Pancreatic Ductal Adenocarcinoma

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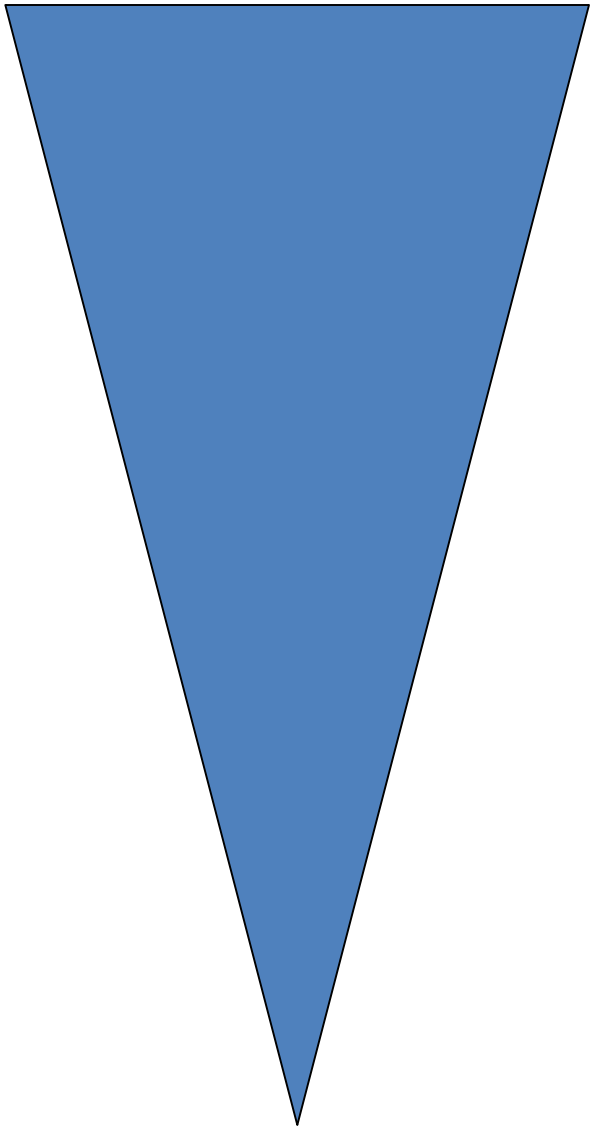
Median Survival of Patients With Pancreatic Cancer

- Localized/ Resectable 15 - 24 months 10%
- Locally Advanced 6 - 15 months 30%
- Metastatic/ Advanced 3 - 12 months 60%

Importance of Supportive and Palliative Care

Pancreatic cancer symptom burden

- Asthenia 85%
- Weight loss
- Anorexia
- Abdominal / epigastric pain
- Dark urine
- Jaundice
- Nausea
- Back pain
- Diarrhea
- Vomiting
- Steatorrhea
- Abdominal fullness
- Thrombophlebitis 2-3%



Recent guidelines call for early palliative care as a new standard

Potentially Curable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline 2016**:**

“Patients should have full assessment of symptoms, psychological status, and social supports and should receive palliative care early”

www.asco.org/guidelines/PCPC

Supportive and Palliative Care

- Start supportive and palliative care as soon as diagnosis is suspected – pancreatic cancer is an EMERGENCY
- Assess symptoms and their speed of development
- Consider pain, weight loss, exocrine pancreatic insufficiency, jaundice*, delayed gastric emptying*, VTE, depression, etc.

* Biliary obstruction: endoscopic stent placement

* Duodenal obstruction: endoscopic metal stent placement

Many patients assume they can be cured with palliative measures

- 1193 patients participating in the Cancer Care Outcomes Research and Surveillance (CanCORS) study receiving chemotherapy for stage IV lung or colorectal cancers

- 69% lung and 81% colorectal cancer patients did not understand that their treatment was not at all likely to cure their cancer.

- Inaccurate beliefs were higher among patients who rated their communication with physicians very favorably !

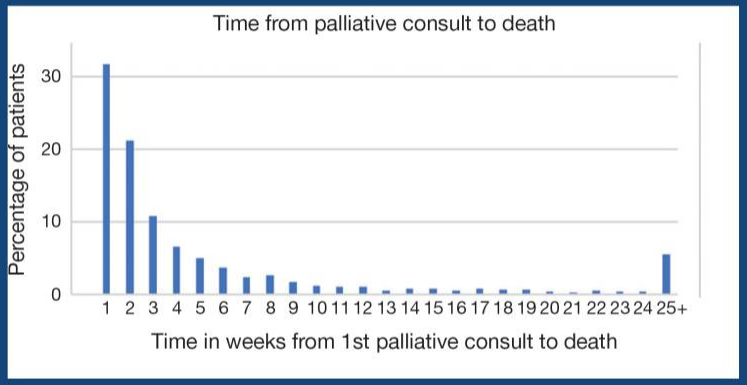
- Educational level, functional status, and the patient's role in decision making were not associated with such inaccurate beliefs about chemotherapy

  - Weeks JC, et al. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med. 2012 Oct 25;367(17):1616-25.

Recent Randomized Trials document Impact of EARLY Palliative Care

- Benefits of OUTPATIENT concurrent palliative care:
  - Avoided admissions and readmissions, increase referral to hospice,
  - Better communication and satisfaction
  - Equal or lowered costs to the health system
  - Equal or better symptom management
  - Equal or improved quality of life
  - Equal or LONGER survival
  - Not a single trial showed harm, added cost, or burden

Most Palliative Care consults in Medicare beneficiaries with Pancreatic cancer are placed close to death



	No Palliative care	Palliative care
ED Visits*	↓	↑
ED Charges *	↓	↑
ICU stays	↔	↔
Days in ICU	↔	↔
ICU Charges	↔	↔

Bhulani *et al*. Palliative care and end-of-life health care utilization in elderly patients with pancreatic cancer. *J Gastrointest Oncol 2018*

UT Southwestern Harold C. Simmons Comprehensive Cancer Center | NCI Designated Comprehensive Cancer Center

Locally advanced inoperable / metastatic Pancreatic Cancer

Predicting Prognosis in advanced PDAC
The MSKCC Prognostic Score (MPS)

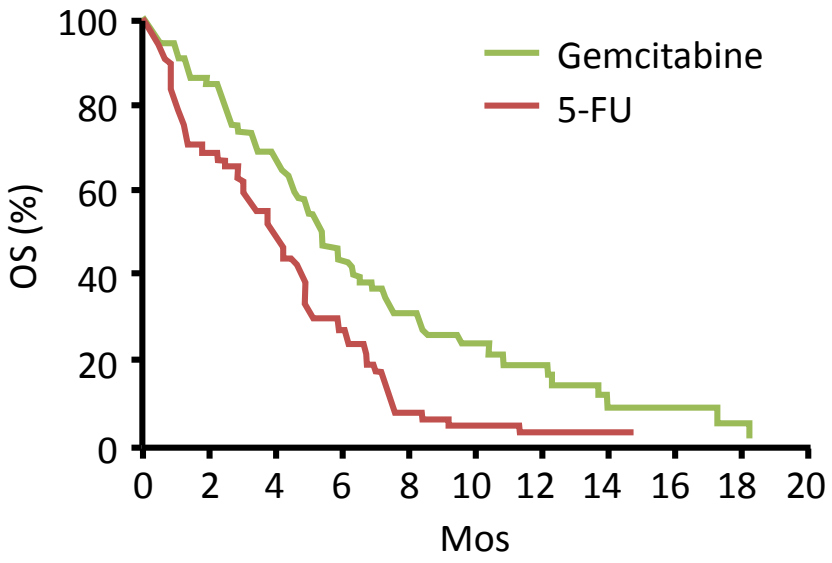
- A modification of the Glasgow Prognostic Score
  (CRP >10 and Albumin < 3.5 g/dl)
- Neutrophil / Lymphocyte Ratio (NLR) >4 and Albumin < 4 g/dl) get each 1 point

Cohort	Median OS (months)	Interquartile Range
MPS 0 (n = 213)	14.7	8.5-26.3
MPS 1 (n = 332)	10.3	4.5-21.9
MPS 2 (n = 288)	6.2	2.3-14.8
Overall (n = 833)	10.2	4.4-21.5

Andrew Cheung Yang, Abstract 4105, ASCO 2017

Gemcitabine Established as Treatment Standard for PDAC over 20 Years Ago

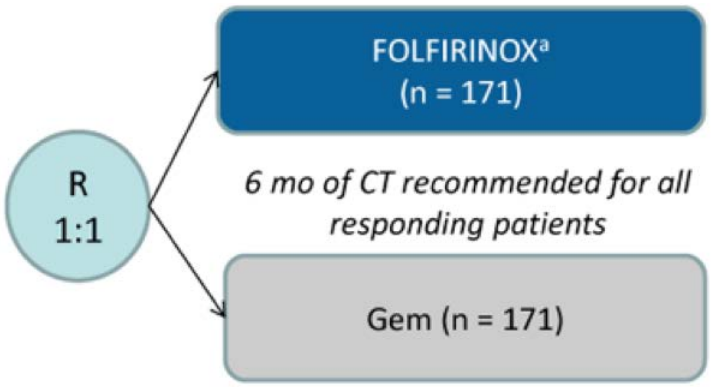
- First-line gemcitabine vs bolus 5-FU in advanced pancreatic cancer
  - Median OS: 5.7 vs 4.4 mos (*P* = .0025); 1-yr OS: 18% vs 2%
  - Clinical benefit (pain + KPS + weight): 23.8% vs 4.8% (*P* = .0022)



Burris HA, et al. J Clin Oncol. 1997;15:2403-2413

FOLFIRINOX Trial

Trial Schema

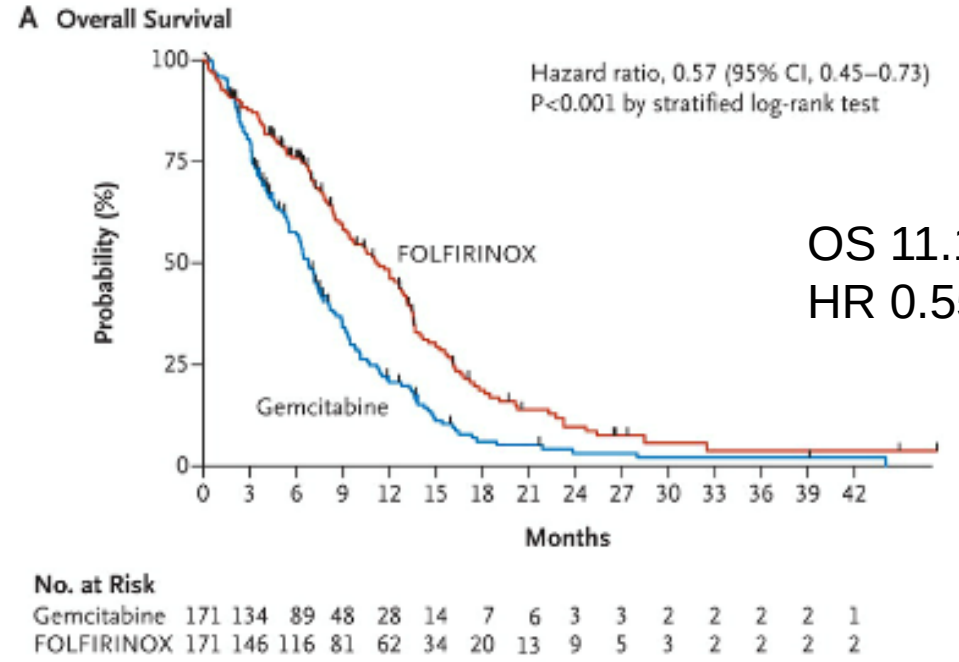


Patient Characteristics

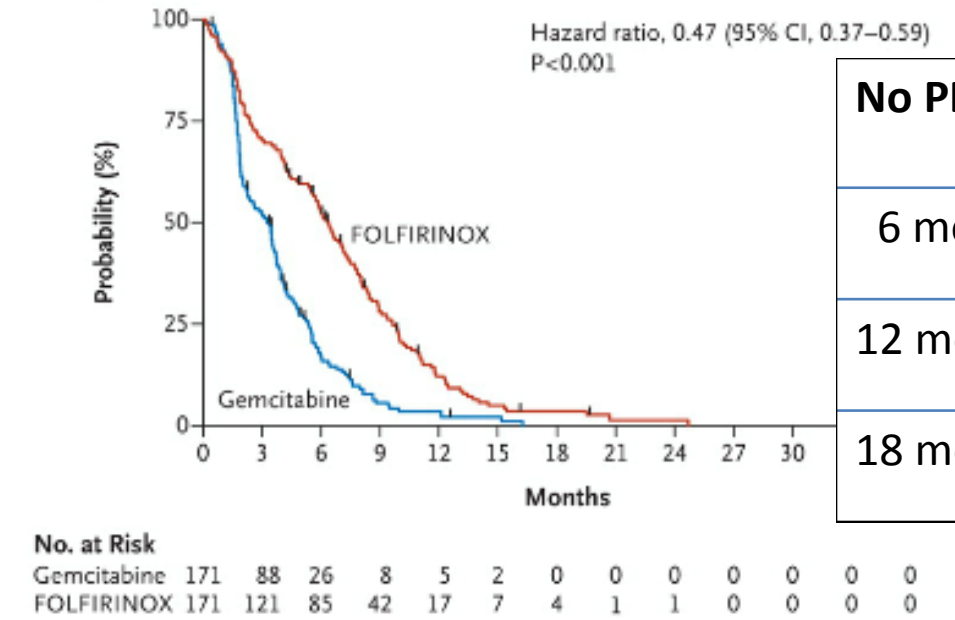
ECOG performance status score — no. (%)		
0	64 (37.4)	66 (38.6)
1	106 (61.9)	105 (61.4)
2	1 (0.6)	0
Pancreatic tumor location — no. (%)		
Head	67 (39.2)	63 (36.8)
Body	53 (31.0)	58 (33.9)
Tail	45 (26.3)	45 (26.3)
Multicentric	6 (3.5)	5 (2.9)
Biliary stent — no. (%)		
Yes	27 (15.8)	22 (12.9)
No	144 (84.2)	149 (87.1)
No. of metastatic sites involved		
Median	2	2
Range	1–6	1–6

FOLFIRINOX Trial - Toxicity

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	no. of patients/total no. (%)		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

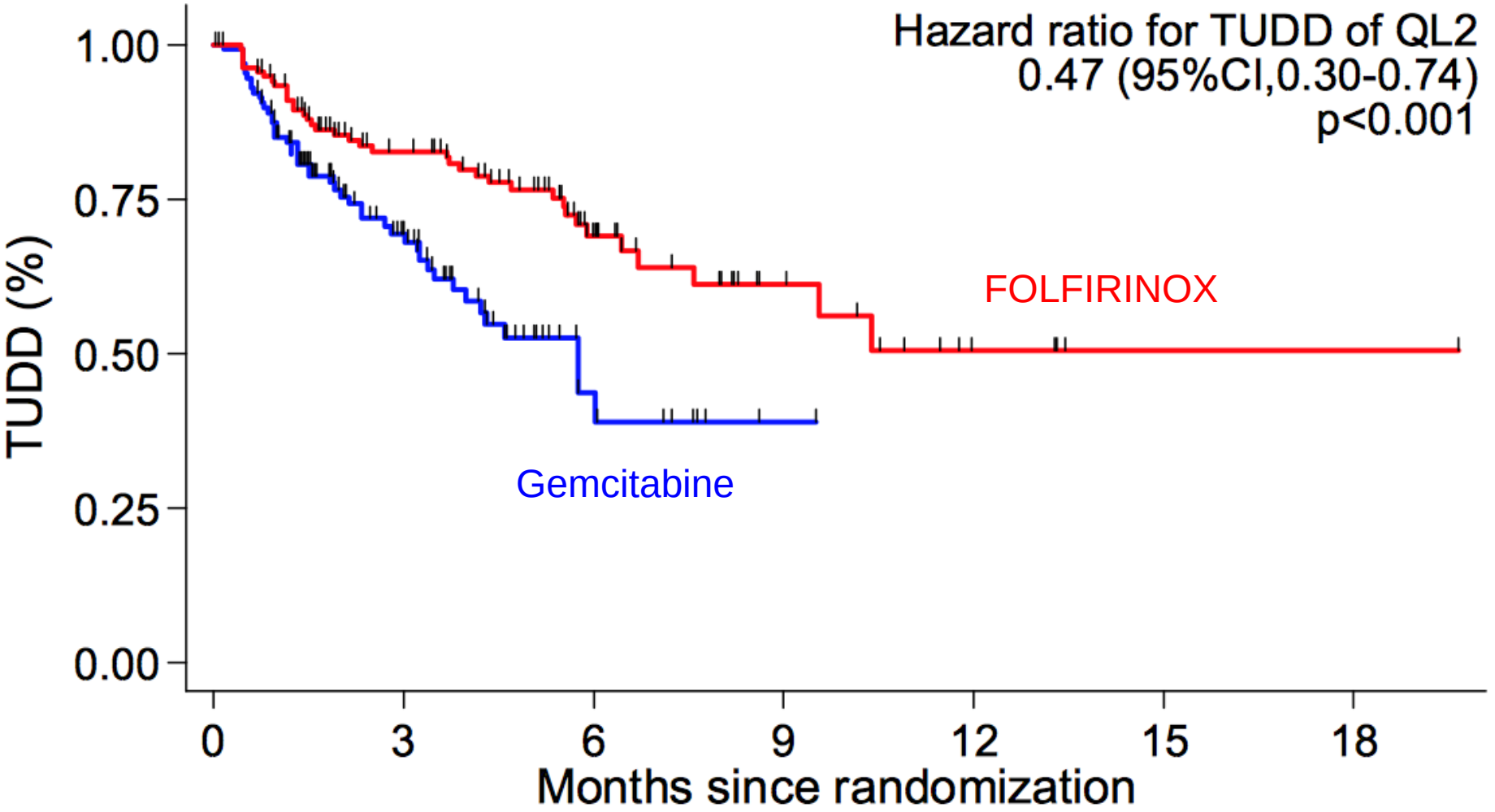


OS 11.1 vs. 6.8 months
HR 0.55, p< 0.001

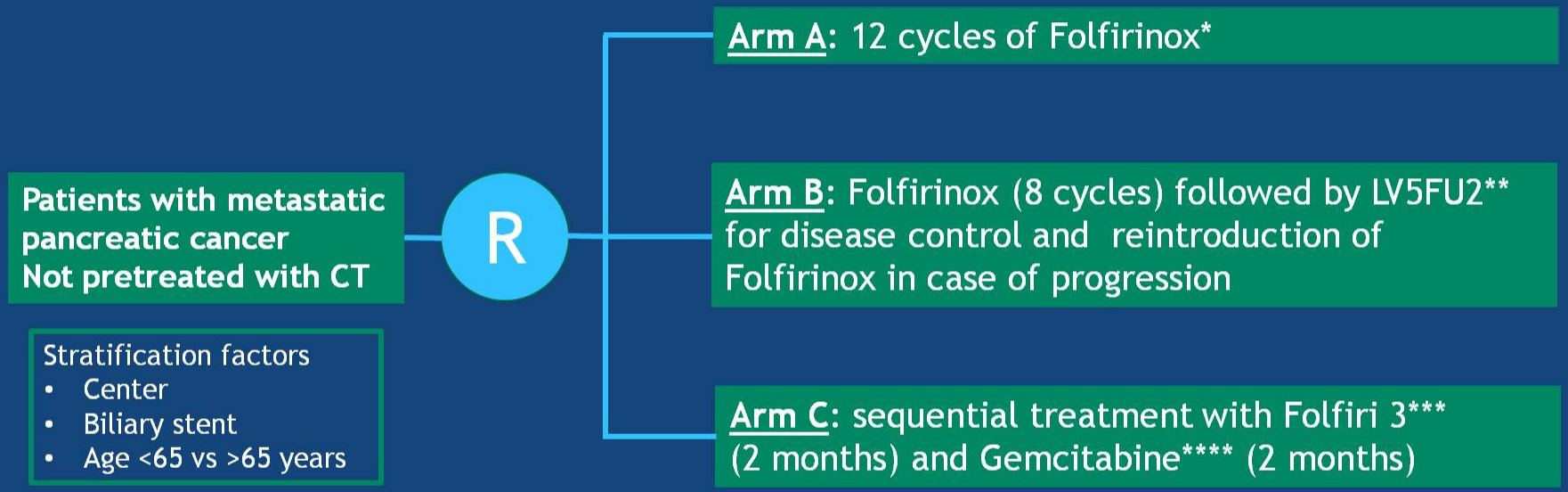


No PD at	FOLFIRINOX	Gem
6 months	52.8%	17.2%
12 months	12.1%	3.5%
18 months	3.3%	0 %

Time until definitive deterioration of QoL



Design of PRODIGE 35 PANOPTIMOX study



*Oxaliplatine 85 mg/m2, Irinotecan 180 mg/m2, Leucovorin 200 mg/m2, 5FU bolus 400 mg/m2, 5FU infusion 2400 mg/m2 46h; 14 days cycle

** Leucovorin 200 mg/m2, 5FU bolus 400 mg/m2, 5FU infusion 2400 mg/m2 46h; 14 days cycle

*** Irinotecan 90 mg/m2 D1, leucovorin 200 mg/m2, 5FU bolus 400 mg/m2, 5FU infusion 2400 mg/m2 46h, Irinotecan 90 mg/m2 D3; 14 days cycle

****Gemcitabine 1000 mg/m2 D1,D8,D15; 28 days cycle

Presented By Laetitia Dahan at 2018 ASCO Annual Meeting

PRIMARY ENDPOINT (mITT): 6 months Progression Free Survival rate

	Arm A (N = 87)	Arm B (N = 91)	Arm C (N = 88)
6 months PFS rate : N (%) [95% one-sided CI]	41 (47.1)	40 (44.0) [35.1 ; 53.1]	30 (34.1) [25.7 ; 43.3]

- Arm A results were consistent with PRODIGE 4 survival rate
- Firgem (arm C) was considered as ineffective
- **Folfirinox with maintenance by 5FU (arm B) was considered as effective**

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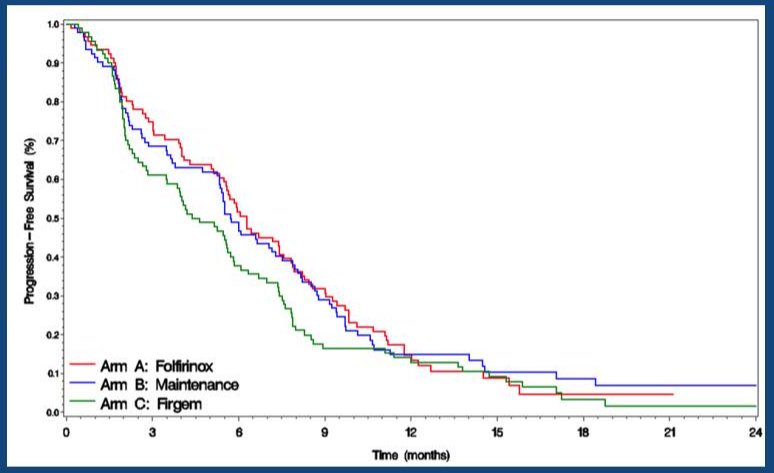
PROGRESSION FREE SURVIVAL (PFS)

ITT Set	Arm A (N = 91)	Arm B (N = 92)	Arm C (N = 90)
Overall PFS* (mo) - Median - 95%CI	 6.3 5.3-7.6	 5.7 5.3-7.5	 4.5 3.5-5.7
9 months PFS (%)	31.9	29.1	16.4
12 months PFS(%)	14.7	14.9	12.9

*PFS was defined by first progression as any chemotherapy received



In arm B (maintenance therapy):
- PFS2 (progression during Folfirinox regimen): 7.1 months [5.32-8.05]
- Reintroduction of Folfirinox 29.7% (27 patients among 52 disease control at 6 months)

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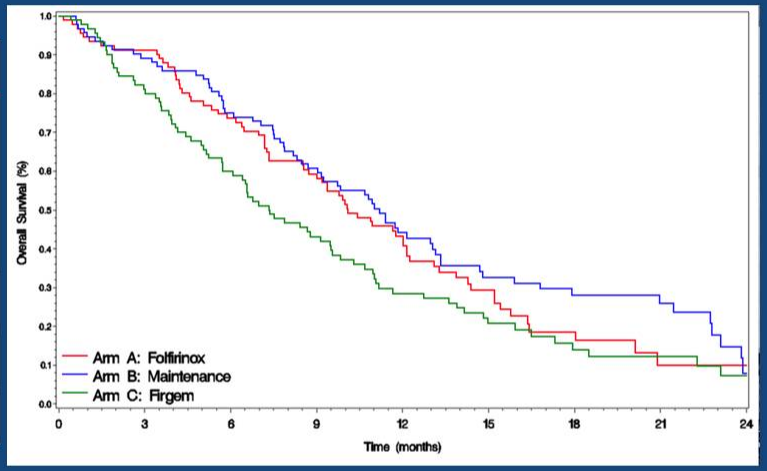
OVERALL SURVIVAL (OS)

ITT Set	Arm A (N = 91)	Arm B (N = 92)	Arm C (N = 90)
Overall survival (months) - Median - 95% CI	 10.1 8.5-12.2	 11.0 8.7-13.1	 7.3 5.7-9.5
6 months OS (%)	73.6	75.0	60.0
12 months OS (%)	43.3	44.1	28.5
18 months OS (%)	18.5	28*	13.9



*Exploratory analysis for overall survival: $p < 0.05$

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TOLERANCE:
Most common grade 3-4 adverse events

Two patients died from treatment-related cause: one from sepsis in the folfirinox arm, one from hypertonicity-induced coma in the firgem group

SP Set	Arm A (N = 88)	Arm B (N = 91)	Arm C (N = 87)
Hematologic	1 (1.1)	5 (5.5)	1 (1.1)
- Neutropenia	25 (28.4)	23 (25.3)	28 (32.2)
- Febrile neutropenia	1 (1.1)	5 (5.5)	-
- Thrombopenia	4 (4.5)	5 (5.5)	7 (8.0)
- Anemia	6 (6.8)	7 (7.7)	6 (6.9)
Non hematologic			
- Asthenia	22 (25.0)	28 (30.8)	28 (32.2)
- Vomiting	11 (12.5)	13 (14.3)	13 (14.9)
- Diarrhea	10 (11.4)	16 (17.6)	16 (18.4)
- **Sensory neuropathy**	9 (10.2)	17 (18.7)	0 (0)

TOLERANCE: Neurotoxicity grade 3-4

	Arm A (N = 88)	Arm B (N = 91)
Neurotoxicity Gr 3-4 (ITT)- N (%)	9 (10.2)	17 (18.7)
Neurotoxicity Gr 3-4 within First 6 months- N (%)	9 (10.2)	10 (11.0)
Max Grade neurotoxicity reached (whatever max grade is)		
- First 6 months N (%) - After 6 months N (%)	64 (94.1) 4 (5.9)	49 (70.0) 21 (30.0)
Median ratio of oxaliplatine (%)* [Range]	83 [46.9;102.5]	92 [92.1; 104.6]

*Ratio between received dose and targeted dose

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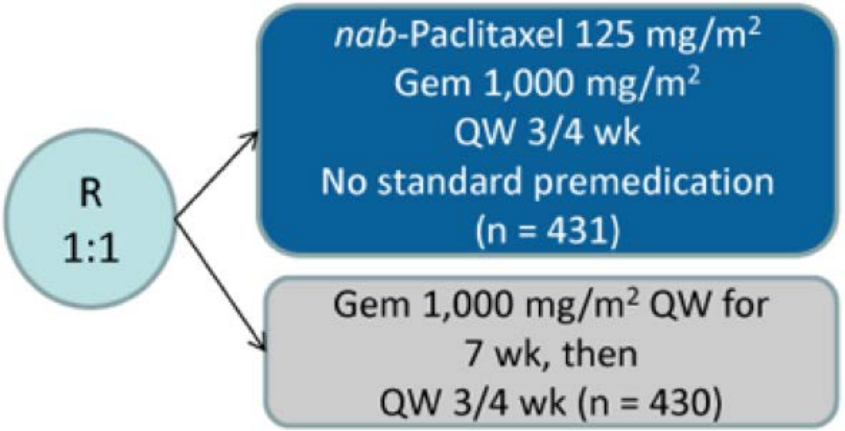
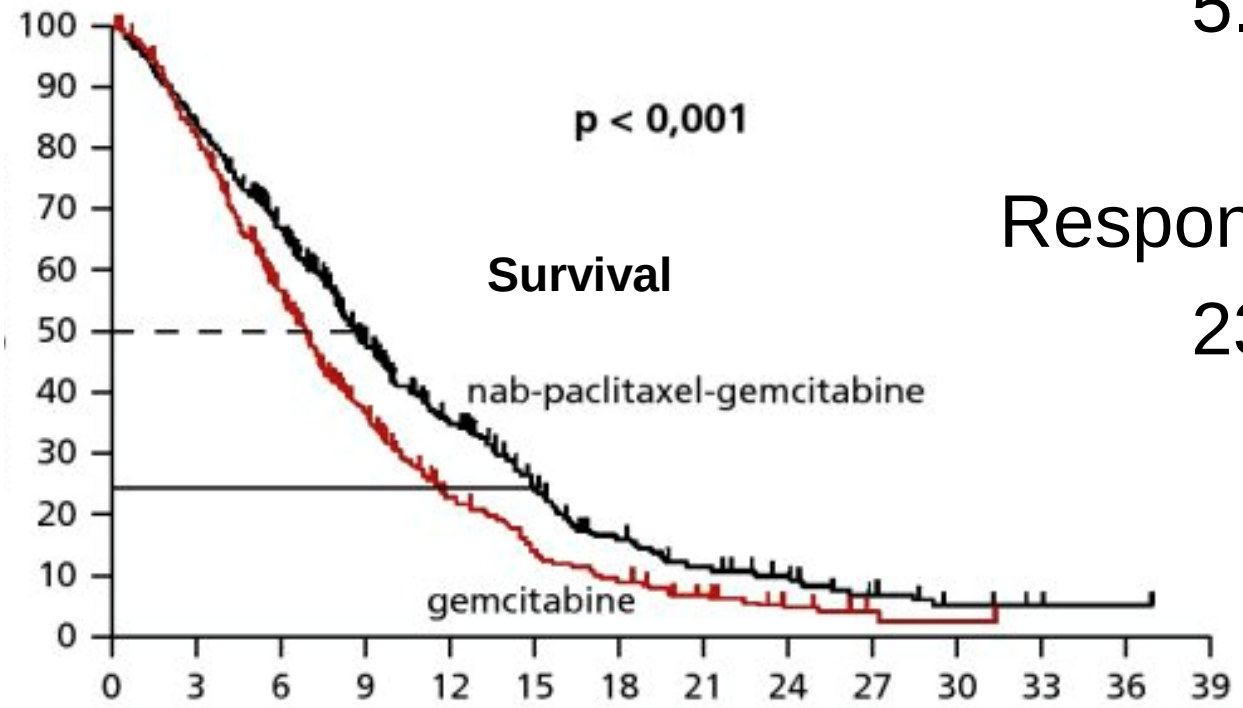
MPACT Trial





Median OS

8.5 vs. 6.7 months

Median PFS

5.5 vs. 3.7 months

Response Rate

23% vs. 7%

Sequential nab-pacli followed by gem 24 hours later might be superior

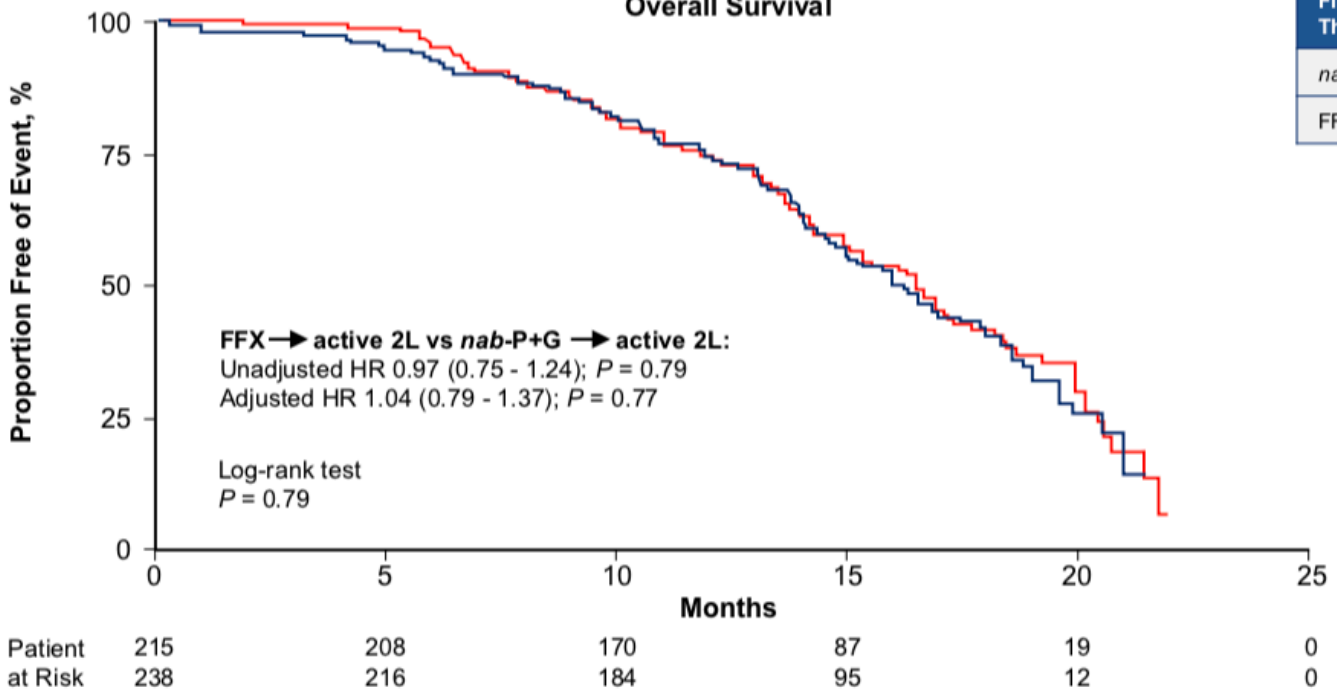
- PDAC mouse model suggested that *nab*P potentiates GEM activity by reducing cytidine deaminase levels and scheduling may be important
- 146 patients randomized to concurrent vs. sequential nabP and Gem

	Sequential	Concomitant	
6 m PFS	47%	33%	
Median PFS	5.8	4 months	HR 0.66, CI .46-.95
Median OS	10.1 months	7.9 months	HR .88, CI 0.61-1.29

- More side effects (hematological, fatigue, QoL deterioration) in SEQ group

Philippa Corrie, Abs 4100 ASCO 2017

Comparative Effectiveness of *nab*-Paclitaxel Plus Gemcitabine vs FOLFIRINOX in Metastatic Pancreatic Cancer: A Nationwide Chart Review in the United States

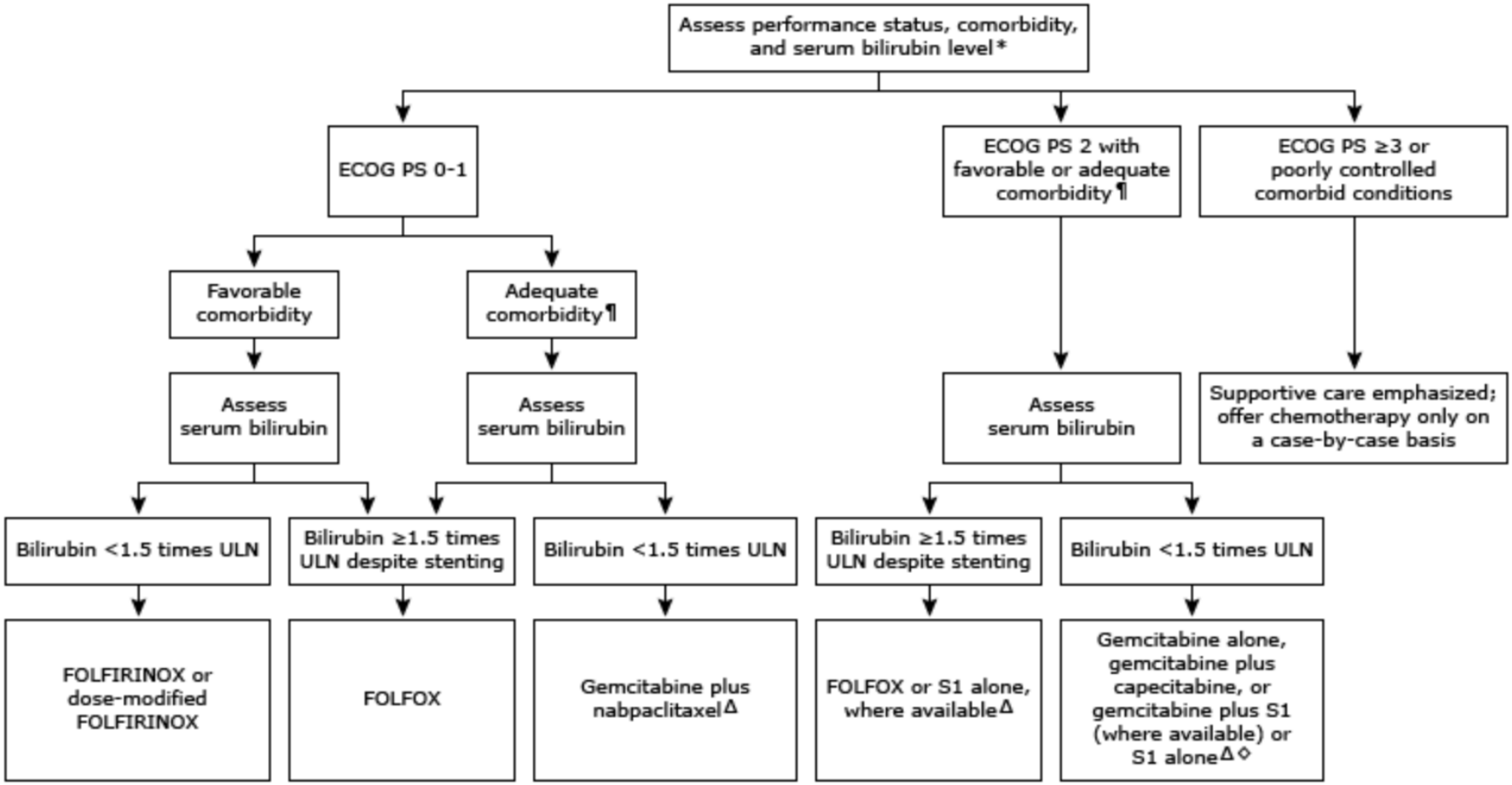


First-Line Therapy	Median Time to Event, months	95% CI
nab-P+G	16.07	14.98 - 18.10
FFX	16.56	15.11 - 18.30

Treatment Sequence (active 2L)
FFX → active 2L
nab-P+G → active 2L

Sunnie Kim et al, ASCO GI Cancers Symposium 2018

First-line systemic chemotherapy for metastatic pancreatic adenocarcinoma



UpToDate 2018

Second Line Therapy

Meta-analysis on 2nd line Therapy for PDAC

- 5 Studies with 895 patients receiving monofluoropyrimidine(FP) chemo or combinations of FP and Irinotecan or Oxaliplatin
- HR FP+Iri vs. FP 0.64 (0.47-0.87, p=0.005) for PFS and 0.7 (0.55-0.89, p=0.004) for OS
- HR FP+Ox modest improvement for PFS and none for OS

Sunbol et al, Cancer, 2017; 123: 4680-4686

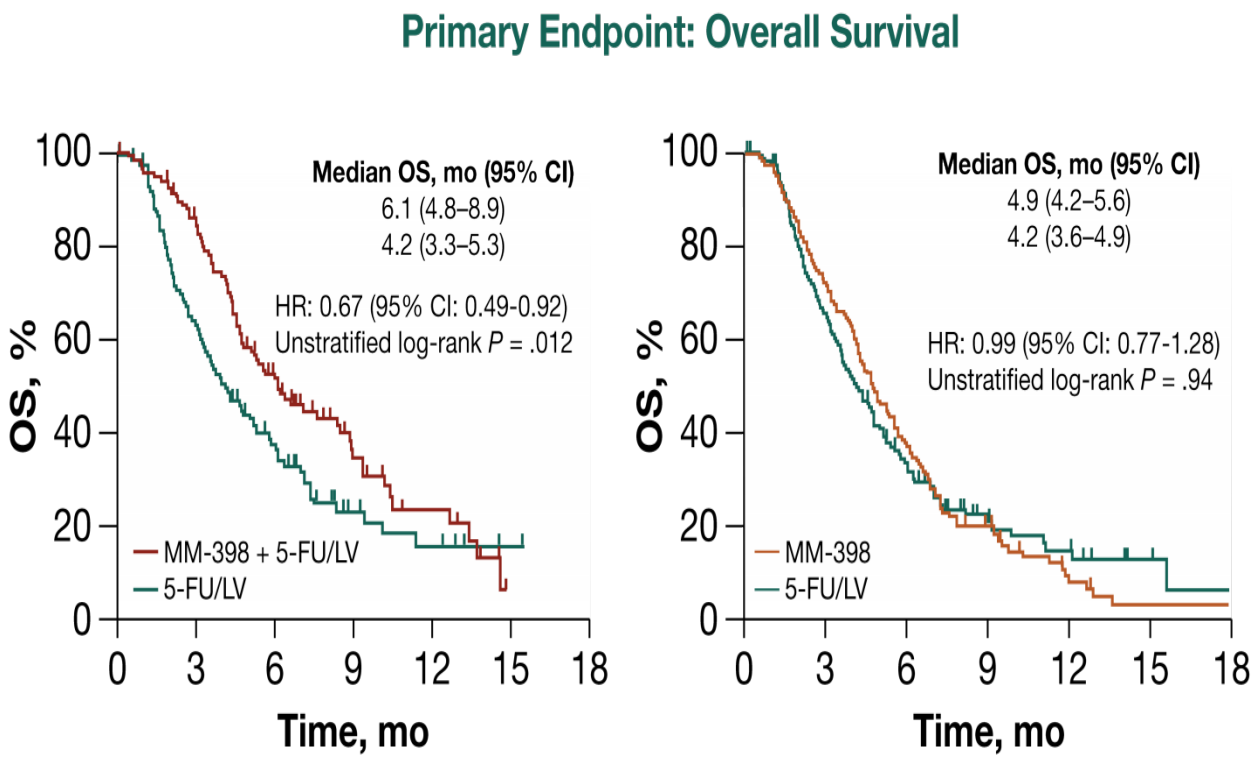
NAPOLI-1: Nanoliposomal Irinotecan With 5-FU/LV After Previous Gemcitabine-Based Treatment

Study design:
- Phase 3, open-label RCT;
- mPDAC
- progress on Gem-based treatment

Randomization:
- nal-IRI (MM-398) (n = 151)
- 5-FU + LV (n = 119)
- or nal-IRI + 5-FU + LV (n = 117)

- **Primary endpoint:** OS
- **Secondary endpoints**: PFS, TTF, ORR, and safety

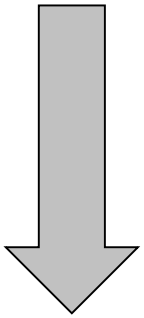
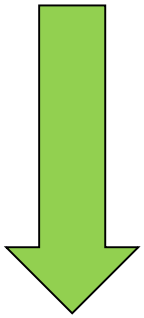
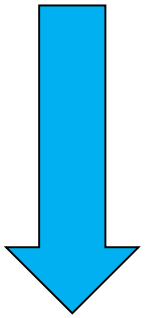
As yet unpublished data suggest QoL maintained under Nanoliposomal Iri + 5FU/LV



Nanoliposomal irinotecan: Enhanced tumor penetration and retention - EPR

. Wang-Gillam A et al;. *Lancet.* 2016;387:545–557.

Optimal therapeutic sequence ?

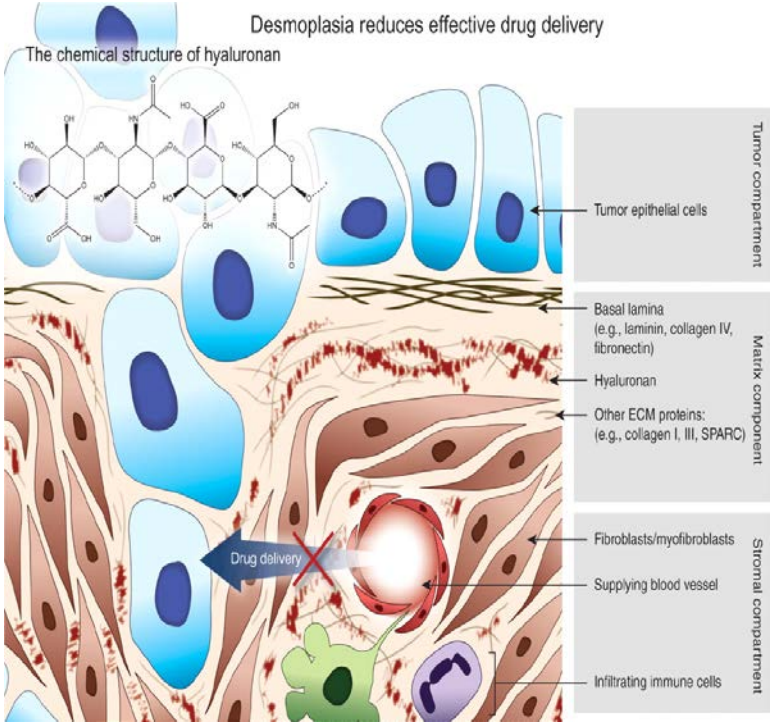
First-line	**FOLFIRINOX**	**Gem**	**Gem + *Nab*-P**
			
Second-line	**Gemcitabine** **Gem + *Nab*-P?**	**Nal-IRI + 5-FU** **FOLFIRI** **Ox + FP?** **FOLFIRINOX?**	**Nal-IRI + 5-FU?** **FOLFIRI?** **Ox + FP?** **FOLFIRINOX?**

Quality of life is paramount in this setting – we need data!

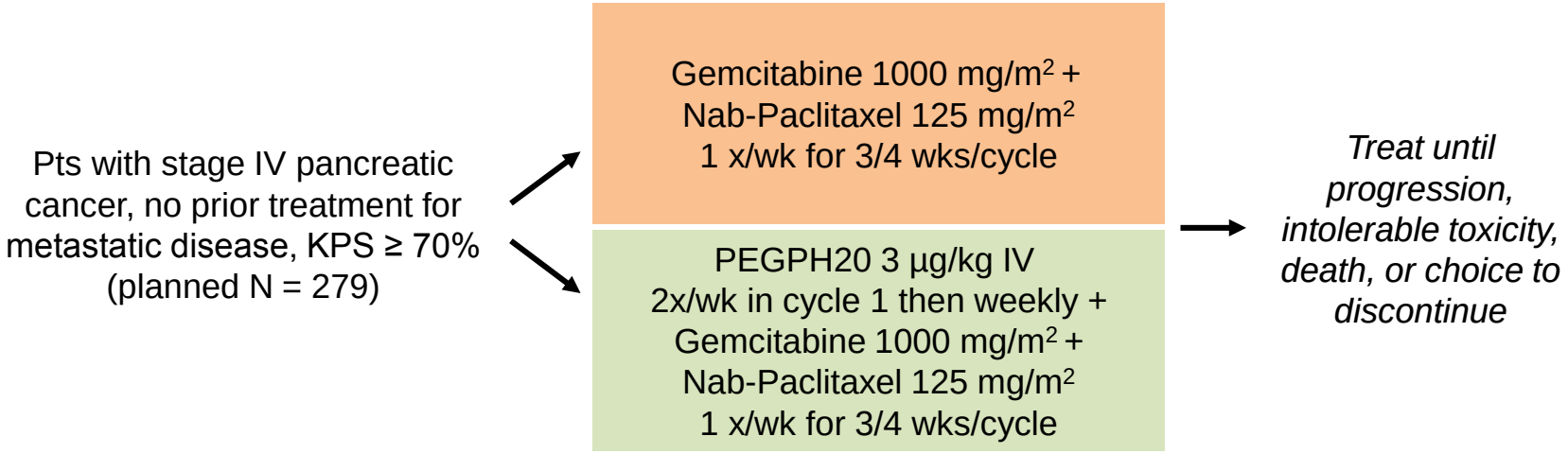
Novel Approaches to PDAC Systemic Treatment

Hyaluronan: Major Component of the Extracellular Matrix

- PEGPH20: recombinant human hyaluronidase
- Hyaluronan degradation can
  - Normalize tumor interstitial pressure
  - Improve drug delivery



Phase II HALO-109-202: Addition of PEGPH20 to Gem/Nab-Pac in Metastatic Pancreatic Cancer



- Primary endpoint: PFS
- Secondary endpoints: ORR, OS, safety, PK

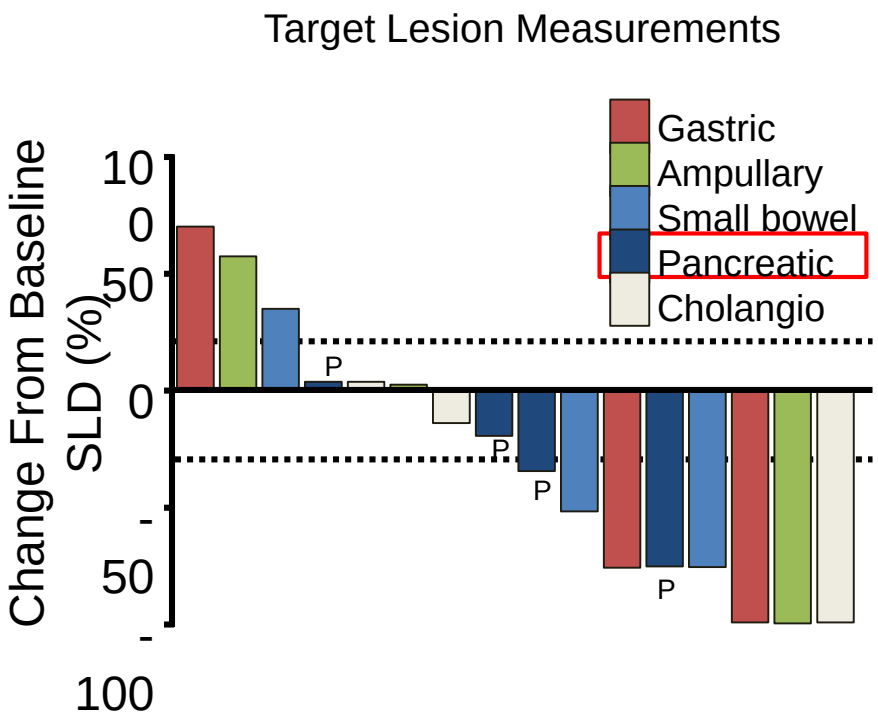
Phase II HALO-109-202: Preliminary Results

Outcome by Population	Gem + Nab-P + PEGPH20	Gem + Nab-P	*P* Value	HR
Total				
▪ Median PFS, mos	5.7	5.2	.11	0.69
▪ ORR, % (n/N)	41 (30/74)	34 (21/61)	.48	
HA-high				
▪ **Median PFS, mos**	**9.2**	**4.3**	**.05**	**0.39**
▪ **ORR, % (n/N)**	**52 (12/23)**	**24 (5/21)**	**.04**	
HA-low				
▪ Median PFS, mos	5.3	5.6	.74	0.89
▪ ORR, % (n/N)	37 (14/38)	38 (9/24)	.96	

- Higher rate of thromboembolic events on PEGPH20-containing arm during first stage of enrollment (42% vs 25%); mitigated during second stage with addition of prophylactic enoxaparin[1]
- Phase III HALO-109-301 study of gem/nab-P ± PEGPH20 limited to HA-high pts currently enrolling[2]

Immune Checkpoint Inhibitors in PDAC

- Minimal to no activity in advanced PDAC
- 1% of pancreatic cancers associated with defective mismatch repair (dMMR/MSI-high) I
  - 2 of 4 dMMR/MSI-high pts on pembrolizumab had objective responses



BRCA- or PALB2-mutation carriers

- Objective responses in early trials:
  - Rucaparib: 3/19 (16%)
  - Olaparib: 5/23 pts (22%)
  - Veliparib: 0/16 pts

Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update

Sohal, et al.

Non-metastatic Pancreatic Cancer

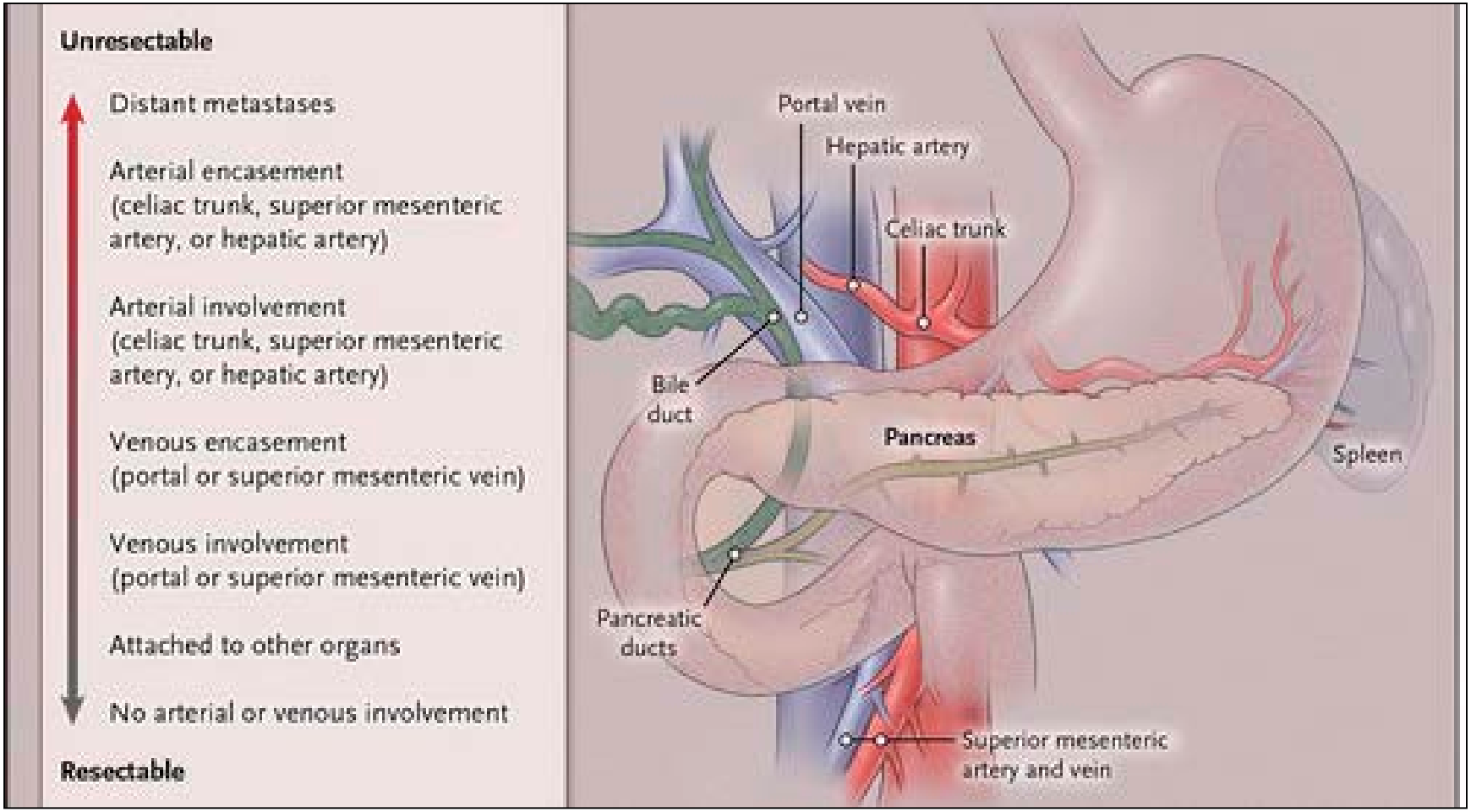
Pancreatic Cancer Resection Categories

- Resectable
- Borderline resectable
  - A distinct category
  - Neoadjuvant therapy increases likelihood of R0 resection
- Unresectable (eg, locally advanced or metastatic)

Ryan, David et al, New England Journal of Medicine. 371(11):1039-1049, 2014

Cancer of the pancreas: ESMO Clinical Practice Guidelines, Ducreux M et al, 2015
https://doi.org/10.1093/annonc/mdv295

Resectability in Pancreatic Adenocarcinoma

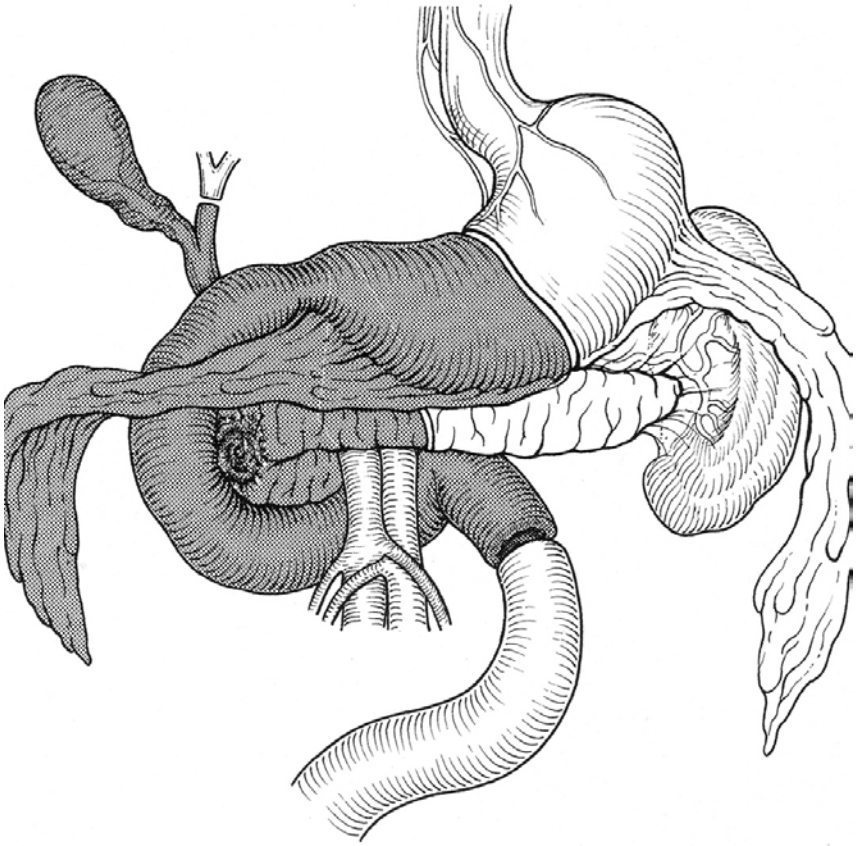


Pancreatic Adenocarcinoma.
Ryan, David; Hong, Theodore; Bardeesy, Nabeel
New England Journal of Medicine. 371(11):1039-1049, 2014.
DOI: 10.1056/NEJMra1404198

Whipple Procedure (Pancreatoduodenectomy)

en bloc removal of:

- Distal stomach
- Duodenum
- Head of pancreas
- Distal bile duct
- Gallbladder
- Proximal jejunum



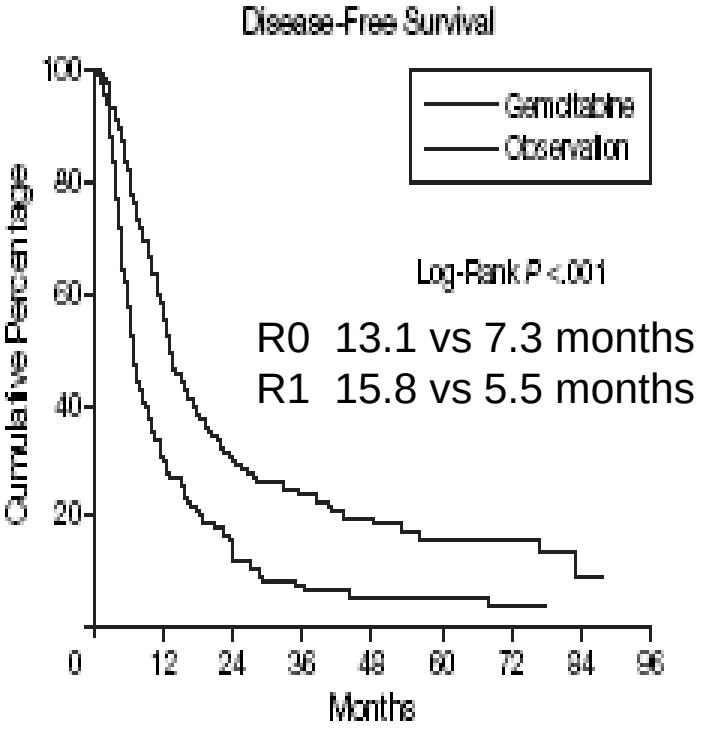
53 resectable PDAC trials on clinicaltrials.gov

Showing: 1-25 of **53** studies 25 studies per page

Show/Hide Columns

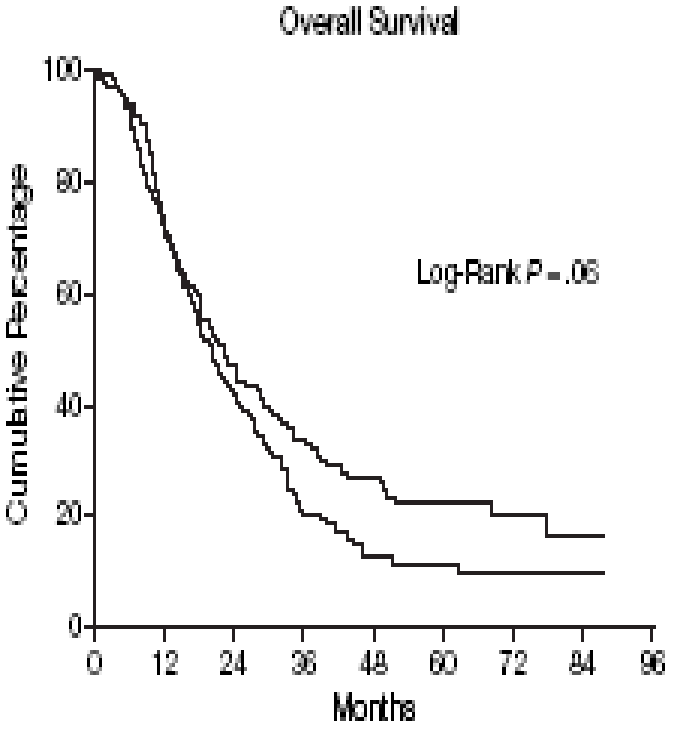
Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Pre-Operative Trial (PGHA vs. PGH) for **Resectable Pancreatic Cancer**	• **Pancreatic Cancer Resectable**	• Drug: Gemcitabine, Nab-Paclitaxel, hydroxychloroquine and Avelumab • Drug: Gemcitabine, Nab-Paclitaxel, and hydroxychloroquine	• UPMC Hillman Cancer Center Pittsburgh, Pennsylvania, United States
2	☐	Recruiting	Evaluation of Survival Prognostic Factors for Patients With Exocrine **Pancreatic Cancer Resectable** or Potentially **Resectable**	• **Pancreatic Cancer**	• Other: Additional biological samples	• Centre Hospitalier Régional Universitaire de Besançon Besançon, France • Centre Georges François Leclerc Dijon, France • Centre Hospitalier Universitaire de Dijon Dijon, France • (and 5 more...)
3	☐	Recruiting	Phase II Study of Chemo-Radiotherapy in Patients With **Resectable** and Borderline **Resectable Pancreatic Cancer**	• **Pancreas Neoplasm Malignant Resectable**	• Drug: Folfox6 • Drug: Gemcitabine • Radiation: Radiation Therapy • Procedure: Pancreaticoduodenectomy with retroperitoneal lymphadenectomy	• Henry Ford Health System Detroit, Michigan, United States
4	☐	Recruiting	Gemcitabine/Nab-Paclitaxel With HIGRT in **Resectable Pancreatic Cancer**	• **Resectable Pancreatic Cancers**	• Drug: Gemcitabine/nab-Paclitaxel • Radiation: Radiation therapy • Other: Sugical resection • Drug: Adjuvant chemotheapy	• Duke Cancer Center Durham, North Carolina, United States
5	☐	Recruiting	Efficacy of Doxycycline on Metakaryote Cell Death in Patients With **Resectable Pancreatic Cancer**	• **Resectable Pancreatic Cancer**	• Drug: Doxycycline	• Medical College of Wisconsin Milwaukee, Wisconsin, United States
6	☐	Recruiting	A Phase I Dual Dose Escalation Study of Radiation and Nab-Paclitaxel in Patients With Unresectable and Borderline **Resectable Pancreatic Cancer**	• Locally Advanced Unresectable **Pancreatic Cancer** Treated With Chemoradiotherapy • Borderline **Resectable Pancreatic Cancer** Treated With Chemoradiotherapy	• Radiation: Radiotherapy • Drug: Gemcitabine 1000 mg • Drug: nab-paclitaxel 125 mg	• Abramson Cancer Center of the University of Pennsylvania Philadelphia, Pennsylvania, United States
7	☐	Recruiting	Low Dose Radiation to Improve T-Cell Infiltration in **Pancreatic Cancer**	• Primarily **Resectable Pancreatic Cancer**	• Radiation: neoadjuvant photon radiation	• Clinic for General, Visceral and Transplantation Surgery Heidelberg, Germany • German Cancer Research Center Heidelberg, Germany
8	☐	Recruiting	Neoadjuvant Plus Adjuvant or Only Adjuvant Nab- Paclitaxel Plus Gemcitabine for **Resectable Pancreatic Cancer**	• **Resectable Pancreatic Cancer** • Ductal Adenocarcinoma of the **Pancreas**	• Drug: perioperative nab-paclitaxel/gemcitabine • Drug: adjuvant nab-paclitaxel/gemcitabine	• University of Ulm, Dept. of Internal Medicine I Ulm, Germany
9	☐	Recruiting	Preoperative Chemoradiotherapy With Gemcitabine for **Resectable Pancreatic Carcinoma**	• **Resectable Pancreatic Carcinoma**	• Radiation: chemoradiotherapy with Gemcitabine • Radiation: Radiation: chemoradiotherapy with Gemcitabine	• National Cancer Center, Korea Goyang-si, Gyeonggi-do, Korea, Republic of
10	☐	Recruiting	Borderline **Pancreas** Study: FOLFIRINOX +SBRT	• **Resectable Pancreatic Cancer**	• Other: Chemotherapy(FOLFIRINOX) + SBRT prior to surgery if applicable • Drug: -Oxaliplatin 85 mg/m2 IV on Day 1 • Drug: -Irinotecan 180 mg/m2 IV on Day 1 • Drug: -5-FU (Fluorouracil) 2,400 mg/m2 IV over 46-48 hours	• University of Maryland Medical Center Baltimore, Maryland, United States
11	☐	Recruiting	Intraoperative Radiation Therapy for **Resectable Pancreatic Cancer**	• **Resectable Pancreatic** Adenocarcinoma	• Radiation: Intraoperative radiation therapy (IORT)	• Gangnam Severance Hospital Seoul, Korea, Republic of
12	☐	Recruiting	Safety and Immunological Effect of Pembrolizumab in **Resectable** or Borderline **Resectable Pancreatic Cancer**	• **Pancreatic Cancer**	• Drug: Pembrolizumab • Radiation: Neoadjuvant Chemoradiation	• University of Miami Miami, Florida, United States • Dana-Farber Cancer Institute Boston, Massachusetts, United States • MD Anderson

CONKO-001
Gemcitabine vs. No Chemotherapy



No. at Risk

Gemcitabine	179	96	43	25	17	11	8	1
Observation	175	52	24	10	6	6	2	0

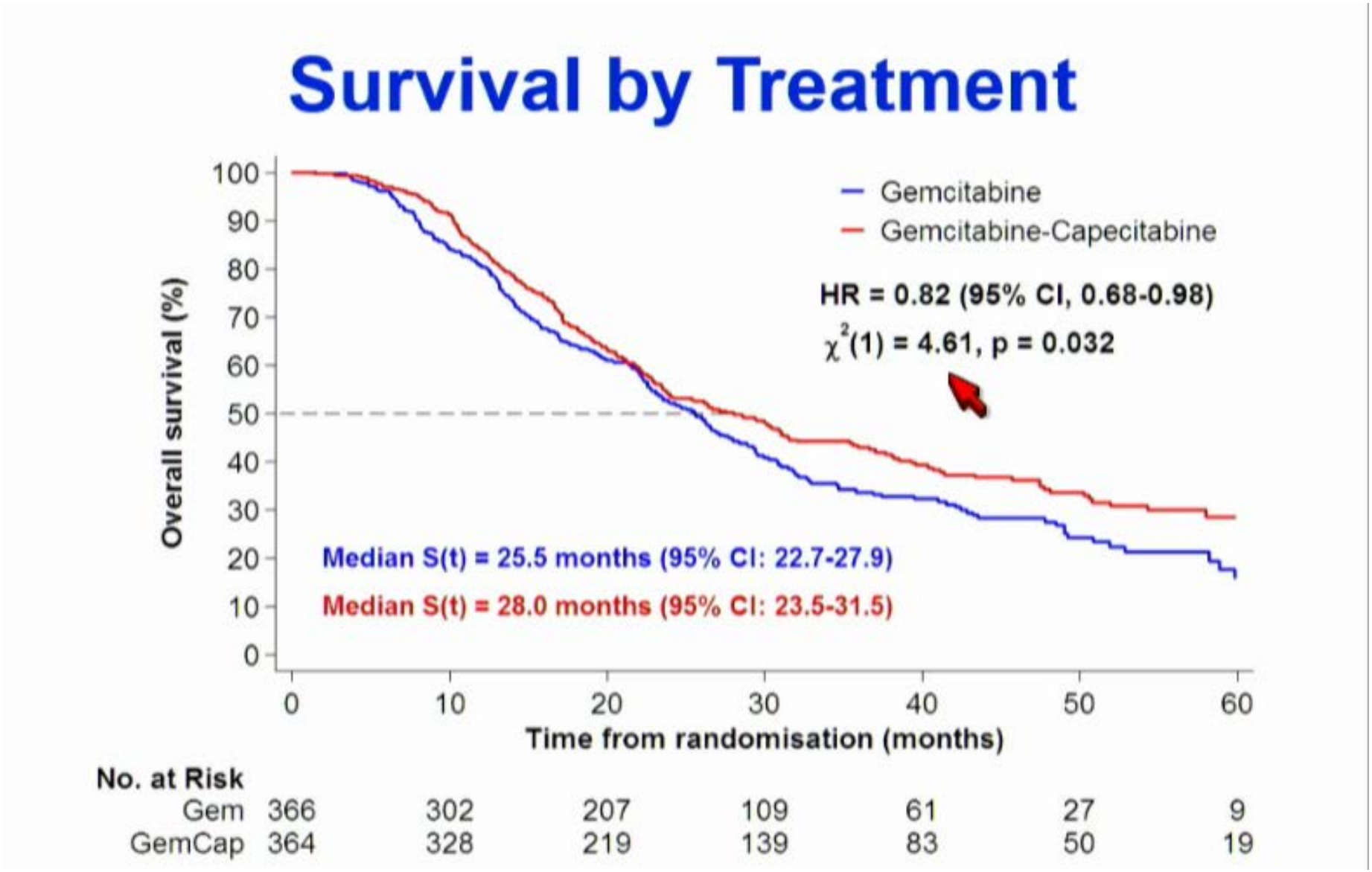


No. at Risk

Gemcitabine	179	128	73	36	23	14	9	2
Observation	175	126	64	25	12	8	4	1

JAMA. 2007;297: 267-277

ESPAC – 4 Data



ASCO 2016

PRODIGE
PARTENARIAT DE RECHERCHE EN ONCOLOGIE DIGESTIVE

Canadian Cancer Trials Group

Groupe canadien des essais sur le cancer

unicancer

LA LIGUE CONTRE LE CANCER

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

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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

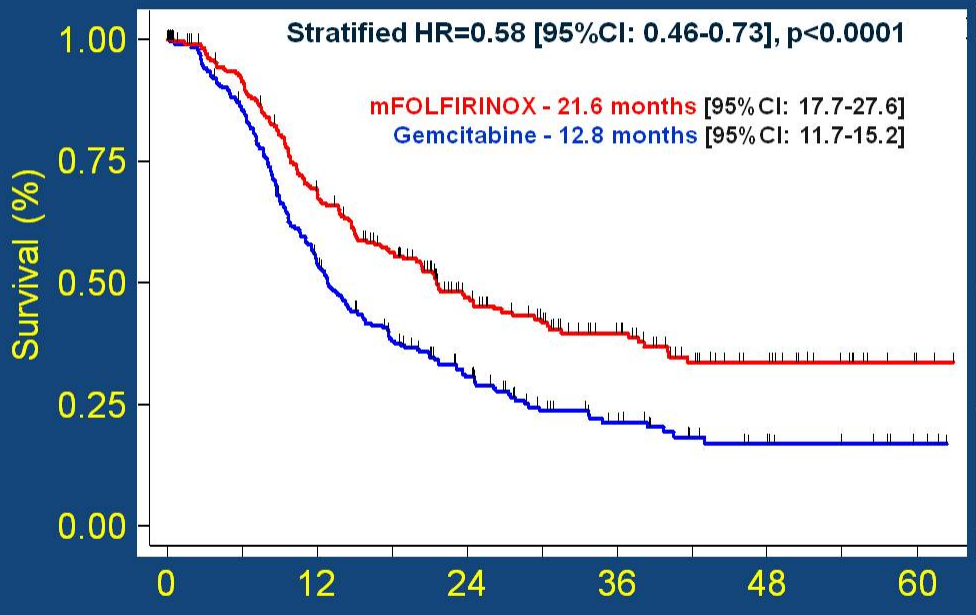
for both arms:
- 6 months of chemotherapy
- CT scans: every 3 months

Six-month treatment completion

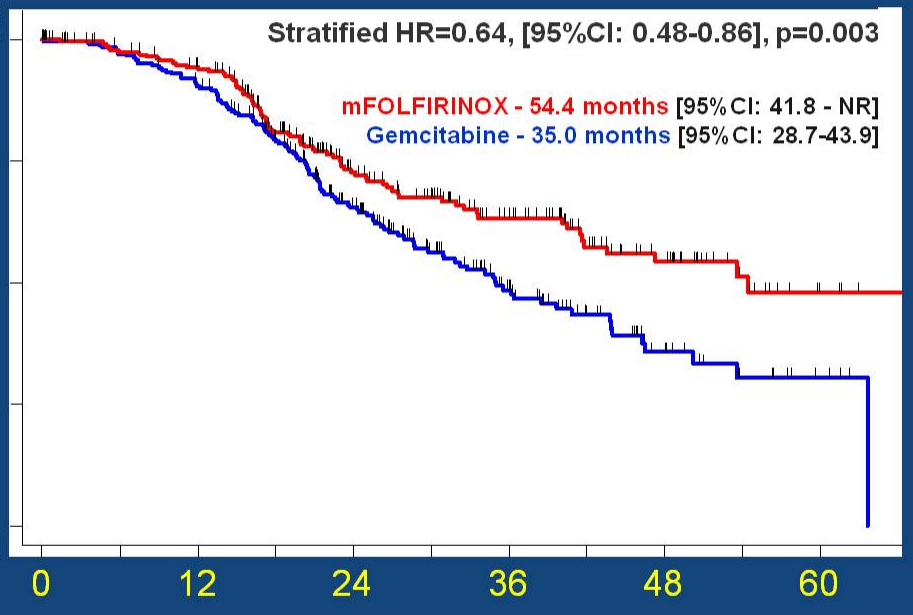
	mFolfirinox No = 238	Gemcitabine No = 243	P
All cycles of chemotherapy	66.4%	79.0%	0.002
Planned administrations Median No. administrations	12 12 [1-12]	18 18 [1-18]	—
No. administrations delayed	14.4%	3.9%	< 0.001
Relative dose-intensity > 0.70	48.7%	91.4%	< 0.001
Early stop due to : - relapse - toxicity - Principal Investigator's decision - patient decision	80 (33.6%) 15 (6.3%) 21 (8.8%) 7 (2.9%) 13 (5.4%)	51 (21.0%) 26 (10.7%) 11 (4.5%) 2 (0.8%) 2 (0.8%)	0.002

PRODIGE 24/CCTG PA.6

Disease-Free Survival



Overall Survival



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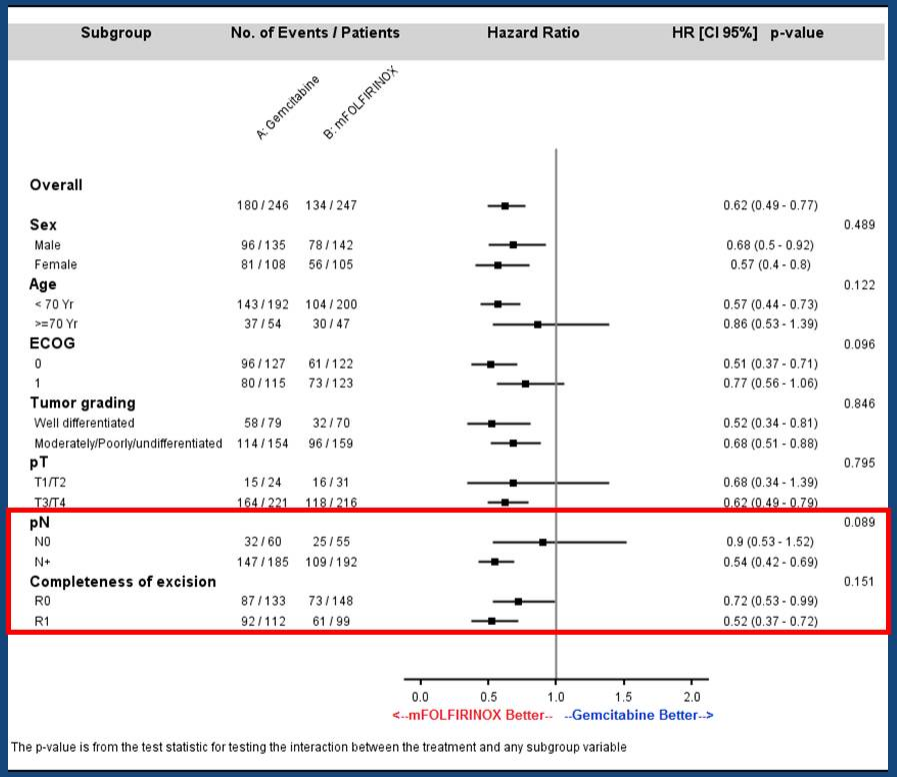
PRODIGE 24/CCTG PA.6

Does FOLFIRINOX Overcome Negative Predictive Value Of:

>> R1 Resection

>> Node Positive Disease



The p-value is from the test statistic for testing the interaction between the treatment and any subgroup variable

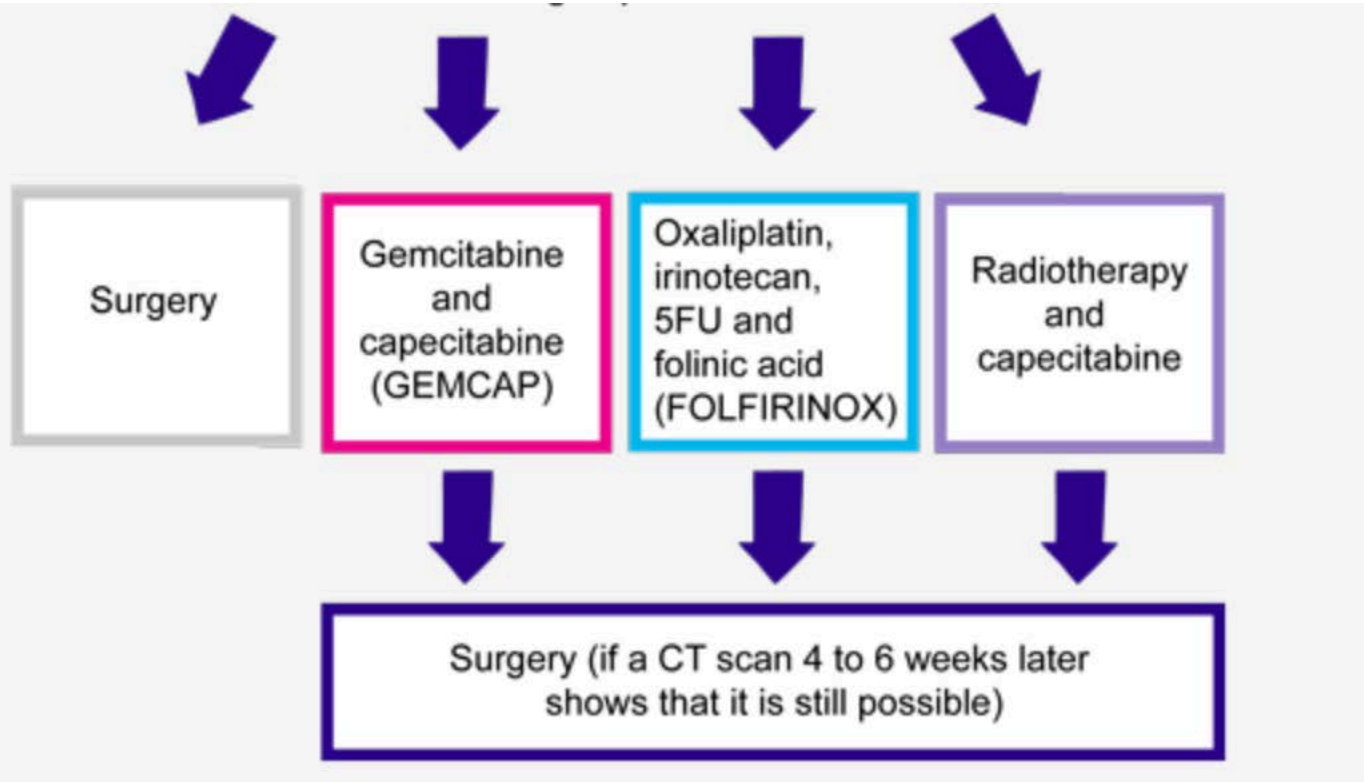
Upfront Resectable Pancreatic Cancer Primary Surgery versus Neoadjuvant Chemo

- Database of 15,237 patients, stage I or II resected pancreatic head Adenocarcinoma
- 2,005 patients receiving Neoadjuvant Chemo matched with 6,015 patients with primary surgery
- Chemo first group had improved survival compared with Surgery first group:
  - median survival: 26 months versus 21 month, P < 0.01; HR 0.72
- Surgery first patients vs. Chemo first patients:
  - higher pathologic T stage (pT3 and T4: 86% v 73%; P < .01)
  - higher positive lymph nodes (73% v 48%; P < .01)
  - higher positive resection margin (24% v 17%; P < .01)

Mokdad AA et al. J Clin Oncol 2016, Sept

Many ongoing trials looking at best strategy

ESPAC-5F: randomised patients to 4 approaches



Preoperative radiochemotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC) :
A randomized, controlled, multicenter phase III trial of the Dutch Pancreatic Cancer Group

Geertjan van Tienhoven, radiation oncologist, AMC, Amsterdam

Eva Versteijne [1)], Mustafa Suker [2)], Karin B Groothuis [3)], Olivier R Busch [4)], Bert A Bonsing [5)], Ignace H de Hingh [6)], Sebastiaan Festen [7)], Gijs A Patijn [8)], Judith de Vos -Geelen [9)], Aeilko H Zwinderman [10)], Cornelis J Punt [11)], Casper H van Eijck [2)]

1) *Radiation Oncology, Academic Medical Center, Postbus 22660, 1105 AZ, Amsterdam, the Netherlands.*
2) *Surgery, Erasmus MC, Postbus 2040, 3000 CA, Rotterdam, The Netherlands.*
3) *Clinical Research Department, Netherlands Comprehensive Cancer Organisation (IKNL), Postbus 1281, 6501 BG, Nijmegen, The Netherlands.*
4) *Surgery, Academic Medical Center, Postbus 22660, 1105 AZ, Amsterdam, the Netherlands.*
5) *Surgery, Leiden University Medical Center, Postbus 9600, 2300 RC, Leiden, The Netherlands.*
6) *Surgery, Catharina Hospital, Postbus 1350, 5602 ZA, Eindhoven, The Netherlands.*
7) *Surgery, OLVG, Postbus 95500, 1090 HM, Amsterdam, The Netherlands.*
8) *Surgery, Isala Clinics, Postbus 10400, 8000 GK, Zwolle, The Netherlands.*
9) *Internal Medicine, Division of Medical Oncology, GROW - School for Oncology and Developmental Biology, Maastricht UMC+, The Netherlands.*
10) *Clinical Epidemiologic Biostatics, Academic Medical Center, Postbus 22660, 1105 AZ, Amsterdam, The Netherlands.*
11) *Medical Oncology, Academic Medical Center, Postbus 22660 1105 AZ, Amsterdam, The Netherlands.*

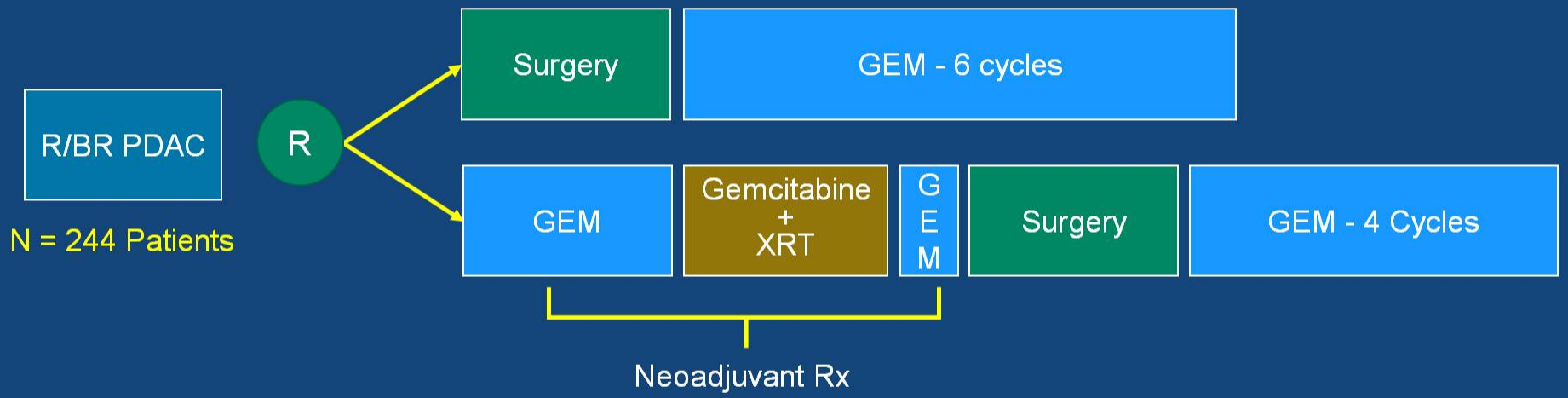
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Geertjan van Tienhoven, AMC

DPCG Dutch Pancreatic Cancer Group

Presented By Geertjan Van Tienhoven at 2018 ASCO Annual Meeting

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



N = 244 Patients

Primary Endpoint: ITT Overall Survival

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Resection Rate

	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

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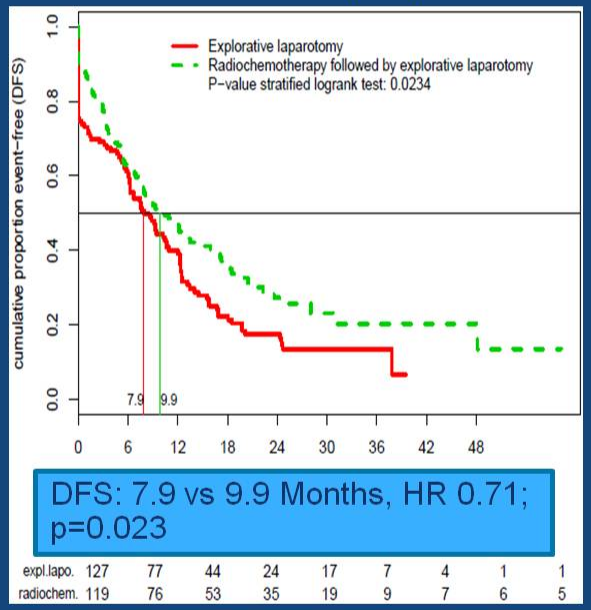
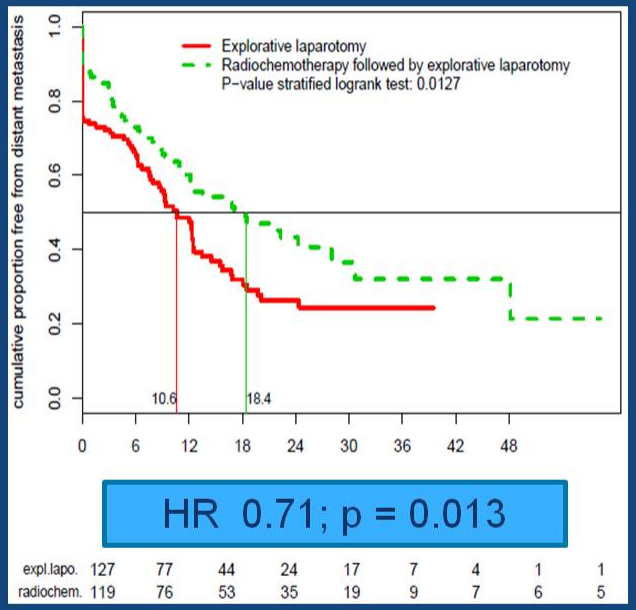
Disease-Free Survival

Overall DFS (ITT)



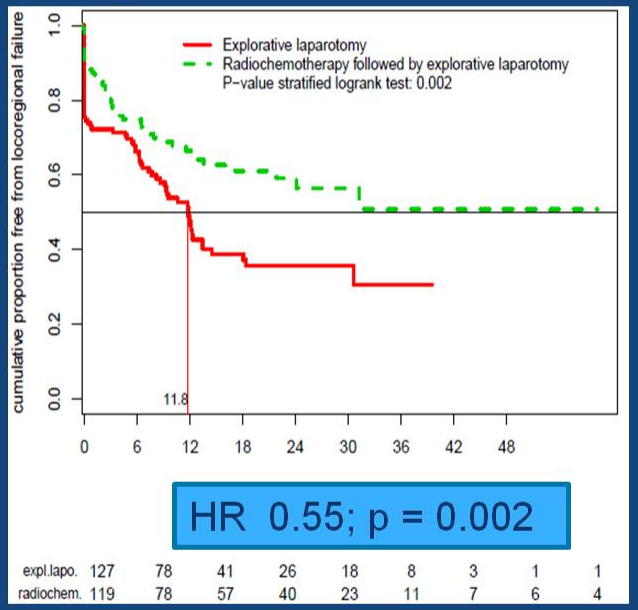
DFS: 7.9 vs 9.9 Months, HR 0.71; p=0.023

Distant Metastasis Free Interval



HR 0.71; p = 0.013

Locoregional Recurrence Free Interval



HR 0.55; p = 0.002

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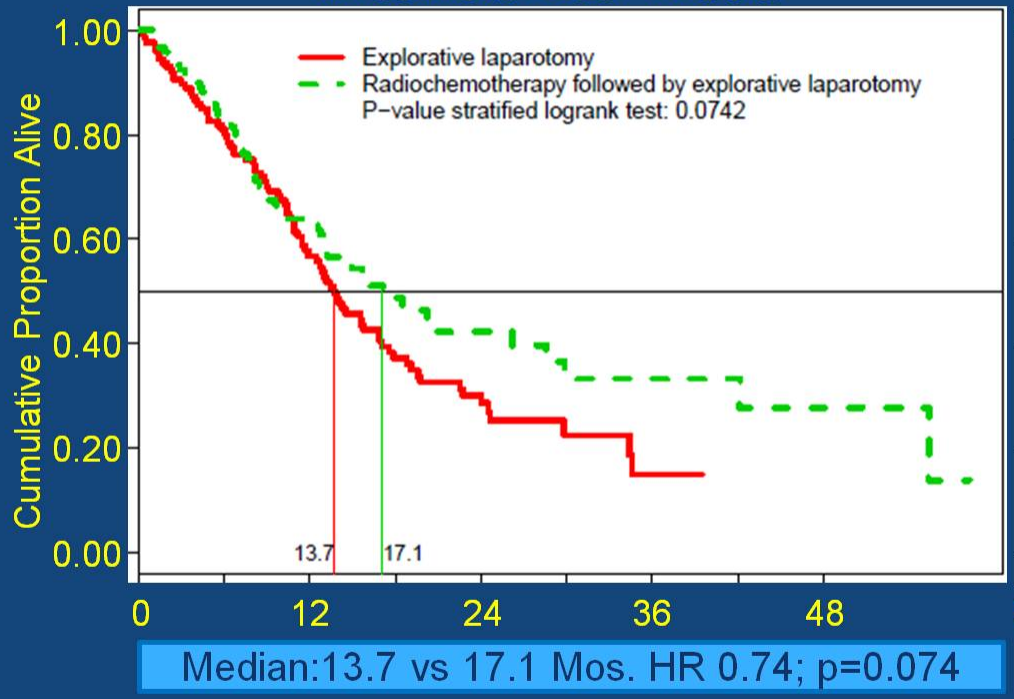
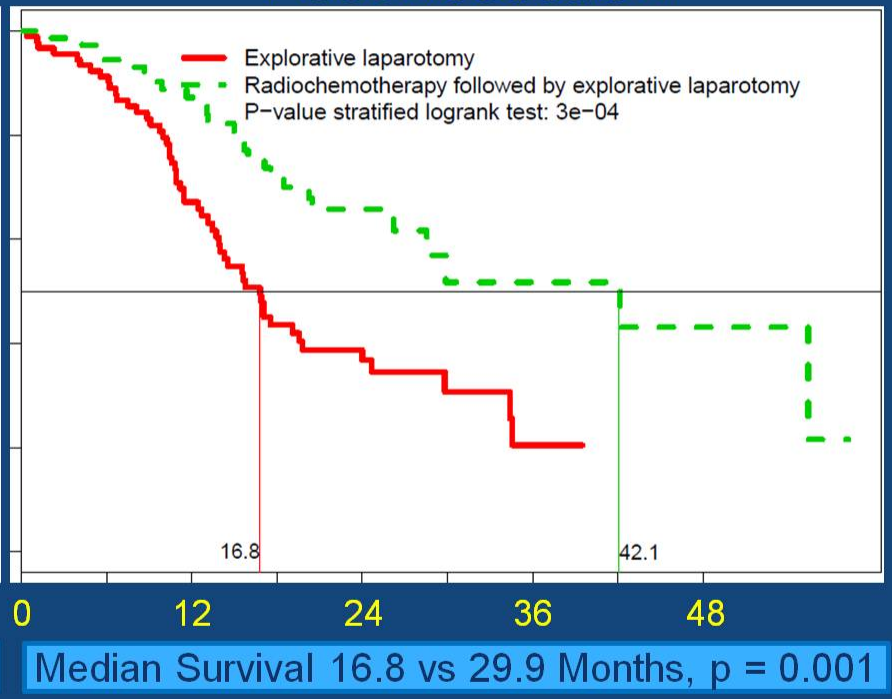
Overall Survival Analyses

Intention to Treat



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

Post Resection



Median Survival 16.8 vs 29.9 Months, p = 0.001

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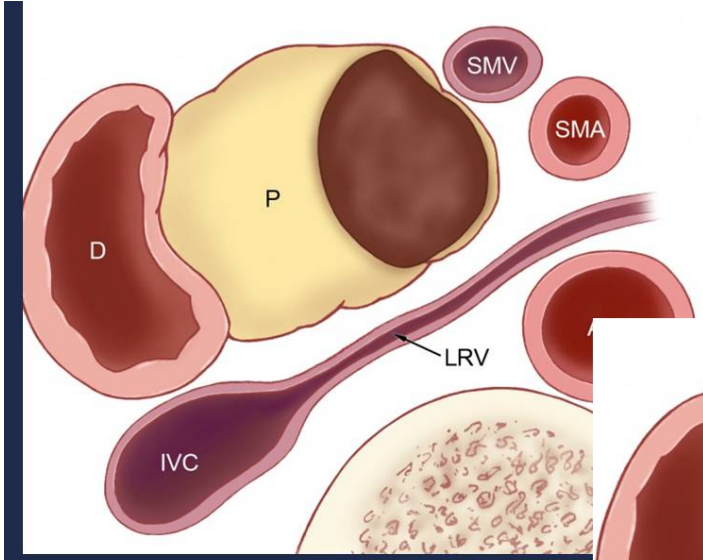
Borderline Resectable Disease

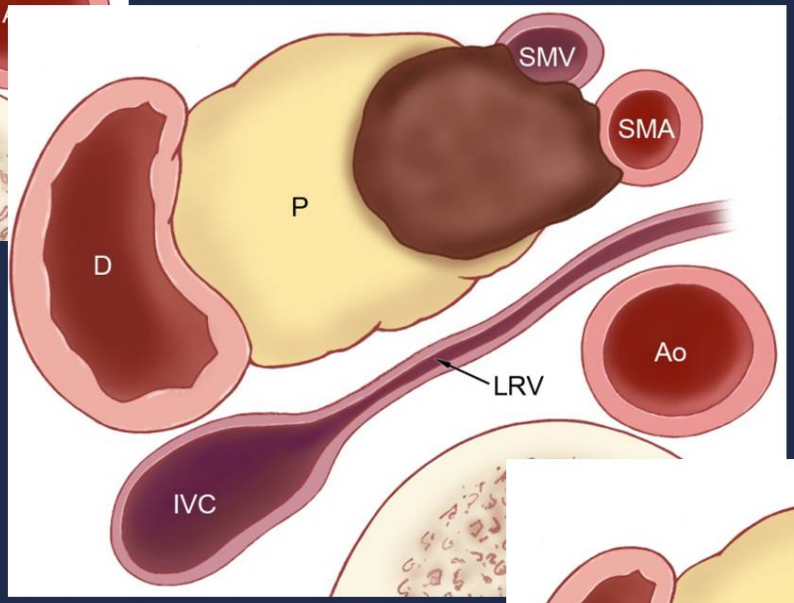
Potential benefits of primary chemotherapy

- Better diffusion of chemotherapy in well-vascularized tissues (before surgery and radiotherapy)
- Better tolerance and feasibility in patients before surgery (50% of adjuvant postoperative treatment not done or uncompleted)
- Decrease of the delay to the first treatment
- Downstaging effect
- Exclusion of patients with rapidly progressive tumours

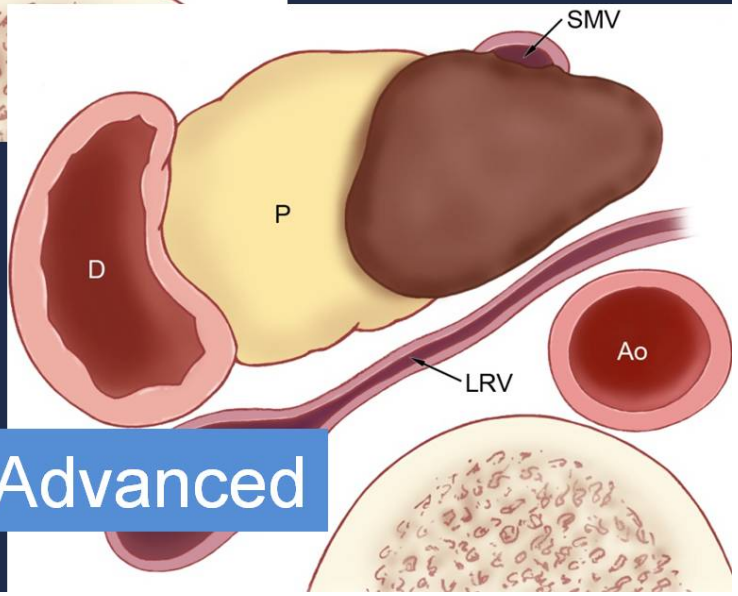
To do clinical trials of neoadjuvant therapy: need to define the study population (accurate staging)



Resectable



Borderline Resectable



Locally Advanced

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Table 1. Staging Classification of Localized Pancreatic Adenocarcinoma: Medical College of Wisconsin

Vascular Structures Which Determine the Stage of Disease for Localized Pancreatic Cancer		Resectable	Borderline Resectable	Locally Advanced	
				Type A	Type B
Tumor-Artery Anatomy	SMA (usually pertains to a tumor of the head or uncinate process)	No radiographic evidence of abutment or encasement	≤180 degrees (abutment)	>180 degrees of (encasement) but ≤270 degrees	>270 degrees of encasement
	Celiac artery (usually pertains to a tumor of the pancreatic body)	No radiographic evidence of abutment or encasement	≤180 degrees (abutment)	>180 degrees (encasement) but does not extend to the aorta and amenable to celiac resection (with or without reconstruction)	>180 degrees and abutment/ encasement of the aorta
	Hepatic Artery (HA) (usually pertains to a tumor of the pancreatic neck/head)	No radiographic evidence of abutment or encasement	Short segment abutment/ encasement without extension to celiac artery or HA bifurcation	>180 degrees of encasement with extension to celiac artery and amenable to vascular reconstruction	>180 degrees of encasement with extension beyond bifurcation of proper HA into right and left hepatic arteries
Tumor-Vein Anatomy	SMV-PV	≤50% narrowing of SMV, PV, SMV-PV	>50% narrowing of SMV, PV, SMV-PV with a distal and proximal target for reconstruction	Occlusion without obvious option for reconstruction	
Traditionally Considered for Resection After Neoadjuvant Therapy		Yes	Yes	No	No

SMA, superior mesenteric artery; SMV, superior mesenteric vein; PV, portal vein; SMV-PV, superior mesenteric-portal vein
Modified from Evans DB, George B, Tsai S. Non-metastatic pancreatic cancer: resectable, borderline resectable, and locally advanced-definitions of increasing importance for the optimal delivery of multimodality therapy. Ann Surg Oncol 2015:22(11):3409-13.

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Non-metastatic Pancreatic Cancer: Resectable, Borderline Resectable, and Locally Advanced-Definitions of Increasing Importance for the Optimal Delivery of Multimodality Therapy

Douglas B. Evans, MD[1], Ben George, MD[2], and Susan Tsai, MD, MHS[1]

[1]Pancreatic Cancer Program, Department of Surgery, The Medical College of Wisconsin, Milwaukee, WI; [2]Pancreatic Cancer Program, Department of Medicine, The Medical College of Wisconsin, Milwaukee, WI

Ann Surg Oncol. 2015;22(11):3409-13. PMID: 26122369.

Vascular structures which determine the stage of disease for localized pancreatic cancer	Borderline resectable	Locally advanced	
		Type A	Type B
May be considered for resection after neoadjuvant therapy	*Yes*	*Yes*	*No*
Tumor–artery anatomy			
SMA (usually pertains to a tumor of the pancreatic head/uncinate)	≤180° (abutment)	>180° encasement but ≤270°	>270°
Celiac artery (usually pertains to a tumor of the pancreatic body)	≤180° (abutment)	>180° but does not extend to the aorta and amenable to celiac resection (with or without reconstruction)	>180° and abutment/encasement of the aorta
Hepatic artery (usually pertains to a tumor of the pancreatic neck/head)	Short segment abutment/encasement without extension to celiac artery or HA bifurcation	>180° encasement with extension to celiac artery and amenable to vascular reconstruction	>180° encasement with extension beyond bifurcation of proper HA into right and left hepatic arteries
Tumor–vein anatomy			
SMV-PV	>50 % narrowing of SMV, PV, SMV/PV, or short segment occlusion, with a distal and proximal target for reconstruction	Occlusion without option for reconstruction: it would be very unusual to have a situation where cavernous transformation of the portal vein (which cannot be reconstructed—without a suitable distal [SMV] or proximal [PV] target for reconstruction) became operable	

Locally advanced pancreas cancer: Staging and goals of therapy

Nikolaos A. Chatzizacharias [a], Susan Tsai [a], Michael Griffin [b], Parag Tolat [b], Paul Ritch [c], Ben George [c], Chad Barnes [a], Mohammed Aldakkak [a], Abdul H. Khan [d], William Hall [e], Beth Erickson [e], Douglas B. Evans [a], and Kathleen K. Christians [a,*]

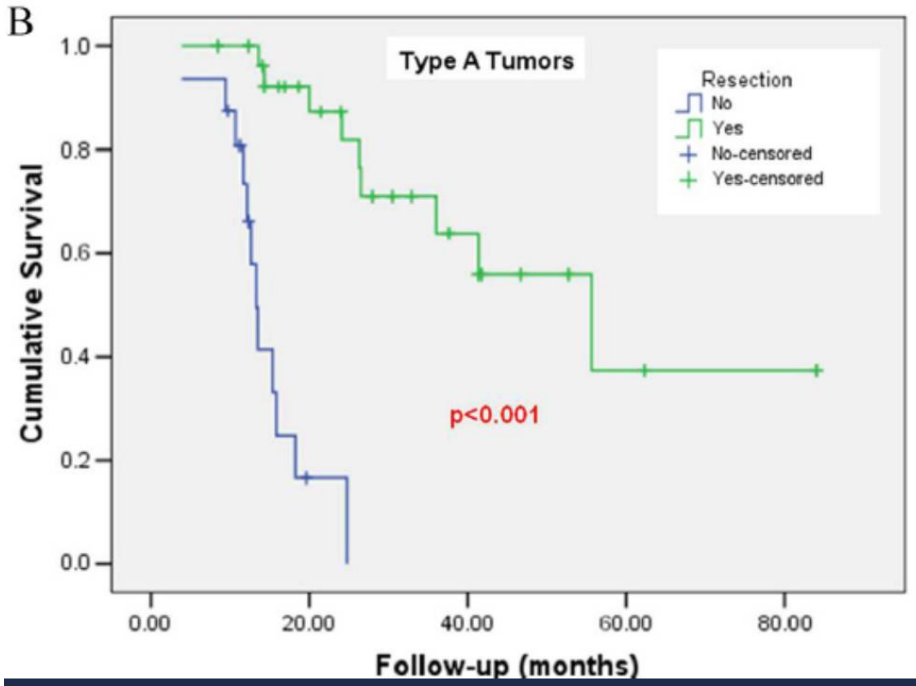
[a] *Department of Surgery, Division of Surgical Oncology, Pancreatic Cancer Program, Medical College of Wisconsin, Milwaukee, WI*

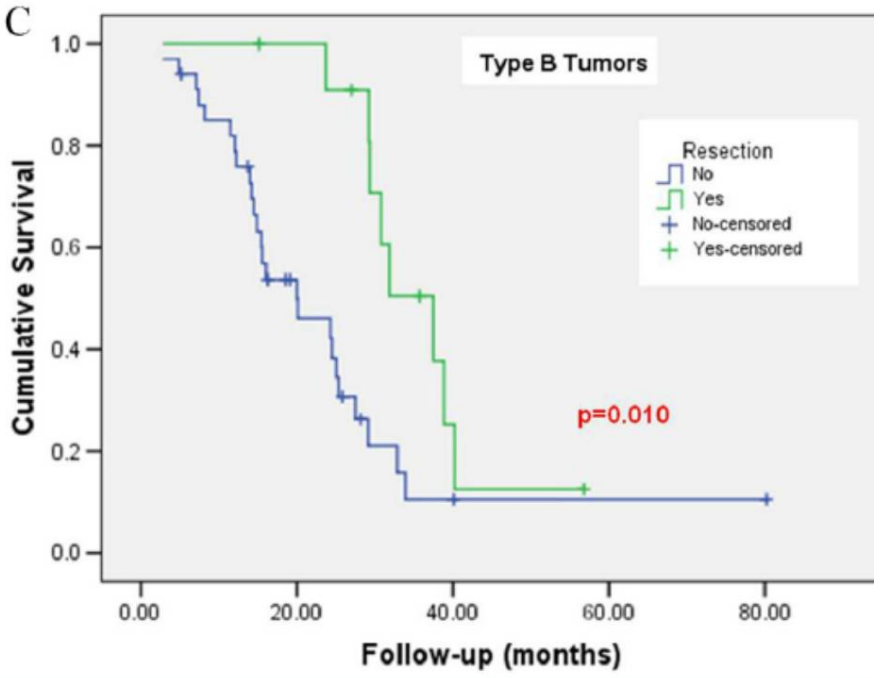
Surgery. 2018. [Epub ahead of print]

Completed all intended therapy to include surgery:

Type A: 28 (**62%**) of 45

Type B: 12 (**24%**) of 51





Med Survival of resected pts: 56 m 38 m

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The Importance of Pre-Treatment Staging 2018

Staging	Potential for Successful Surgery
Resectable	90%
Borderline	75%
LA type A	60%
LA type B	25%

- Surgery necessary but not sufficient for long-term survival
- Surgery remains a focus of attention because patients and medical oncologists like complete responses

- Hope is derived from a clear plan

(and all surgeons do what Medical Oncologists say)

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Surgery ***First*** +/- Adjuvant therapy **24** months

Surgery a bit later (Neoadjuvant: Medical College of Wisconsin)

Aldakkak, *HPB*	**46** months if preop 19-9 NI
Miura, *Surgery*	**37** months
Christians, *Surgery*	**45** months (resectable)

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*

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] MD, MHS,[a] *Milwaukee, WI*

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]

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Gastrointestinal Cancer

Neoadjuvant FOLFIRINOX for Borderline Resectable Pancreas Canc

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]

Arterial resection at the time of pancreatectomy for cancer

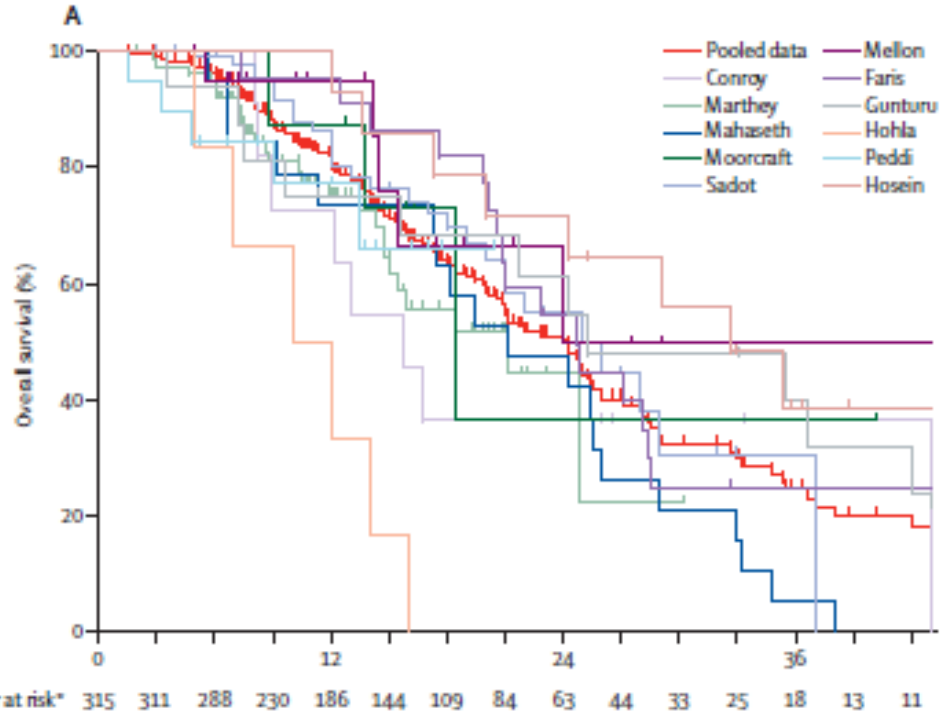
Kathleen K. Christians, MD,[a] Charles H. C. Pilgrim, MD, PhD,[a] Susan Tsai, MD, MS,[a] Paul Ritch, MD,[b] Ben George, MD,[b] Beth Erickson, MD,[c] Parag Tolat, MD,[d] *and* Douglas B. Evans, MD,[a] *Milwaukee, WI*

Recent meta-analysis of primary chemotherapy with FOLFIRINOX

FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis

Mustafa Suker, Berend R Beumer*, Eran Sadot, Lysiane Marthey, Jason E Faris, Eric A Mellon, Bassel F El-Rayes, Andrea Wang-Gillam, Jill Lacy, Peter J Hosein, Sing Yu Moorcraft, Thierry Conroy, Florian Hohla, Peter Allen, Julien Taieb, Theodore S Hong, Ravi Shridhar, Ian Chau, Casper H van Eijck, Bas Groot Koerkamp*

- 13 studies with FOLFIRINOX
- 689 patients
- 355 Locally advanced
- 63.5% received RT-CT after FOLFIRINOX



Suker M et al. Lancet Oncol 2016;17:801-10

Localised Primarily Unresectable Disease

Much controversy

- Primary chemotherapy standard
- Possibly followed by radiochemotherapy *
  (LAP07 trial was negative but a retrospective analysis of 13’004 pts in the National Cancer Database showed that patients receiving (SB)RT did better than those only on chemo – ASCO 2017, Abs 4103)
- Radiological reassessment is poor in identifying patients who are likely resectable -If some response documented resubmit to MDT discussion and consider exploratory surgery
- Trials of intensive chemo and stereotactic RT