PANCREAS CANCER ACADEMY

Pancreatic Cancer Academy

Nov. 29. – 30. 2019

NH Hotel Vienna Airport

CECOG ACADEMY

NEOADJUVANT CHEMOTHERAPY IN **RESECTABLE** PANCREATIC CANCER PATIENTS

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Milano

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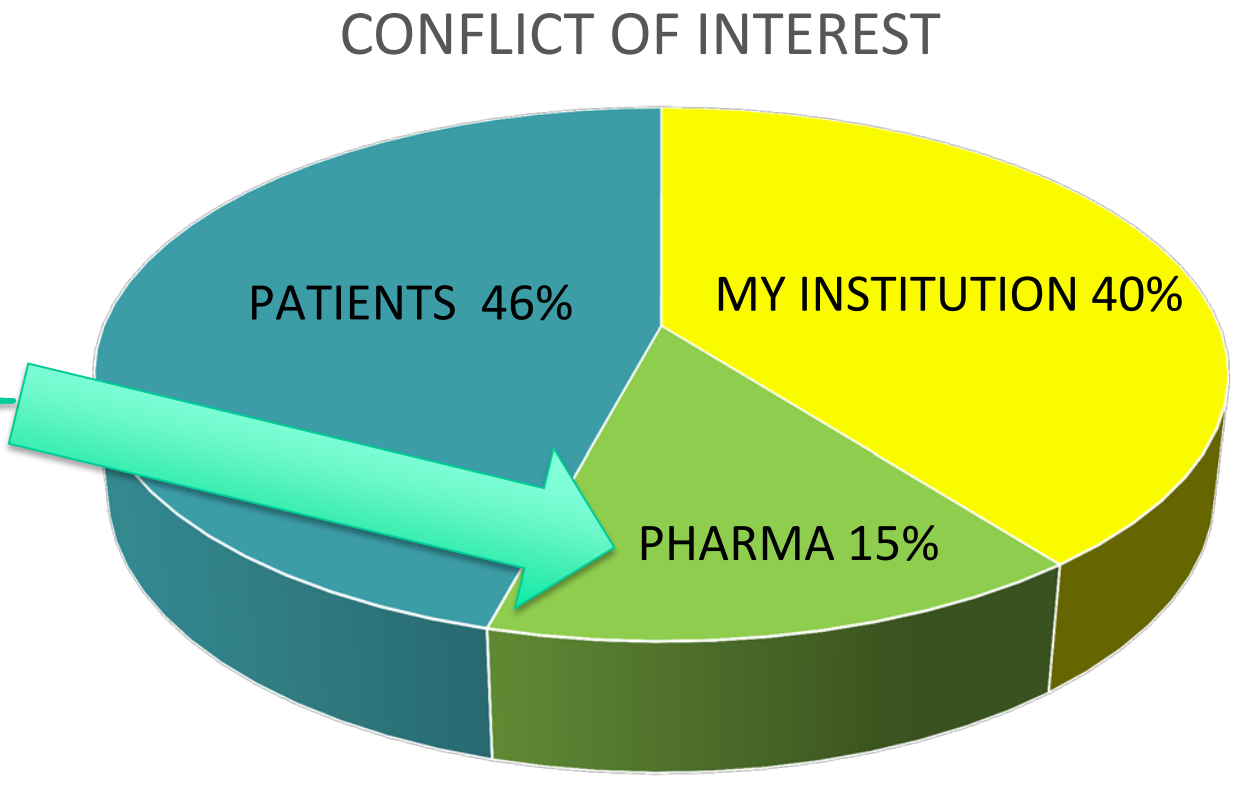
PERSONAL DISCLOSURES

Has received research funding or honoraria from:

Celgene
Baxalta
Eli-Lilly
Pfizer
Novocure
Novartis
Astra-zeneca
Shire



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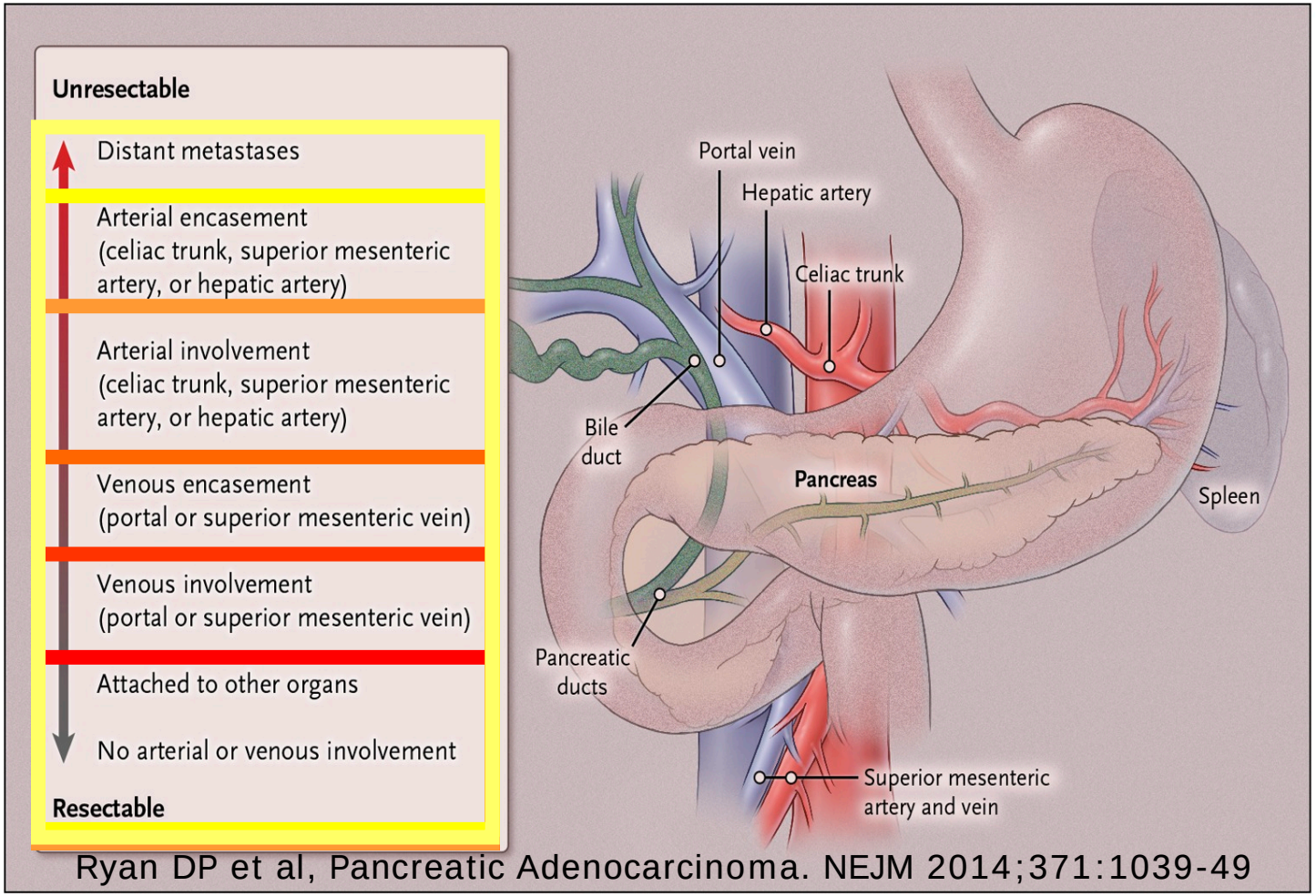
RESECTABILITY – A MOVING BORDER



Ryan DP et al, Pancreatic Adenocarcinoma. NEJM 2014;371:1039-49

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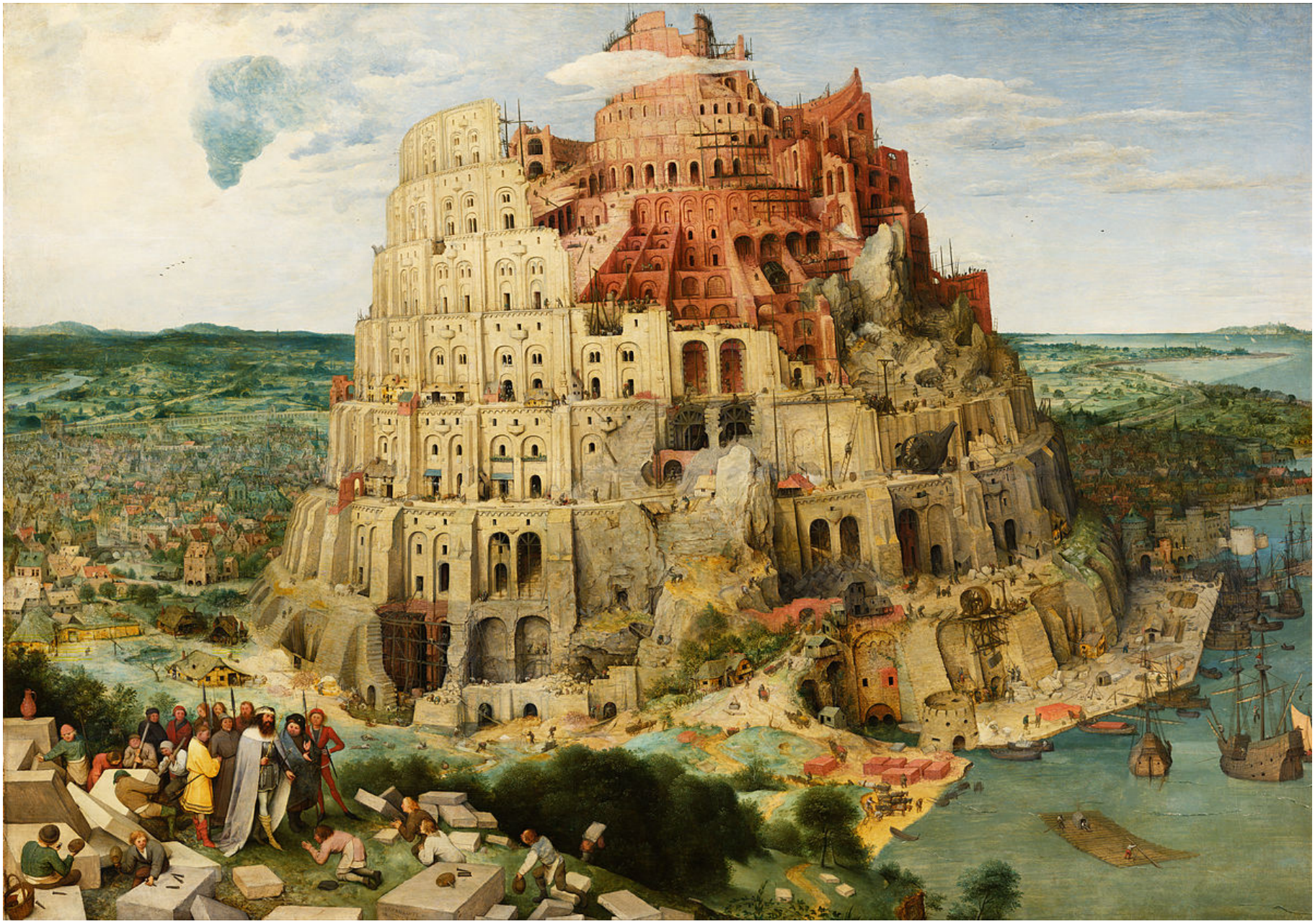
WHAT IS ‘RESECTABLE’ ?



STANDARD TREATMENT

RESECTED PATIENTS

STANDARD TREATMENT

=

⇨ ADJUVANT THERAPY

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RESECTED ≠ RESECTABLE

- Surgical mortality
- Intraop M+
- Early postop M+
- slow/no post-op recovery

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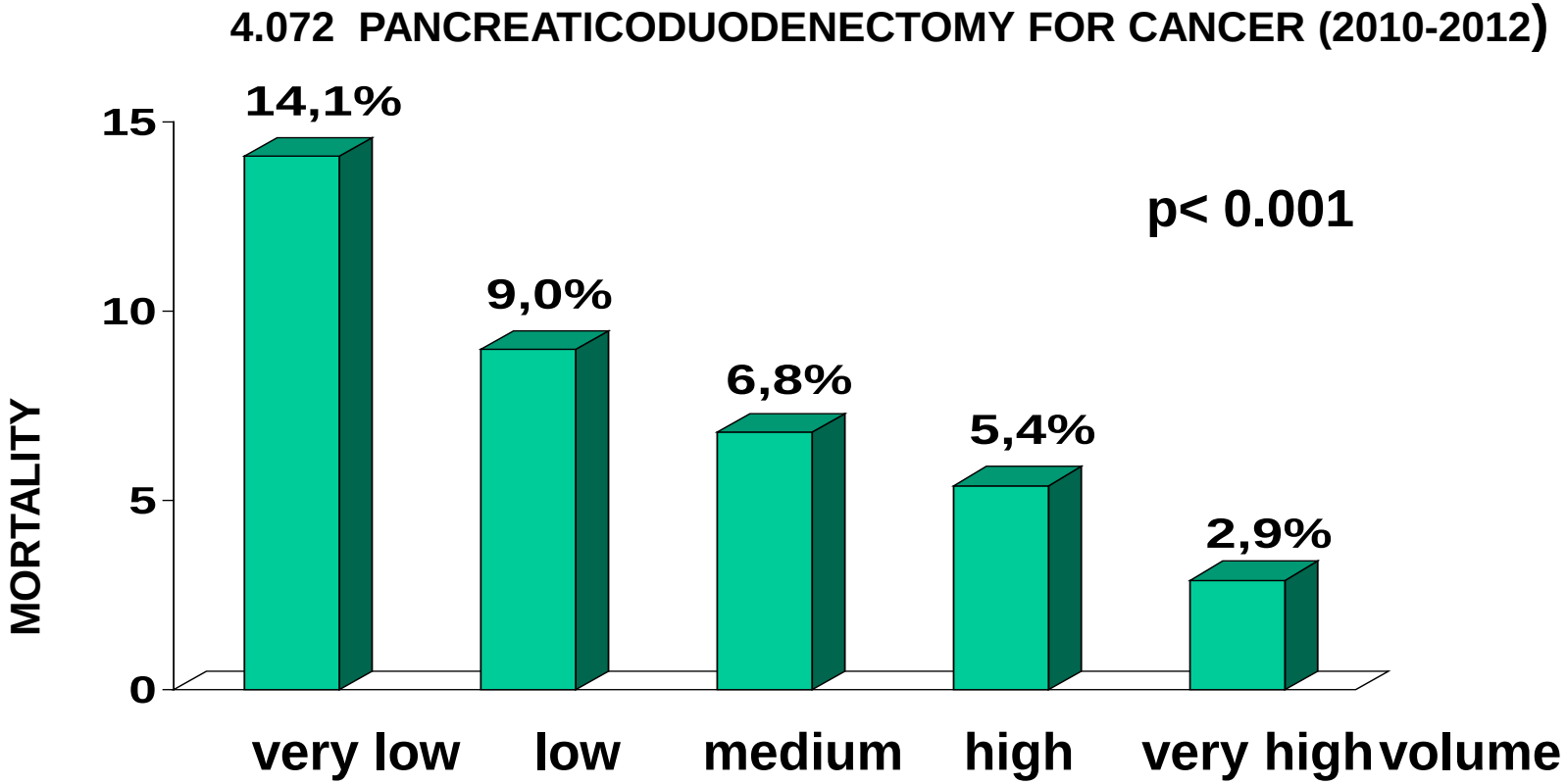
SURGICAL MORTALITY: 3-14%



ORIGINAL ARTICLE

Overuse of surgery in patients with pancreatic cancer. A nationwide analysis in Italy *HPB 2016*

Gianpaolo Balzano[1,2], Giovanni Capretti[1,2], Giuditta Callea[3], Elena Cantù[3], Flavia Carle[4,5] & Raffaele Pezzilli[2,6]

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SURGICAL MORTALITY: 3-14%

Hospitals splitted according to volume (number of pancreatic resections)

ORIGINAL ARTICLE *HPB 2016*

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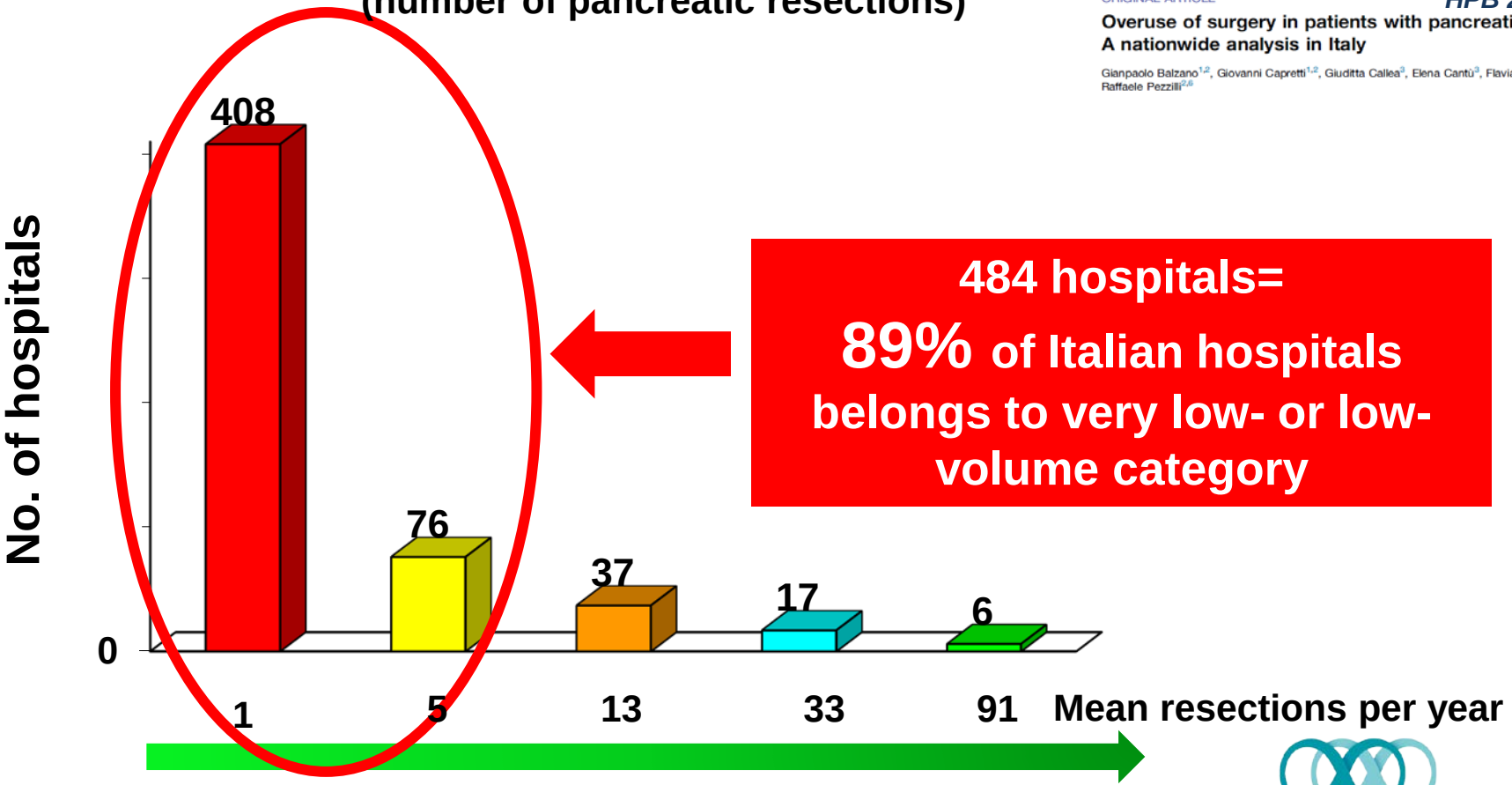

484 hospitals=

89% of Italian hospitals belongs to very low- or low-volume category

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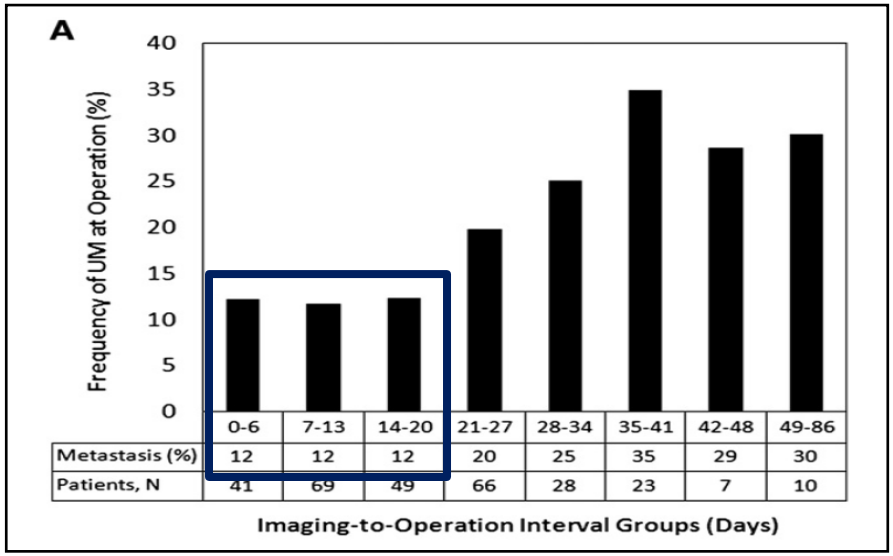
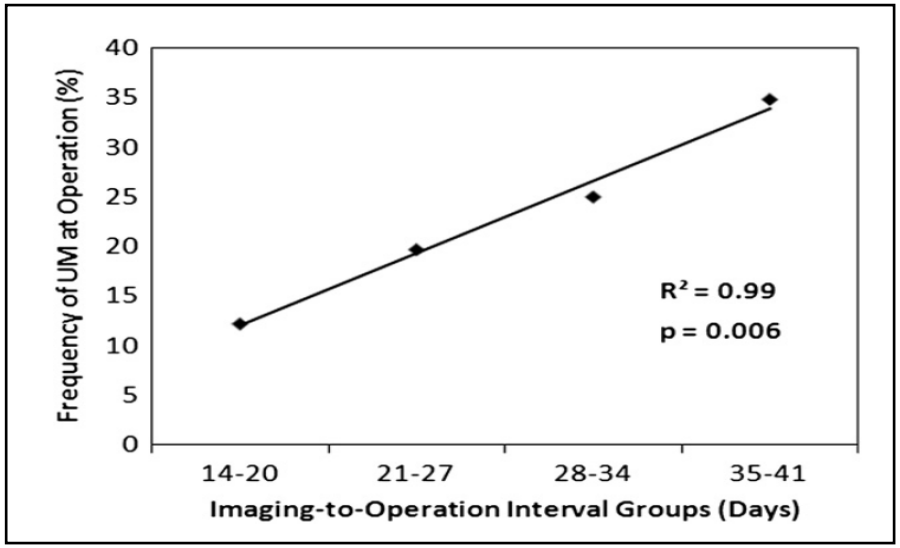
FAILURE DURING SURGERY

>10% of intraoperative unanticipated metastasis (UM)





Glant JA, Surgery 2011

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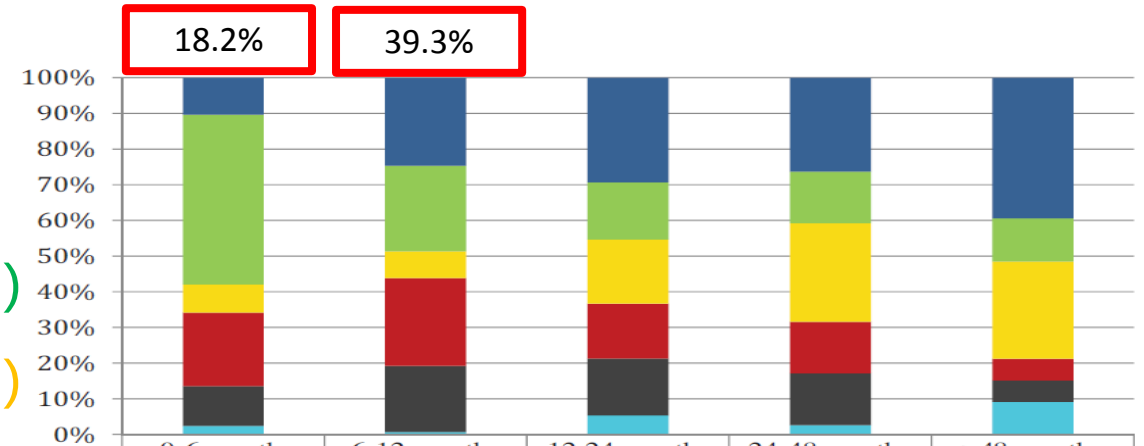
EARLY FAILURE AFTER SURGERY

N=692

DISTANT 45% (73%)

LOCAL 18% (27%)



	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, VP et al. Ann Surg 2017

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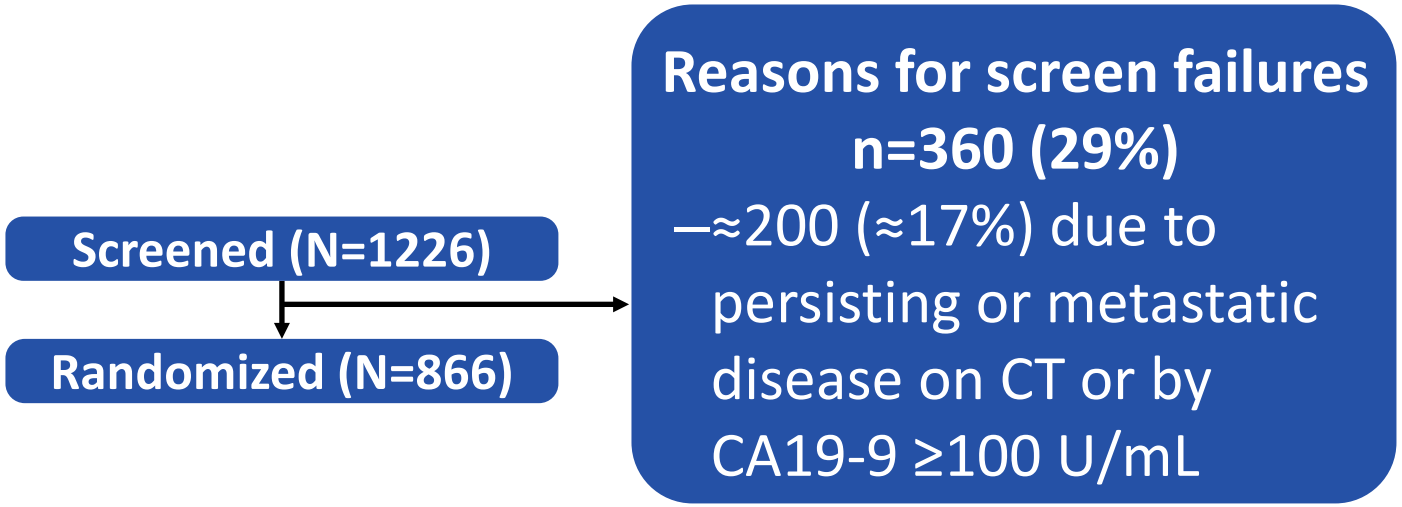
EARLY FAILURE or SCREENING FAILURE AFTER SURGERY



APACT TRIAL

Reni M et al. WGI 2019:abstr 88

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ENTIRE "PACKAGE" COMPLETION

Author	Institution	Resected (n)	Adjuvant (%)
Mayo SC, et al JACS 2012	SEER	2,461	51
Wu W, et al ASO 2014	John Hopkins	1,194	53.4
Akaori T, et al Am J Surg 2016	Nara	146	61.6

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RESECTED ≠ RESECTABLE

- Surgical mortality	3-14%
- Intraop M+	10-15%
- Early postop failure	15-20%
- slow/no post-op recovery	20-30%

RESECTED « RESECTABLE

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ADJ CHEMO: COMPLETION RATE

Author	Institution	Resected (n)	Adjuvant (%)
Oettle H, et al JAMA 2007	multicentric	179	62%
Neoptolemos JP, et al Lancet Oncol 2017	multicentric	730	54-63%
Conroy T, et al NEJM 2018	multicentric	493	66-79%
Tempero M, et al ASCO 2019	multicentric	866	66-71%

GREEN= experimental arm

BLACK= GEMCITABINE

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ANY EVIDENCE FOR NEOADJ ?

- No phase III data
- Phase I
- Phase II (no control arm, small sample size)
- Retrospective data
- Pooled-analyses heterogeneous in terms of:

  study period

  chemotherapy

  RT techniques and doses

  resectability criteria

  borderline resectable definition & analysis

  R0 resection definition

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NEOADJUVANT CHEMO

Jan 2000 – Apr 2015

N=14 trials (3 randomized) - N=616 patients

CR = 1.8%

PR = 14.6%

SD = 62.2%

PD = 13.4%

Resection rate 73%

mOS 17.8 months

Zhan HX, et al. Cancer Medicine 2017; 6: 1201-1219

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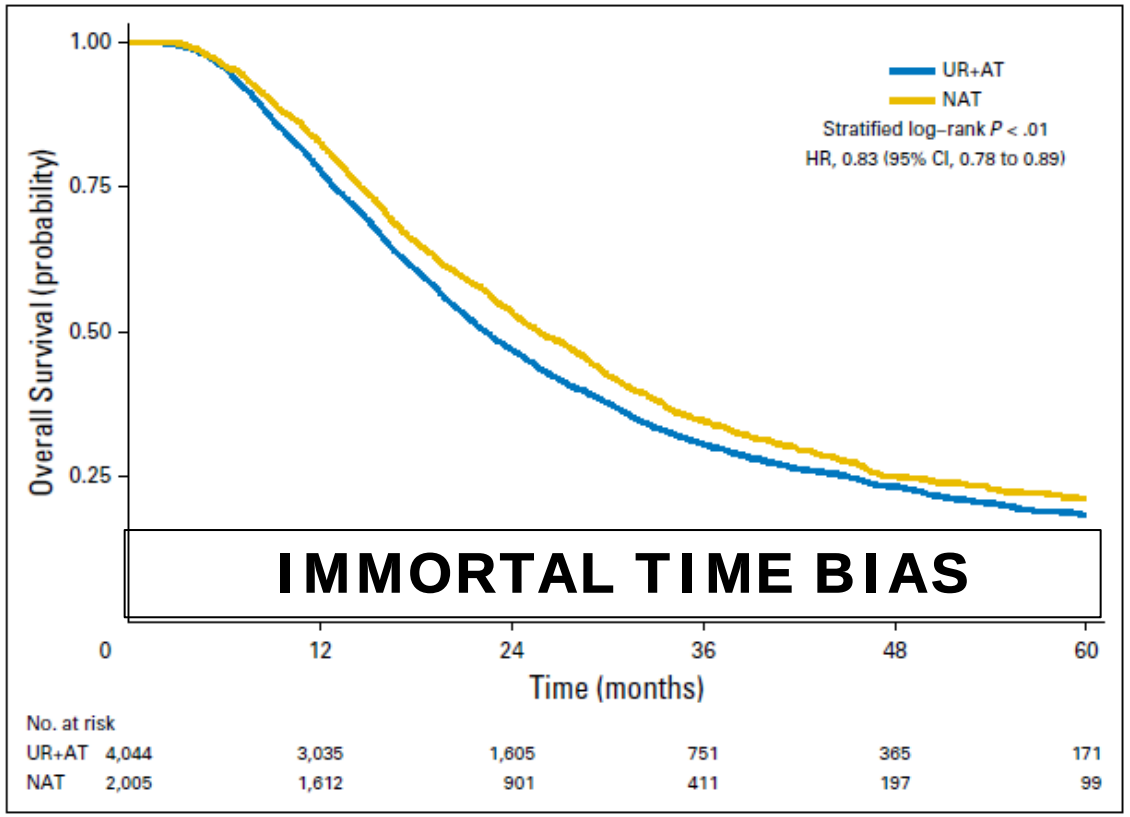
NEOADJ > UPFRONT SURGERY ?

US National Cancer Database (2006-2012): 15,237 pts: 2,005 NAT; 6,015 UR

Analysis Propensity score matched



	survival (mo)	P
surgery + adjuvant	23	< .01
neoadjuvant	26	

Mokdad AA, et al. J Clin Oncol 2017; 35:515-522

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NEOADJ > UPFRONT SURGERY ?

Systematic review (2000-2016; 38 of 18828 studies; 3RCT)

INTENTION TO TREAT

	N	survival (mo)	Resection rate
UPFRONT SURGERY	**819**	**17.7**	**77%**
neoadjuvant	**857**	**18.2**	**67%**

Versteijne E, et al. BJS 2018; 105:946-958

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NEOADJUVANT CHEMO

chemo in resectable disease

	N=24 GEM	N=26 GEM+CDDP
	PR: 0% SD: 67% resected: 38%	PR: 4% SD: 62% resected: 70%
mOS	9.9	15.6

Palmer – Ann Surg Oncol 2007

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NEOADJUVANT CHEMO

Published in final edited form as:

Ann Surg. 2014 July ; 260(1): 142–148. doi:10.1097/SLA.0000000000000251.

A Single-Arm, Non-Randomized Phase II Trial of Neoadjuvant Gemcitabine and Oxaliplatin in patients with Resectable Pancreas Adenocarcinoma

Eileen M. O'Reilly, M.D.[1], Anna Perelshteyn, M.D.[1], William R. Jarnagin, M.D.[2], Mark

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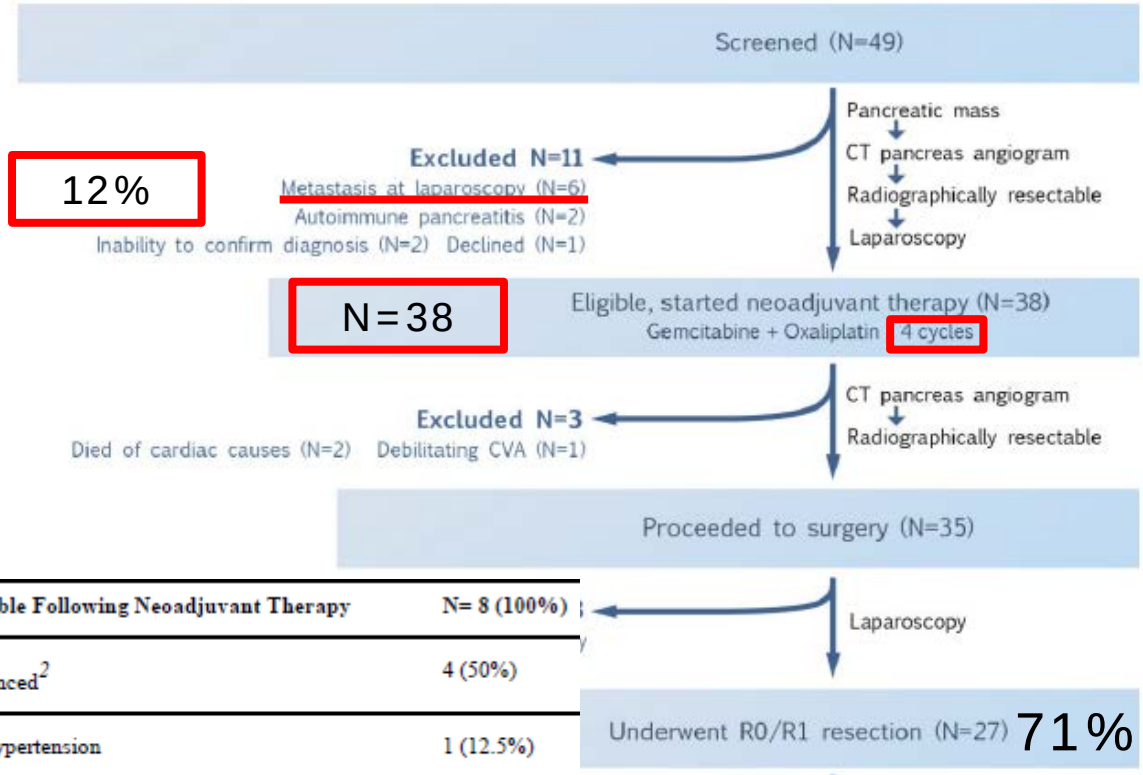
NEOADJUVANT CHEMO



II. Unresectable Following Neoadjuvant Therapy	N= 8 (100%)
T4, locally advanced[2]	4 (50%)
Varices/portal hypertension	1 (12.5%)
Metastases (N= 2 liver; N= 1 peritoneum)	3 (37.5%)

Toxicity	Grade 2	Grade 3	Grade 4	Grade 5
I. Hematologic Toxicity				
Anemia	11 (29%)	4 (11%)		
Neutropenia	1 (2%)	2 (5%)		
Leukopenia	4 (11%)	2 (5%)		
Coagulopathy (PT/PTT/INR)		1 (2%)		
Platelets	2 (5%)			
AST/ALT	25 (66%)	16 (42%)		
Hyperbilirubinemia	15 (39%)	5 (13%)		
Alkaline phosphatase	10 (26%)	6 (16%)		
Hypoalbuminemia	11 (29%)			
Electrolyte abnormalities[1]	8 (21%)	8 (21%)		
Hyperglycemia	11 (29%)	18 (47%)		
Hypoglycemia	1 (3%)			
Amylase		3 (8%)		
Lipase		1 (3%)		
II. Non-Hematologic Toxicity				
Gastrointestinal symptoms				
Abdominal pain	4 (10.5%)			
Ascites (non-malignant)		1 (3%)		
Constipation	1 (3%)			
Nausea/vomiting	2 (5%)			
Infection (cholangitis/abscess)	2 (5%)	1 (3%)	1 (3%)	
Hemorrhage, Lower GI tract[2]		1 (3%)		
Hemorrhoids	1 (3%)			
Constitutional Symptoms				
Fatigue/Lethargy	3 (8%)			
Weight loss	1 (3%)			
Other Toxicities				
Atrial fib				
Hypersen				
Anxiety				
Cerebrovascular accident				1 (3%)
Edema (limb)	1 (3%)			
Hypertension	1 (3%)			
Injection Site reaction (extravasation)	1 (3%)			
Fever/infection (normal ANC)	7 (18%)	1 (3%)	1 (3%)	
Renal/GU	1 (3%)		1 (3%)	
Sudden death (cardiac)[4]				2 (5%)

GRADE 5 !!

8%

NEOADJUVANT CHEMO

RECIST Response (N= 38)	No. Patients (%)
Partial Response	4 (10.5%)
Stable Disease	28 (73.7%)
Progression of Disease	3 (7.9%)
Inevaluable[1]	3 (7.9%)

of 37 patients would allow differentiation of an 18-month overall survival (OS) of 53% and 73% with type I and II error rates of 10% each using a single-stage binomial design. The

for a total of 23 patients (60.5%) who completed all planned therapy. The 18-month survival was 63% (24 patients alive). The median overall survival for all 38 patients was 27.2 months (95% CI

Conclusion—This study met its endpoint and provided a signal suggesting that exploration of neoadjuvant systemic therapy is worthy of further investigation in resectable pancreas

T stage	
T1	1 (4%)
T3	26 (96%)
Median Tumor Size (range), cm	2.8 (1.7-4.6)
Nodal Status	
N0	9 (33.5%)
N1	18 (66.5%)
Resection Margin	
R0	20 (74%)
R1	7 (26%)

mOS 27.2

N0: 9/38 = 24%

R0: 20/38 = 53%

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PACT-15 TRIAL

Reni, M et al. Lancet Gastroenter & Hepatol 2018

- ✓ Pathological diagnosis of PC
- ✓ Clinical stage I-II
- ✓ No AMS, VMS, VP, AE, CT invasion
- ✓ No symptomatic duodenal stenosis
- ✓ Karnofsky > 60%
- ✓ Age 18-75 y

Safety and efficacy of preoperative or postoperative chemotherapy for resectable pancreatic adenocarcinoma (PACT-15): a randomised, open-label, phase 2–3 trial

Michele Reni, Gianpaolo Balzano, Silvia Zanon*, Alessandro Zerbi, Lorenza Rimassa, Renato Castoldi, Domenico Pinelli, Stefania Mosconi, Claudio Doglioni, Marta Chiaravalli, Chiara Pircher, Paolo Giorgio Arcidiacono, Valter Torri, Paola Maggiora, Domenica Ceraulo, Massimo Falconi, Luca Gianni*

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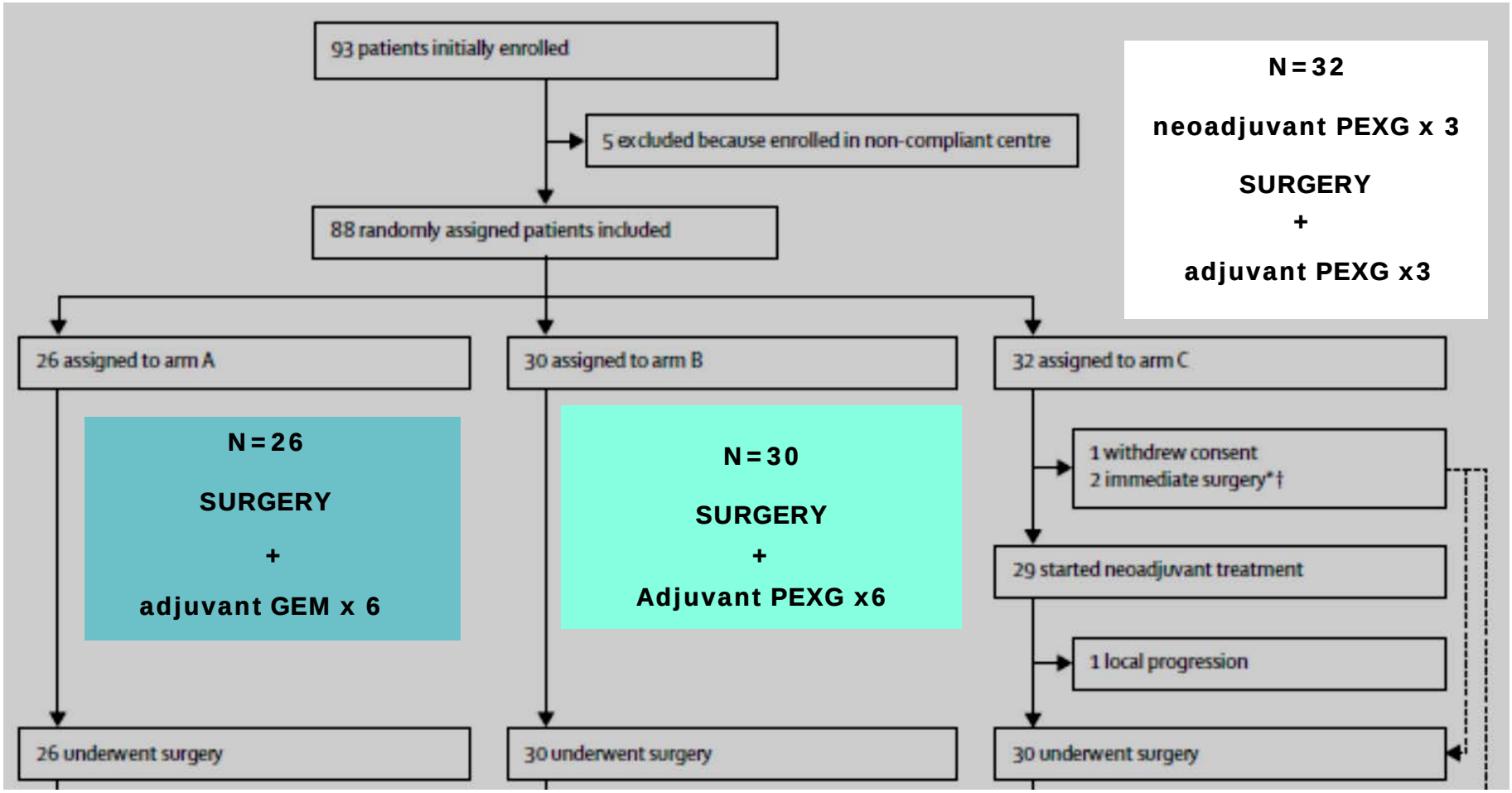
PACT-15 – TRIAL DESIGN



Reni, M et al. Lancet Gastroenter & Hepatol 2018

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PACT-15 - STUDY POPULATION

	Group A (n=26)	Group B (n=30)	Group C (n=32)
Sex			
Male	14 (54%)	13 (43%)	25 (78%)
Female	12 (46%)	17 (57%)	7 (22%)
Age (years)	65 (37–74)	68 (49–75)	64 (39–75)
Karnofsky performance status >80	24 (92%)	27 (90%)	29 (91%)
Baseline CA19-9			
>5× ULN	9 (36%)*	16 (53%)	15 (48%)*
>ULN	18 (72%)*	24 (80%)	23 (74%)*
Baseline CA19-9	179 (39–3337)	240 (40–12000)	173 (43–4510)
Cancer site			
Pancreatic head	25 (96%)	26 (87%)	28 (88%)
Pancreatic body	0	3 (10%)	2 (6%)
Pancreatic tail	1 (4%)	1 (3%)	2 (6%)
Jaundice at diagnosis	21 (81%)	24 (80%)	23 (72%)
Biliary drainage at diagnosis	13 (50%)	15 (50%)	21 (66%)
Lack of pathological confirmation at enrolment	0	1 (3%)	1 (3%)

Reni, M et al. Lancet Gastroenter & Hepatol 2018

Table 1: Baseline characteristic of the patients

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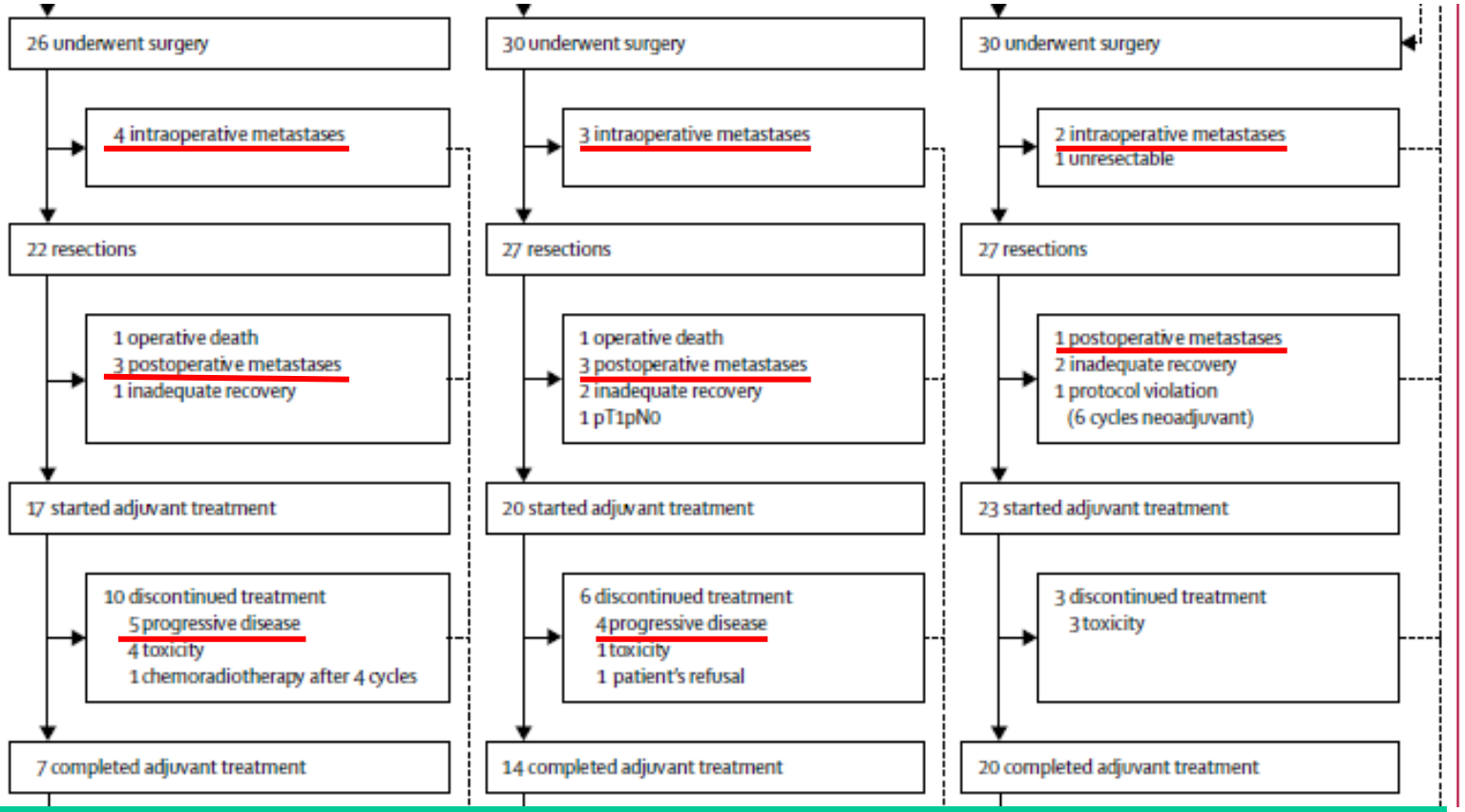
PACT-15 - RESULTS



Early failure	12 (46%)	10 (33%)	3 (9%)

Reni, M et al. Lancet Gastroenter & Hepatol 2018

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PACT-15 - RESULTS

	Group A (n=22)	Group B (n=27)	Group C (n=27)
pT1	1 (5%)	1 (4%)	4 (15%)
pT2	1 (5%)	0	1 (4%)
pT3	20 (91%)	26 (96%)	22 (81%)
pN0	6 (27%)	7 (26%)	13 (48%)
pN1	16 (73%)	20 (74%)	14 (52%)
Node ratio	16·3% (4–77)	13·6% (3–64)	13·9% (5–29)
R0	6 (27%)	10 (37%)	17 (63%)
R1	16 (73%)	17 (63%)	10 (37%)
Grade 3	13 (59%)	16 (59%)	7 (26%)
Tumour size (cm)	2·5 (1·5–5·0)	2·1 (1·5–7·0)	2·0 (0·0–6·0)
Pathological response[18]			
Marked	NA	NA	9/25 (36%)
Moderate	NA	NA	8/25 (32%)
Poor	NA	NA	8/25 (32%)

Data are n (%), median (range), or n/N (%). Pathological response was calculated for 25 patients receiving preoperative chemotherapy. NA=not applicable.

Table 3: Pathological characteristics in patients who underwent resection

N0: 13/29 = 45%

R0: 17/29 = 59%

Reni, M et al. Lancet Gastroenter & Hepatol 2018

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PACT-15 - OUTCOME

m follow-up 56 months	ARM A	ARM B	ARM C	P (A vs C)
1y EFS	23%	50%	66%	
mEFS	4.7	12.4	16.9	0.002

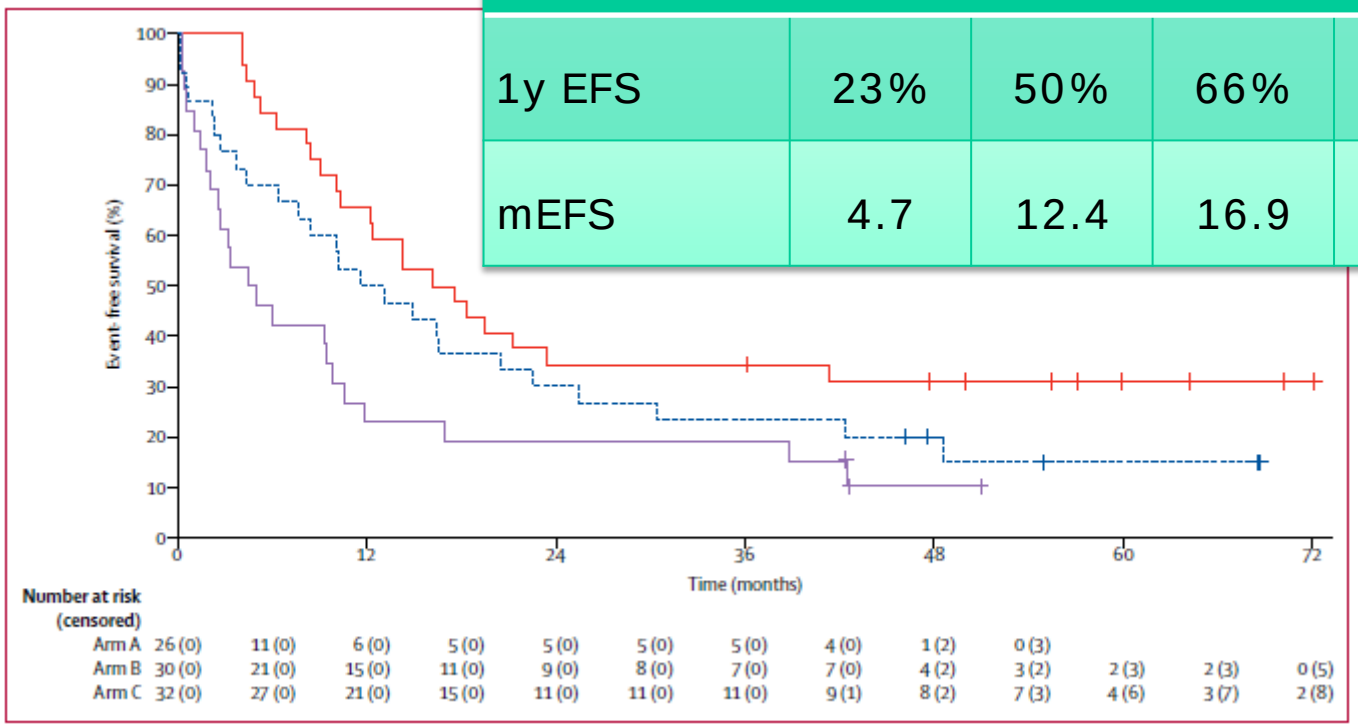

Figure 2: Event-free survival

Reni, M et al. Lancet Gastroenter & Hepatol 2018

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PACT-15 - OUTCOME

m follow-up 56 months	ARM A	ARM B	ARM C	P (A vs C)
mOS	20.4	26.4	38.2	
3y OS	35%	42%	55%	0.03
5y OS	13%	24%	49%	

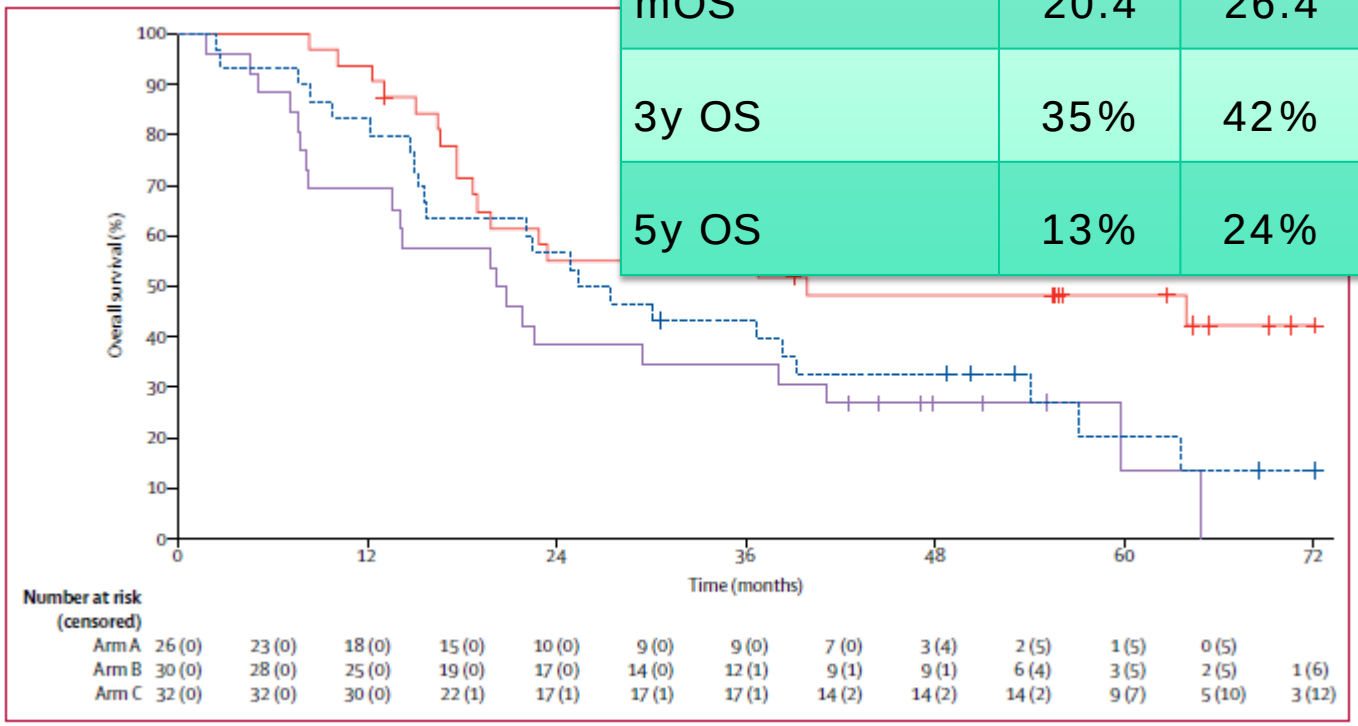

Figure 3: Overall survival

Reni, M et al. Lancet Gastroenter & Hepatol 2018

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HOW LONG TO TREAT ?

	Phase	Surgical evaluation	Treatment	Treatment length before surgery
*Heinrich et al 2008[5]	II	Resectable	4 cycles Gemcitabine + Cisplatin	2 months
*Motoi et al 2013[6]	II	Resectable + borderline resectable	2 cycles (1,8 q21) Gemcitabine + S1	2 months
*O'Reilly et al 2014[7]	II	Resectable	4 cycles Gemcitabine + Oxaliplatin	2 months
*Reni et al 2018[3]	II/III Randomized	Resectable	6 cycles PEXG -> surg -> 6 cycles PEXG Vs Surgery -> 12 cycles PEXG	3 months
°NEOPAC NCT01314027[8]	III	Resectable	4 cycles Gemcitabine + Oxaliplatin -> Surgery—6 Cycles Gemcitabine Vs Surgery -> 6 cycles Gemcitabine	2 months
°NEOPAC NCT01521702[32]	III	Resectable	4 cycles Gemcitabine + Oxaliplatin -> Surgery Vs Surgery -> 6 cycles Gemcitabine	2 months
**NCT01771146[9]	II	Resectable	6 cycles FOLFIRINOX	3 months
**NEONAX NCT02047513[10]	II Randomized	Resectable	2 cycles Gemcitabine + Nab-paclitaxel - > surgery - > 4 cycles Gemcitabine + Nab-paclitaxel Vs surgery -> 6 cycles Gemcitabine + Nab-paclitaxel	2 months
**NCT02172976[11]	II/III Randomized	Resectable	6 cycles FOLFIRINOX - > surgery - > 6 cycles FOLFIRINOX Vs Surgery -> 6 cycles Gemcitabine	3 months
**ACOSOG-Z5041 NCT00733746[12]	II	Resectable	2 cycles gemcitabine + erlotinib -> surgery	2.5 months
**NCT02178709[13]	II	Resectable	12 cycles FOLFIRINOX	6 months
*Maurel J et al 2018[14]	II	Resectable	3 cycles gemcitabine + erlotinib -> 5 weekly Gemcitabine + RT + erlotinib	4 months
°NCT02243007[15]	II Randomized	Resectable	Neoadjuvant FOLFIRINOX vs gemcitabine + nab-paclitaxel	??
°NCT02030860[16]	Pilot	Resectable	Neoadjuvant gemcitabine + nab-paclitaxel 1/- paricalcitol	??
**NCT02562716[33]	II Randomized	Resectable	6 cycles FOLFIRINOX - > surgery - > 6 cycles FOLFIRINOX Vs 3 cycles Gemcitabine + Nab-paclitaxel -> surgery -> 3 cycles Gemcitabine + Nab-paclitaxel	3 months
°NorPACT-1 NCT02919787[34]	II/III Randomized	Resectable	Surgery -> 6 cycles gemcitabine+capecitabine Vs 4 cycles FOLFIRINOX -> surgery -> 4 cycles gemcitabine+capecitabine	2 months
**NCT02959879[35]	II Randomized	Resectable	4 cycles FOLFOX -> surgery -> 8 cycles of standard adjuvant chemotherapy Vs 4 cycles FOLFIRINOX -> surgery -> 8 cycles of standard adjuvant chemo	2 months

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HOW LONG TO TREAT ?

April 1997 - May 2016		METASTATIC	NON-METASTATIC
Number		346	163
Gender	Male	195 (56%)	88 (54%)
	Female	151 (44%)	75 (46%)
KPS	90-100	185 (53%)	102 (63%)
	70-80	154 (45%)	58 (36%)
	60	7 (2%)	2 (1%)
Age	median	60	63
	range	29-76	35-76
CA19-9	median	1417	479
	range	41-739108	39-12473
Regimen	Gemcitabine	18 (5%)	9 (6%)
	PEFG/PEXG	225 (65%)	92 (56%)
	AG/PDXG/PAXG	103 (30%)	62 (38%)

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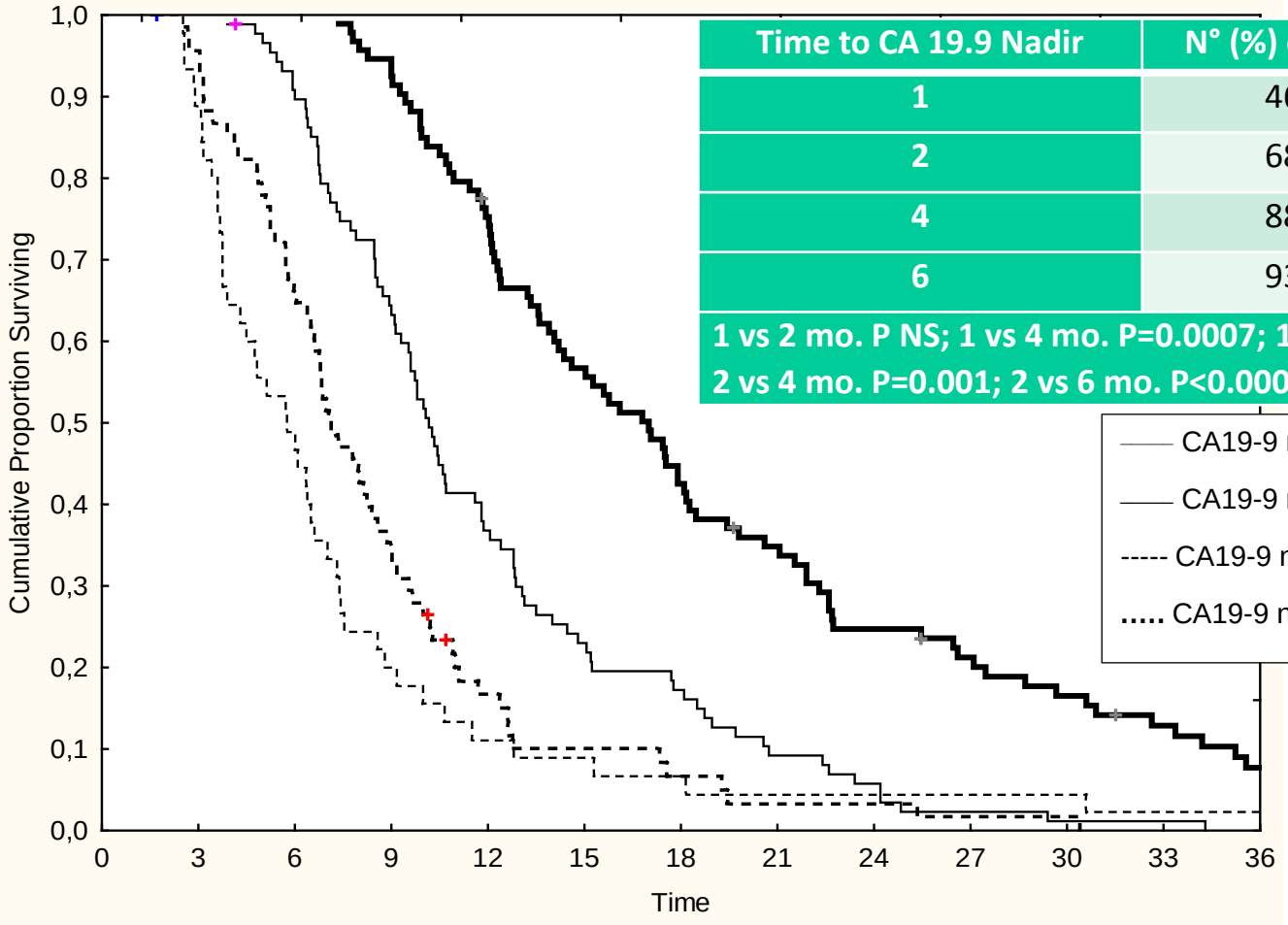
Reni, M et al. SUBMITTED – CONFIDENTIAL UNPUBLISHED DATA

HOW LONG TO TREAT ?

Reni, M et al. SUBMITTED – CONFIDENTIAL UNPUBLISHED DATA

nadir ≥4 mo: M+ **53%**; non-M+ **74%** (p=0.02)
tax-based **73%**; tax-free **52%** (p=0.002)



Time to CA 19.9 Nadir	N° (%) of Patients	Median OS
1	46 (13)	**5.7**
2	68 (20)	**7.1**
4	88 (25)	**10.1**
6	93 (27)	**16.8**

1 vs 2 mo. P NS; 1 vs 4 mo. P=0.0007; 1 vs 6 mo. P<0.00001;
2 vs 4 mo. P=0.001; 2 vs 6 mo. P<0.00001; 4 vs 6 mo. P<0.00001.

CA19-9 nadir at 6 months
CA19-9 nadir at 4 months
----- CA19-9 nadir at 2 months
..... CA19-9 nadir at 1 month

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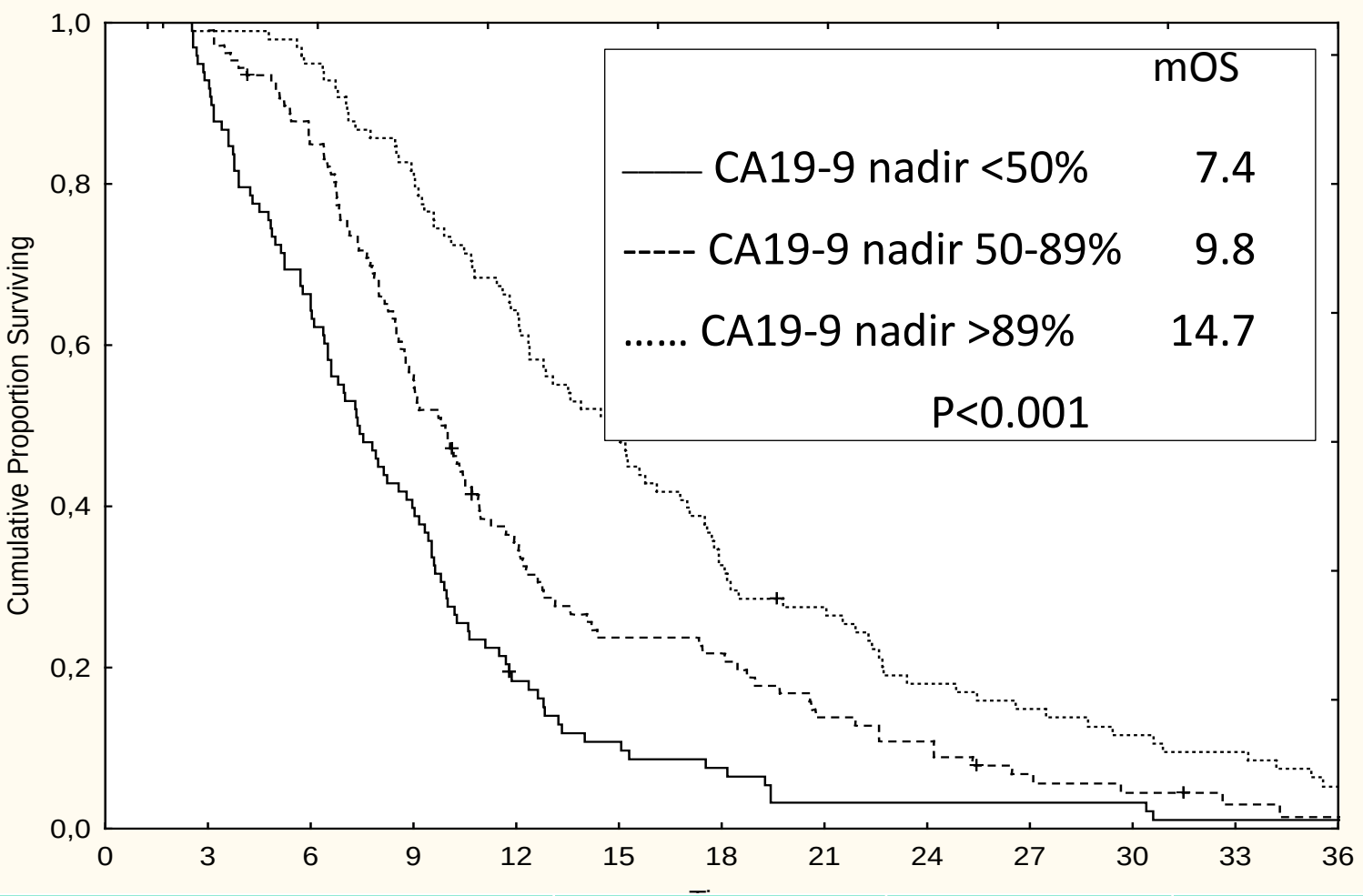
HOW LONG TO TREAT ?



Variable	HR	95%CI	p-value
KPS (continuous variable)	0.54	0.43-0.69	<0.00001
gender (female; male)	0.86	0.70-1.05	0.13
basal CA19-9 (continuous variable)	1.01	1-00-1.02	0.01
age (continuous variable)	0.99	0.98-1.01	0.41
Time to nadir (1 month; 2; 3; 4; 5; 6 months)	0.71	0.66-0.76	<0.00001
CA19-9 reduction (continuous variable)	1.00	0.99-1.01	0.05

TAKE HOME MESSAGE

- Expected outcome with adj therapy is overestimated
- Periop PEXG improved outcome over adj GEM & PEXG
- PACT-15 provides the strongest piece of evidence available in favor of preop chemo in resectable PDAC
- A confirmatory phase III trial is worthwhile
- Longer duration of preop chemotherapy warrants investigation

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