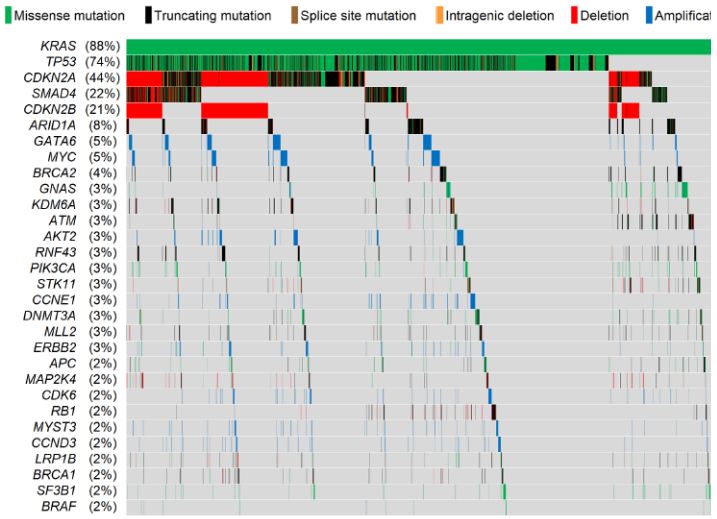
CLONAL HETEROGENEITY IN PDAC

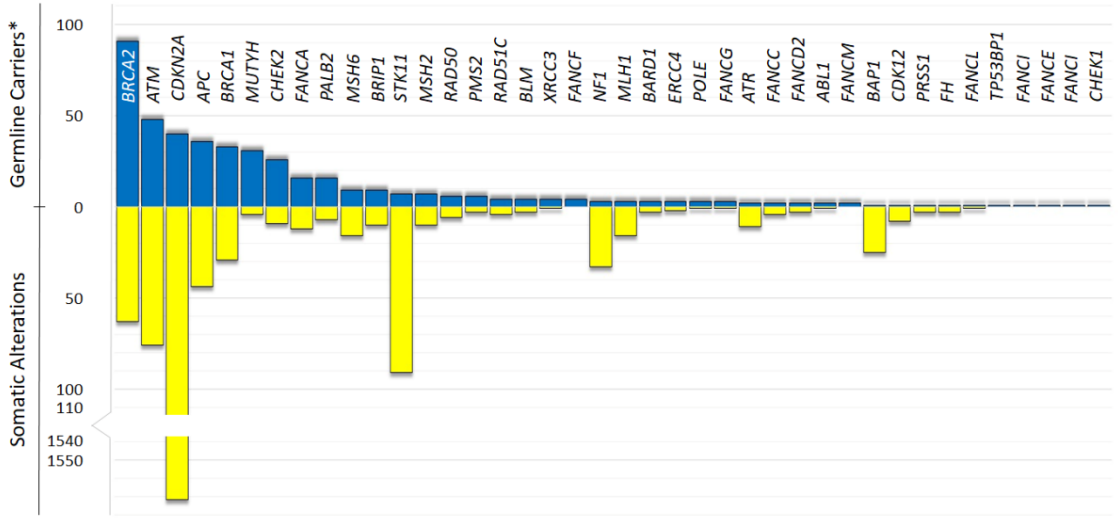




Iacobuzio-Donahue, Gut, 2012

Prospective Comprehensive Genomic Profiling of 3,594 Pancreatic Ductal Adenocarcinomas: A Genomic Framework for Precision Medicine Clinical Trials



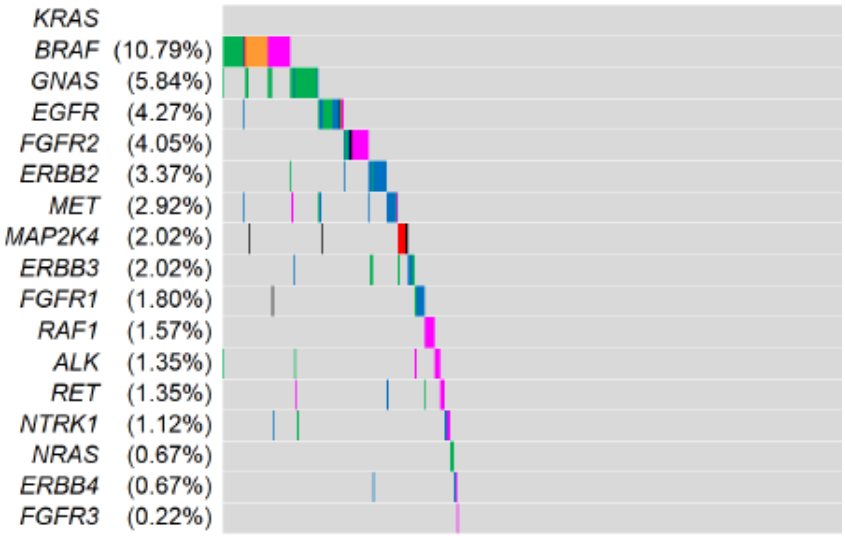


*Singhi, *George, Greenbowe et. al, Gastroenterology, 2019

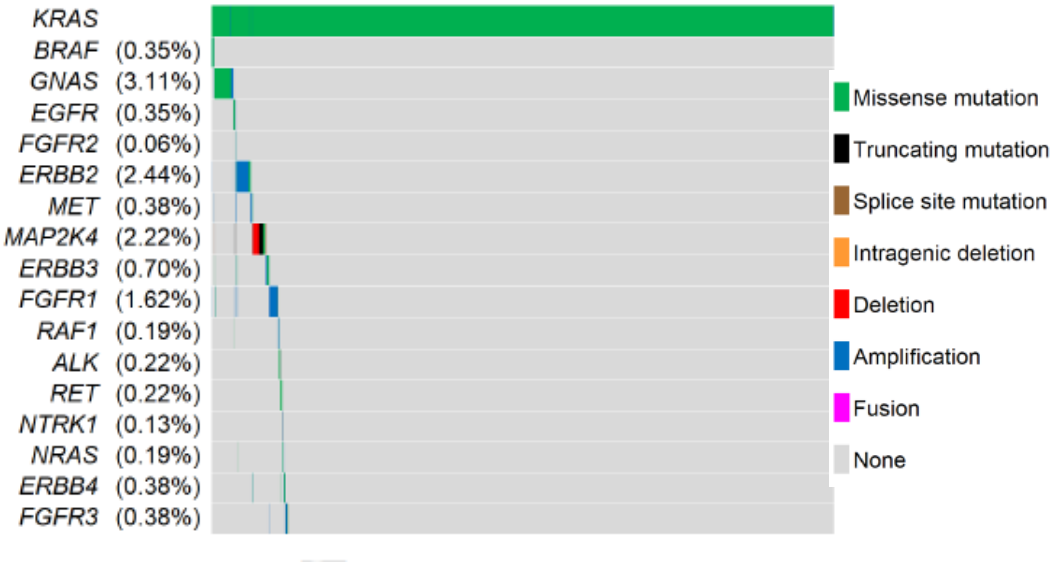
* Equal contribution

Prospective Comprehensive Genomic Profiling of 3,594 Pancreatic Ductal Adenocarcinomas: A Genomic Framework for Precision Medicine Clinical Trials

KRAS WT



KRAS MUT



*Singhi, *George, Greenbowe et. al, Gastroenterology, 2019

* Equal contribution

MOLECULAR CHARACTERIZATION OF PANCREATIC CANCER

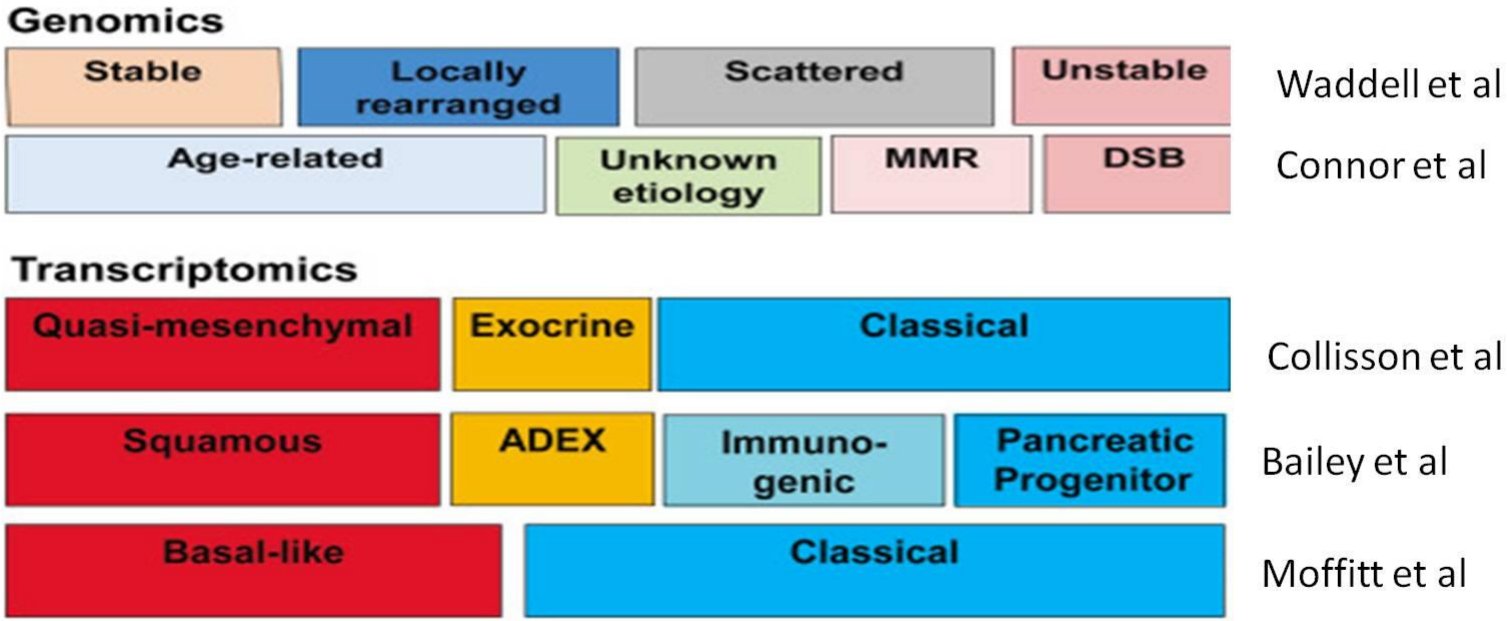
Author	Publication Year	N	Methodology	Discovery
Jones, S [16]	2008	24	Exome Sequencing	Core set of 12 cellular signaling pathways and processes
Collison, EA [18]	2011	2 datasets	Transcriptomic Profiling	(i) Three subtypes - classical, quasi-mesenchymal (QM-PDA) and exocrine-like (ii) Prognostic value of subtypes
Biankin, AV [15]	2012	99	Whole Genome Sequencing, CNV Analysis	(i) 16 significant mutated genes (ii) frequent and diverse somatic aberrations in genes involved in axon guidance (SLIT/ROBO signaling)
Moffitt, RA [19]	2015	206	Transcriptomic Profiling	(i) Basal and Classical tumor subtypes (ii) Normal and Activated Stromal subtypes (iii) Prognostic and predictive value of the subtypes
Waddell, N [17]	2015	100	Whole Genome Sequencing, CNV Analysis	(i) Four subtypes – Stable, Locally Rearranged, Scattered, Unstable (ii) Predictive value of Unstable subtype to platinum based chemotherapy
Bailey, P [14]	2016	456	Whole Genome Sequencing, Deep Exome Sequencing, CNV Analysis, Transcriptomic Profiling	(i) Four subtypes – Squamous, Pancreatic Progenitor, Immunogenic and Aberrantly Differentiated Endocrine Exocrine (ADEX) (ii) Identified 32 recurrently mutated genes grouped into 10 pathways

George, B. Chapter 10: Molecular Profiling in Localized Pancreatic Cancer, Management of Localized Pancreatic Cancer, Springer Nature Publishers, in press

TRANSCRIPTOMIC CLASSIFICATION OF PANCREATIC CANCER

Bailey, Chang, Nones et al, Nature 2016

PDAC classifications from profiling studies: resections



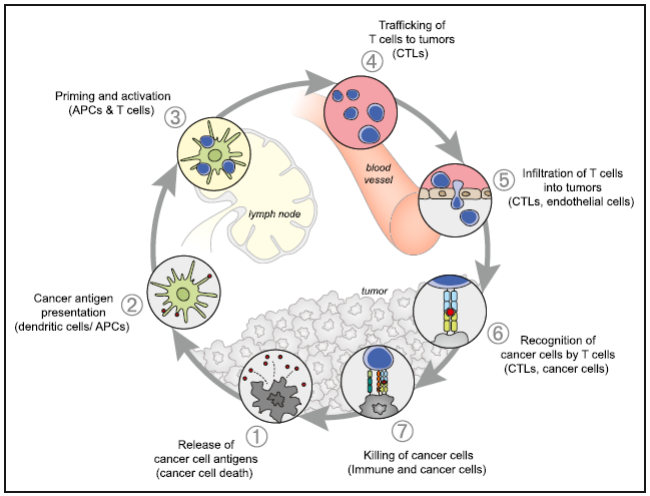
Clinically impactful?

Le Large et al, Seminars in Cancer Biology 2017

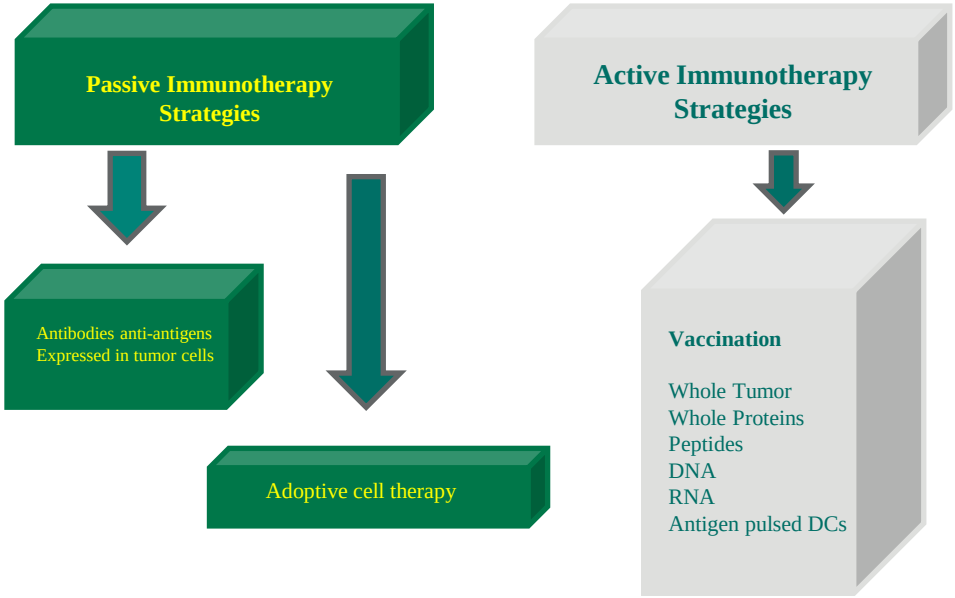
Slide Courtesy: Jennifer J. Knox

EMERGING STRATEGIES

A PHASE 1 STUDY OF PERSONALIZED NEOANTIGEN BASED PEPTIDE VACCINE (NPV) IN PATIENTS WITH LOCALLY ADVANCED PDAC - BACKGROUND



Chen & Mellman, Immunity 2013



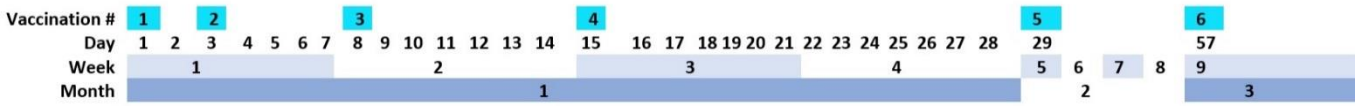
- Characteristics unique to each patient and his/her tumor dictates the variability in response to treatment
- To maximize treatment response and minimize toxicity, we need to exploit host immunity and tumor specific alterations
- Vaccine based treatment strategies recruit the host immune response to fight cancer
  - This has implications in primary prevention, secondary prevention and treatment
- Personalized neoantigen based peptide vaccines take advantage of a patient's tumor specific immunogenic mutations

PI George

A PHASE 1 STUDY OF PERSONALIZED NPV IN PATIENTS WITH LOCALLY ADVANCED PDAC – OBJECTIVES

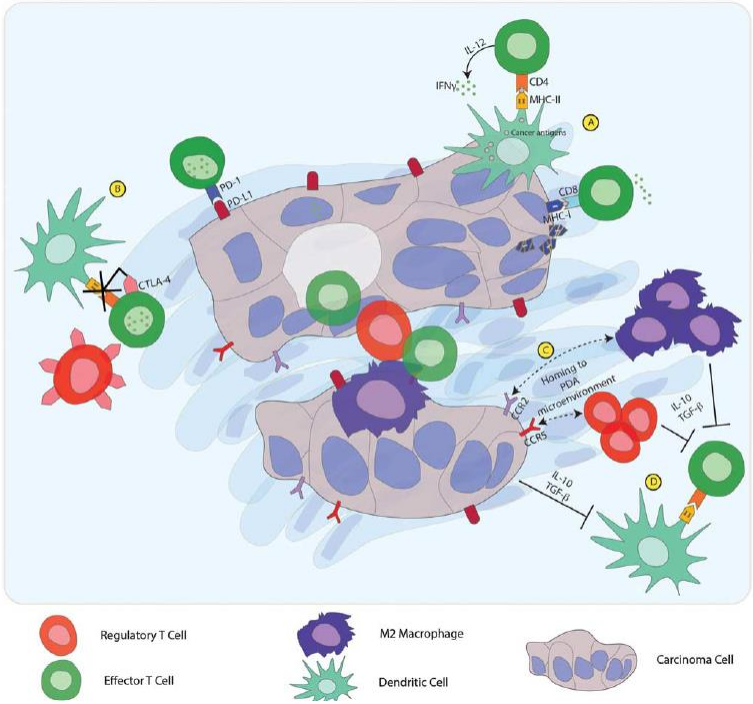
- **Primary Objective**
  - To evaluate the safety profile of personalized NPV in patients with PDAC
  - To assess the induction of vaccine-specific CD4+ and CD8+ T-cell responses (immune monitoring)

- **Secondary Objective**
  - To assess the feasibility of personalized neoantigen-based pancreatic cancer peptide vaccine production
  - To assess the efficacy of personalized neoantigen-based vaccines in patients with PDAC



PI George

A PHASE 1 STUDY OF PERSONALIZED NPV IN PATIENTS WITH LOCALLY ADVANCED PDAC – CORRELATIVE STUDIES



- Evaluate the immune milieu of the pretreatment tumor sample
- Correlate transcriptomic profile of the pretreatment tumor with clinical outcome
- Monitor peripheral blood T cell subsets over time
- Monitor plasma cytokines and chemokines
- Monitor peptide specific T-cell activation
- Monitor changes in somatic mutational profile in circulating tumor DNA (ctDNA)

PI George

PANCREAS CANCER PROGRAM – TRIAL PORTFOLIO

Resectable and Borderline Resectable

- Treatment Naïve
  - CA19-9 Producer
    - **PANC Trial**
  - CA19-9 non-producer
    - **SOFT Trial**
- Prior Neoadjuvant Chemotherapy
  - **SOFT Trial**
- Prior Surgery
  - Rising CA19-9 without radiographic disease
    - **SM-88 RCT (opening April 2019)**
  - Local Recurrence after prior XRT
    - **MRI-LINAC trial (opening March 2019)**

Locally Advanced

- Type A – potentially resectable
  - **SOFT Trial**
  - **Personalized Vaccine Trial (opening June 2019)**
- Type B – inoperable
  - **Radiotherapy dose escalation trial**
- Local Recurrence after prior XRT
  - **MRI- LINAC trial (opening March 2019**

Metastatic

- First Line
  - **RX-3117 + nab-paclitaxel**
  - **HALOZYME (closed)**
  - **MORPHEUS Trial**
- Second Line
  - Previous gemcitabine
    - **ARMO Trial**
  - Previous FOLFIRINOX
    - **BERG (BPM 31510) Trial**
  - Hyaluronan High tumors
    - **PEGPH20 + pembrolizumab (Jan/Feb 2019)**
  - **MORPHEUS Trial**
- Third Line
  - Hyaluronan High Tumors
    - **PEGPH20 + pembolizumab (Jan/Feb 2019)**
- Oligometastatic Disease
  - **SBRT (June 2019)**
- Maintenance therapy after best response
  - **Pembrolizumab + Paracalcitol (March 2019)**

TREATMENT SEQUENCING IN LOCALIZED PANCREATIC CANCER - SUMMARY

- Pancreatic Cancer is a systemic disease
- Accurate clinical staging and multidisciplinary decision making is pivotal
- Optimal delivery of systemic chemotherapy and chemo-radiotherapy needs to be facilitated
  - Surgery is essential but enough for a cure
- A strong interdisciplinary research program is pivotal
- Precision Medicine in Pancreatic Cancer is evolving – there is hope!

Q&A | DISCUSSIONS