Locally advanced pancreatic cancer

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Pancreatic Cancer: Mortality and New Cases

Mortality by Leading Sites* by Sex, United States, 2013 Estimates

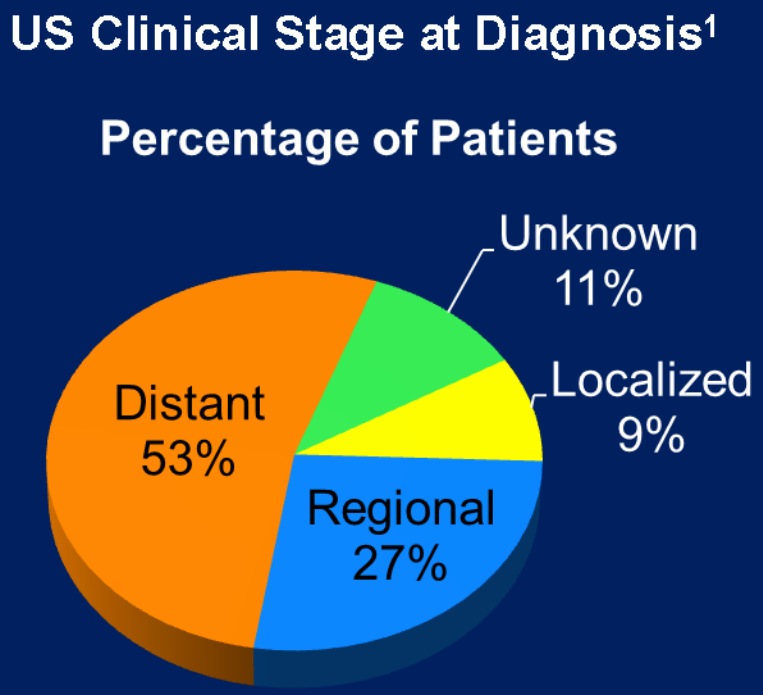
Men		Women	
Lung and bronchus	28%	26%	Lung and bronchus
Prostate	10%	14%	Breast
Colon and rectum	9%	9%	Colon and rectum
Pancreas	**6%**	**7%**	**Pancreas**

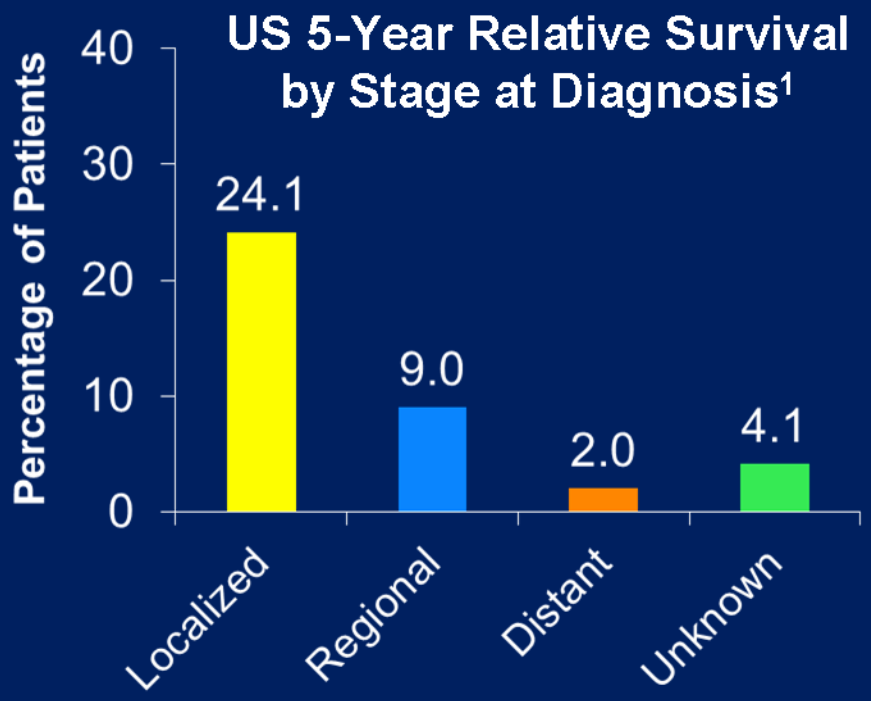
- The 10th most commonly diagnosed cancer and the 4th leading cause of cancer death
  - 44,980 new cases and 38,460 deaths in USA in 2013

*Excludes basal and squamous cell skin cancer, and in situ carcinomas except urinary bladder.
PaC, pancreatic cancer.

1. American Cancer Society. *Cancer Facts & Figures 2013*. Atlanta: American Cancer Society; 2013.

Pancreatic Cancer Survival Rates by Stage

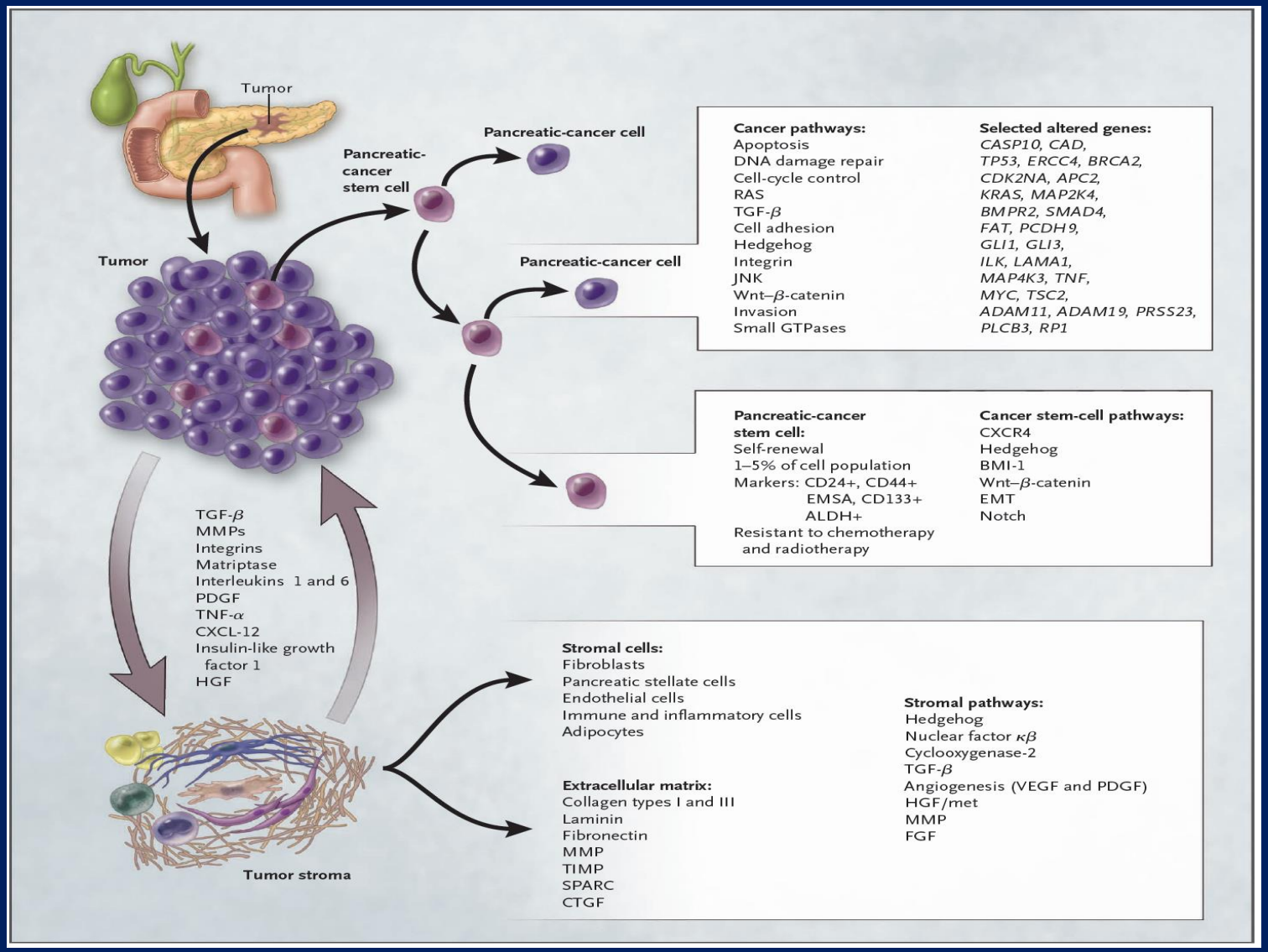




- Majority of patients have inoperable disease at time of diagnosis[1]
  - Only 6% of patients (all stages) survive more than 5 years[1]
- Mortality rates from pancreatic cancer in the United States have slowly increased over the past 10 years[2]

1. SEER cancer statistics. http://seer.cancer.gov/statfacts/html/pancreas.html. Accessed August, 2013. 2. American Cancer Society. *Cancer Facts & Figures 2013*. Atlanta: American Cancer Society; 2013.

Multifaceted Biology of Pancreatic Ductal Adenocarcinoma



M Hidalgo, NEJM 2010

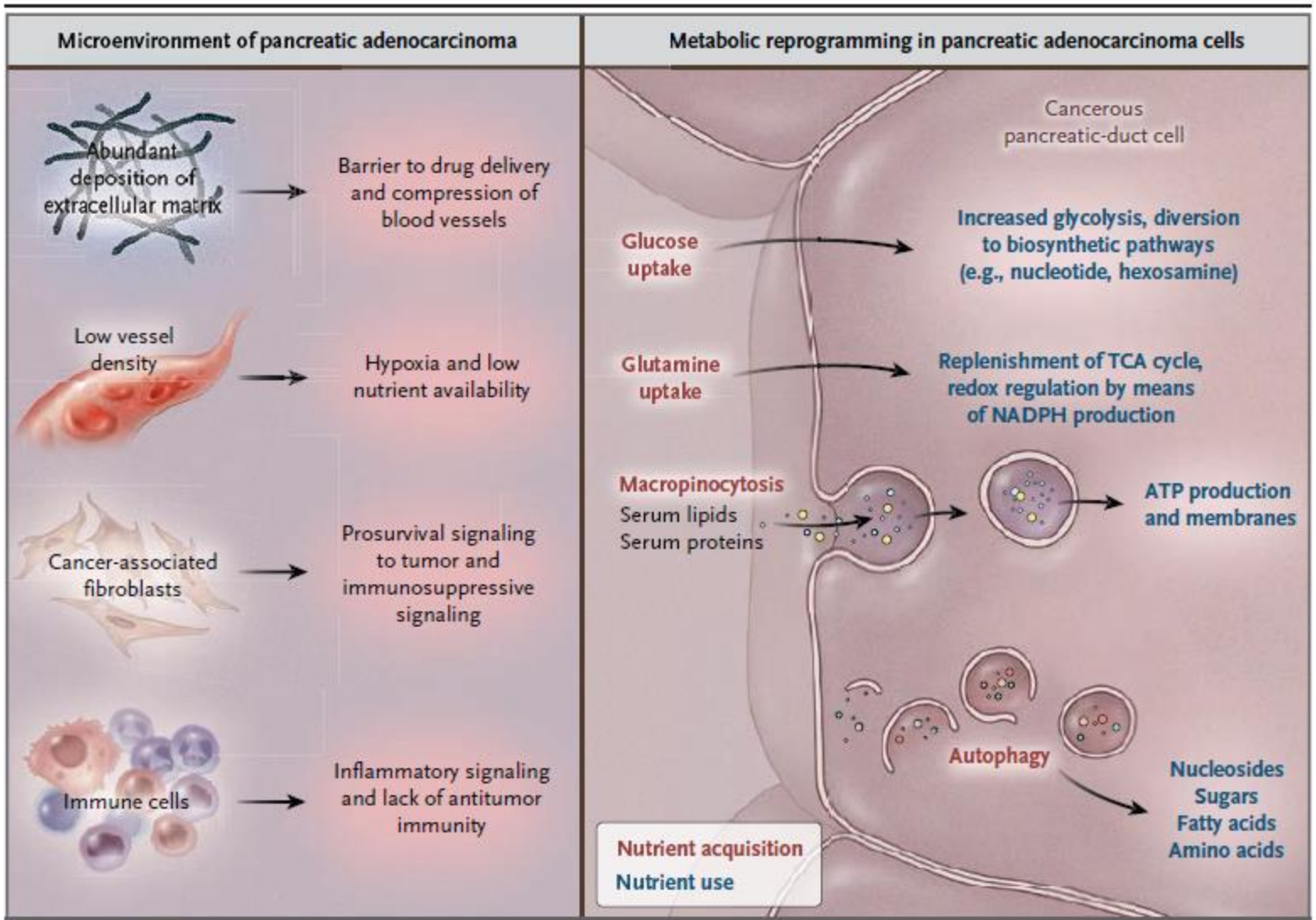


Figure 2. Biologic Features of Pancreatic Cancer.

Pancreatic cancers have a complex microenvironment that might be a target for therapy. TCA denotes tricarboxylic acid.

Ryan D et al. NEJM 2014

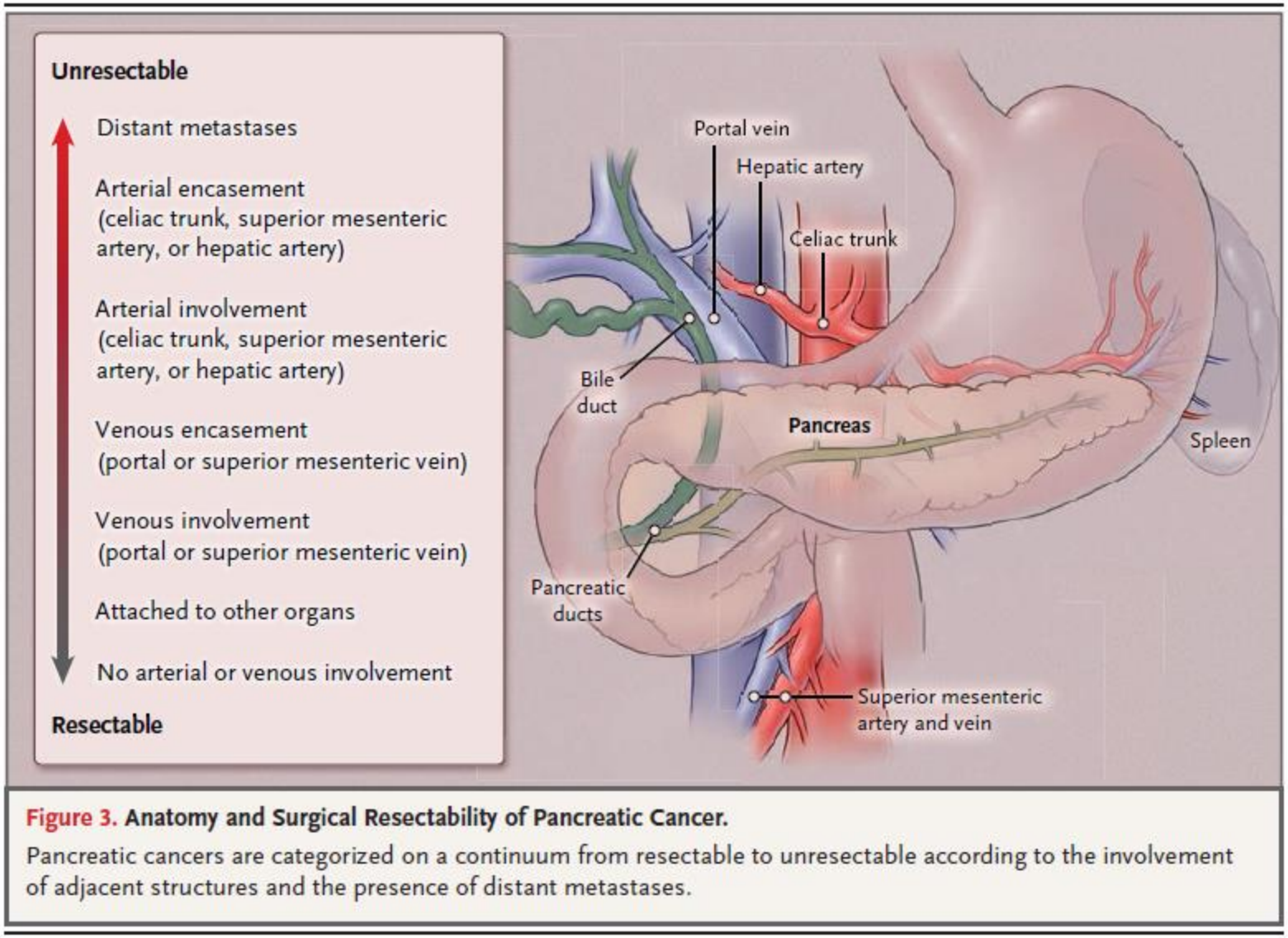


Figure 3. Anatomy and Surgical Resectability of Pancreatic Cancer.

Pancreatic cancers are categorized on a continuum from resectable to unresectable according to the involvement of adjacent structures and the presence of distant metastases.

Ryan D et al. NEJM 2014

Pancreatic adenocarcinoma clinical grouping

- **Metastatic disease**
  - ✓ **Chemotherapy: modest progress**

- **Resectable disease**
- **Borderline resectable disease**
- **Locally advanced, but clearly not resectable disease**

Metastatic pancreatic cancer

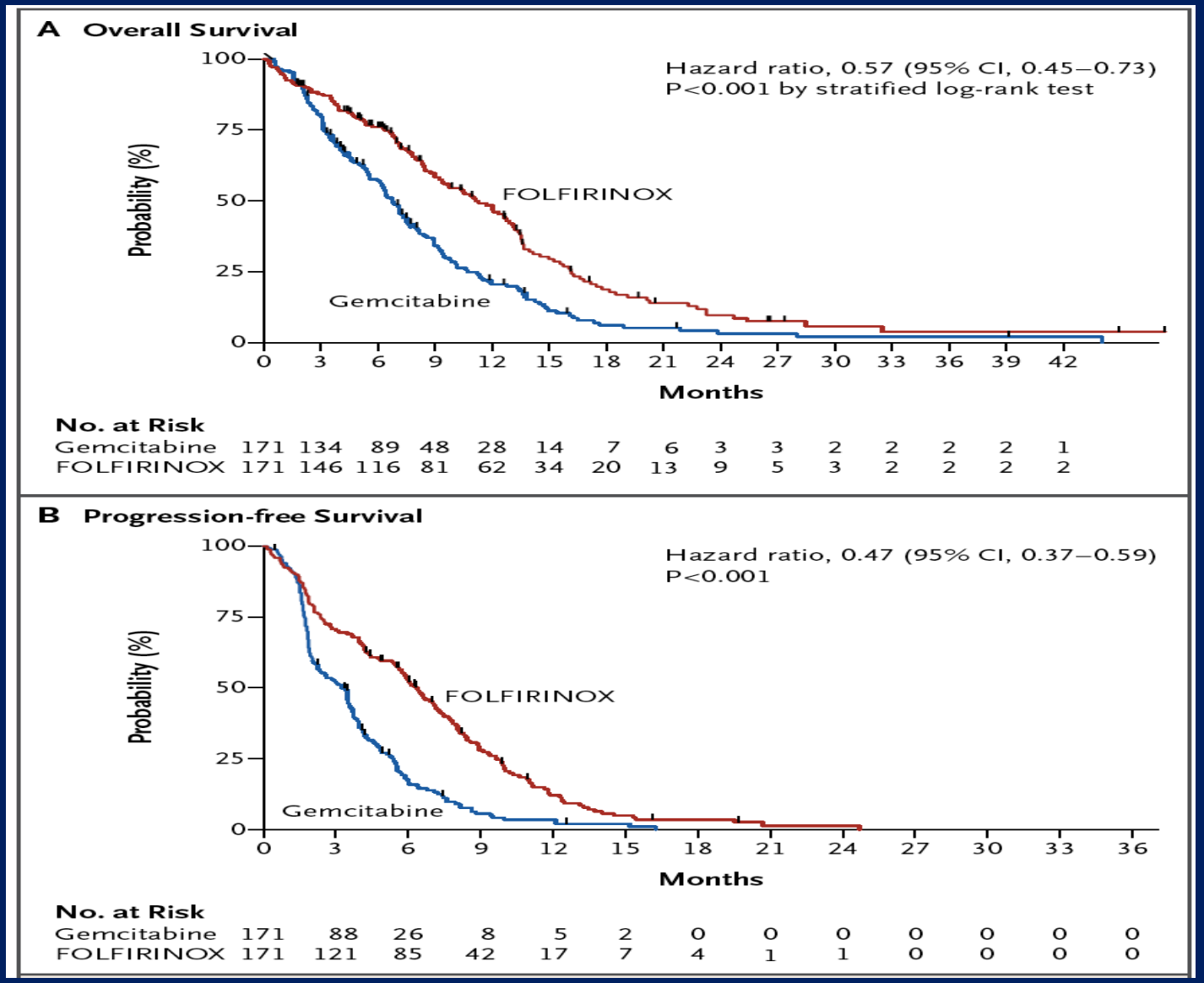
Table 3. Key Clinical Trials in Metastatic Pancreatic Cancer.*

Trial	No. of Patients	Treatment	Median Survival	P Value
			mo	
Burris et al.[70]	126	Fluorouracil Gemcitabine	4.4 5.6	0.002
NCIC[71]	569	Gemcitabine Gemcitabine plus erlotinib	5.9 6.2	0.04
Ueno et al.[72]	834	Gemcitabine S-1	8.8 9.7	<0.001 for non-inferiority
Conroy et al.[73]	342	Gemcitabine FOLFIRINOX	6.8 11.1	<0.001
Von Hoff et al.[74]	861	Gemcitabine Gemcitabine plus nab-paclitaxel	6.7 8.5	<0.001

* FOLFIRINOX denotes fluorouracil, irinotecan, oxaliplatin, and leucovorin; and NCIC National Cancer Institute of Canada.

Ryan D et al. NEJM 2014

ACCORD trial: Gemcitabine vs FOLFIRINOX



Conroy T, et al. N Engl J Med 2011

MPACT Study Design

Planned N = 842

- Stage IV
- No prior treatment for metastatic disease
- KPS ≥ 70
- Measurable disease
- Total bilirubin ≤ ULN
- No age limitation

1:1, stratified by KPS, region, liver metastasis

***nab*-P**
125 mg/m^2 IV qw 3/4
+
Gem
1000 mg/m^2 IV qw 3/4

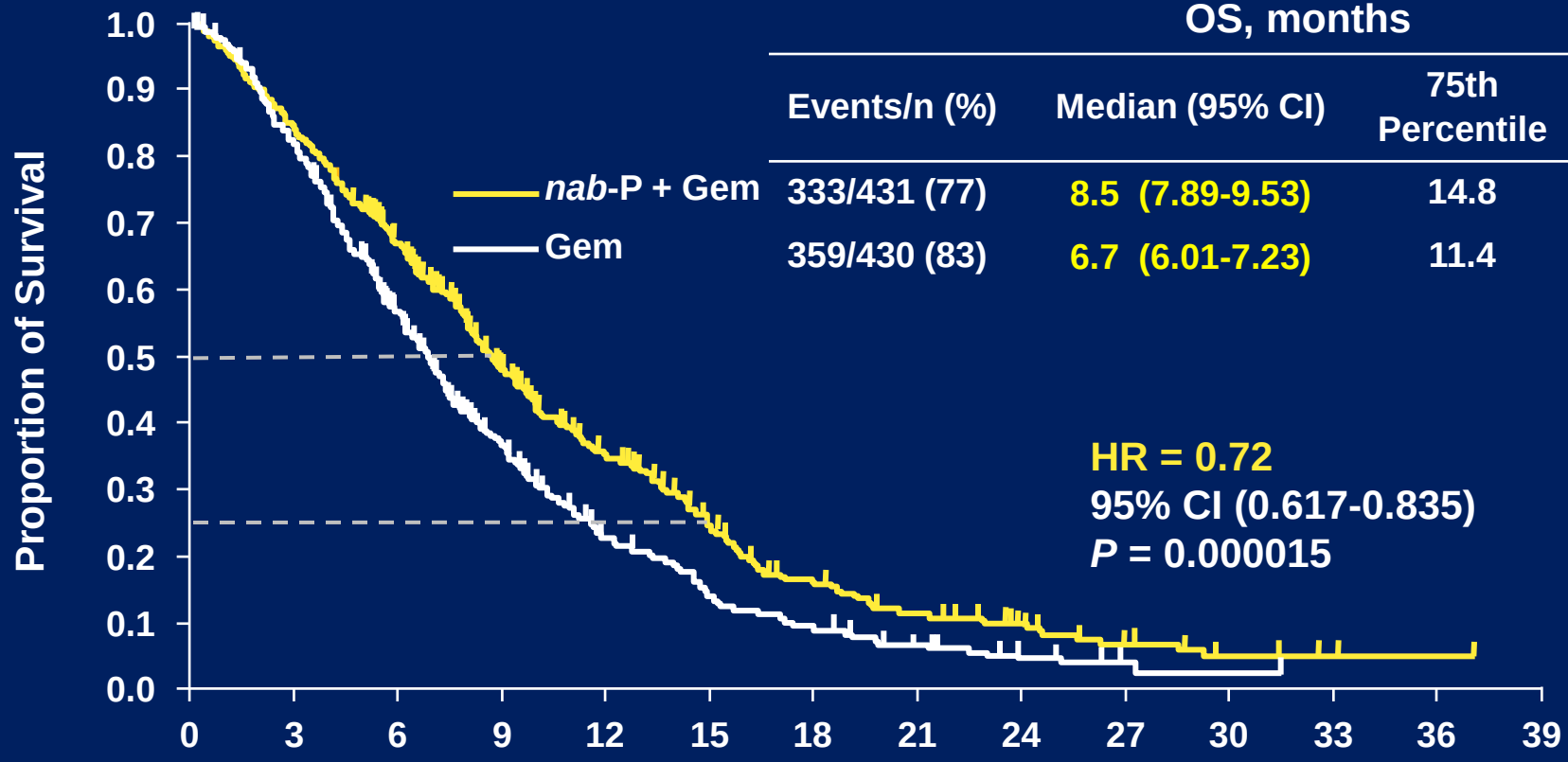
Gem
1000 mg/m^2 IV qw 7/8
then qw 3/4

- ❖ Primary endpoint
  - ✓ OS
- ❖ Secondary endpoints
  - ✓ PFS and ORR by independent review (RECIST)
- ❖ Safety and tolerability
  - ✓ By NCI CTCAE v3.0

- ✓ With 608 events, 90% power to detect OS; HR = 0.769 (2-sided α = 0.049)
- ✓ Treat until progression
- ✓ CT scans every 8 weeks
- ✓ PET scans in an initial cohort of patients at baseline and weeks 8 and 16
- ✓ CA19-9 measurements at baseline and every 8 weeks

Von Hoff D, …Van Cutsem E… et al. N Engl J Med 2013

MPACT trial: Overall Survival



	OS, months		
	Events/n (%)	Median (95% CI)	75th Percentile
nab-P + Gem	333/431 (77)	8.5 (7.89-9.53)	14.8
Gem	359/430 (83)	6.7 (6.01-7.23)	11.4

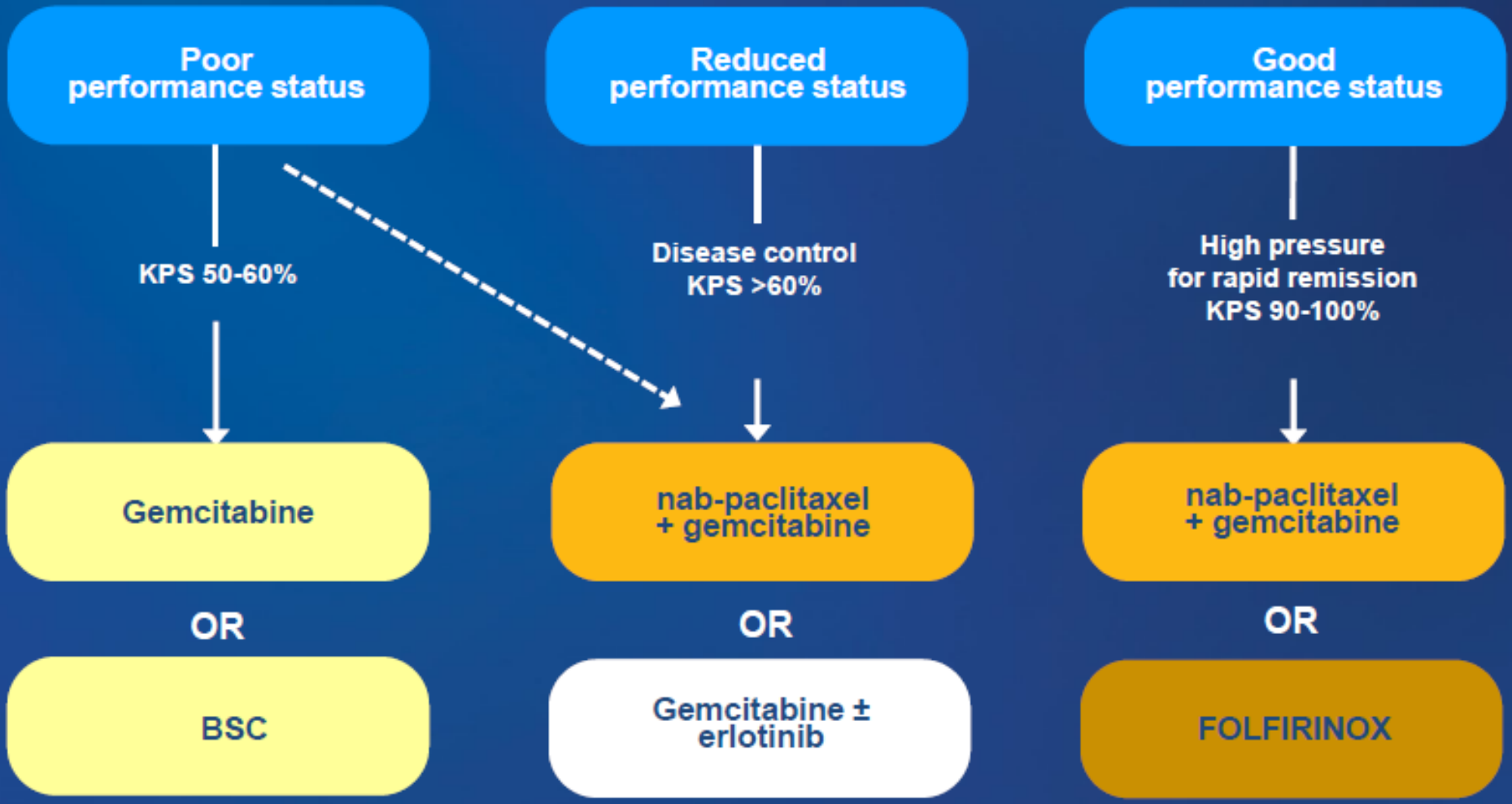
Pts at risk

nab-P + Gem:	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gem:	430	340	220	124	69	40	26	15	7	3	1	0	0	0

- Subsequent therapy: 38% for *nab*-P + Gem and 42% for Gem
- OS censored at time of secondary therapy: 9.4 vs 6.8 months; HR 0.68; *P* = 0.00007
- Trial conclusions not impacted by secondary therapies

Von Hoff D, … Van Cutsem E… et al. N Engl J Med 2013

Suggested treatment algorithm for metastatic pancreatic cancer



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NEWS

Researchers Optimistic About Targeted Drugs for Pancreatic Cancer

Pancreatic adenocarcinoma clinical grouping

- Metastatic disease
- **Resectable disease:**
  - ✓ resection plus adjuvant treatment
- Borderline resectable disease
- Locally advanced, but clearly not resectable disease

Table 2. Adjuvant Therapy for Pancreatic Cancer.*

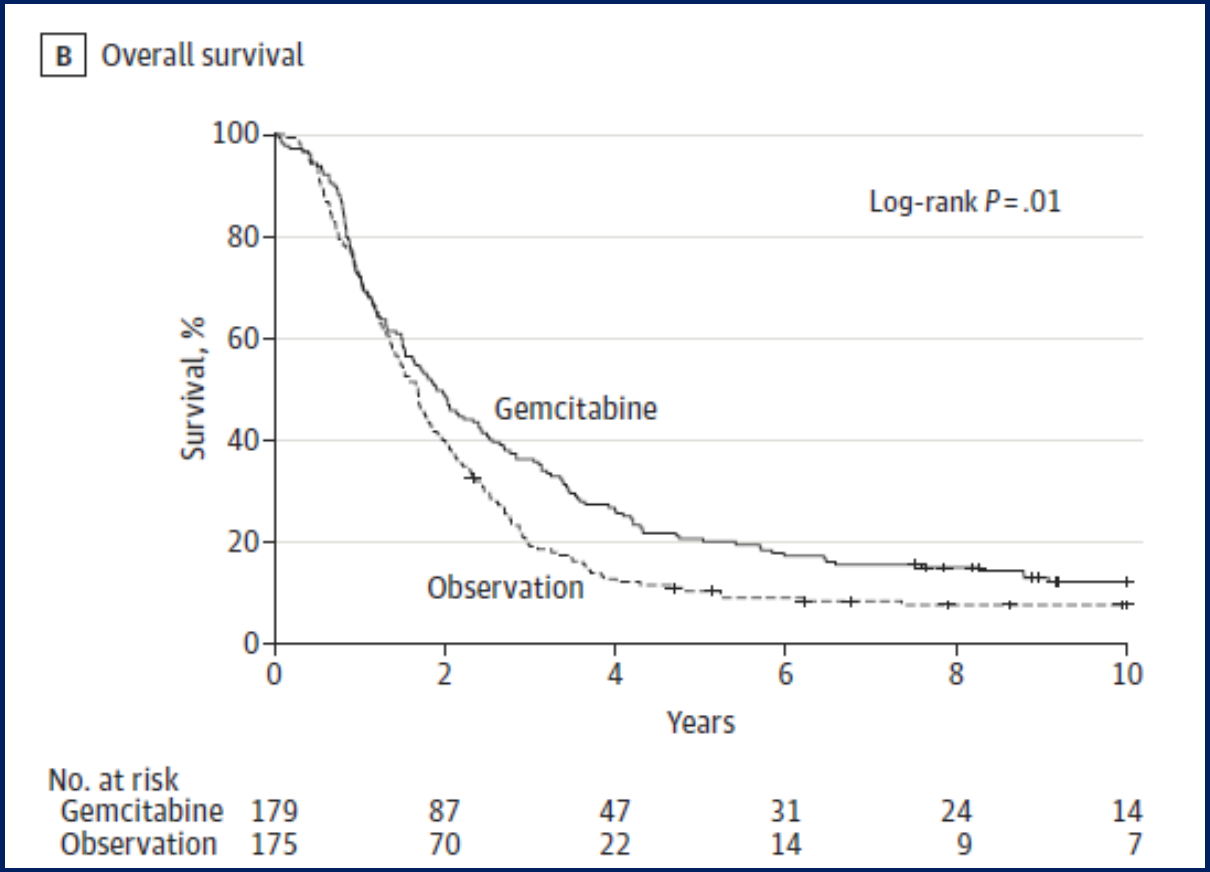
Study	No. of Patients	Treatment	Survival	P Value
GITSG[58]	43	Observation Fluorouracil plus radiotherapy	10% at 2 yr 20% at 2 yr	0.007
EORTC[59]	218	Observation Fluorouracil plus radiotherapy	26% at 2 yr 34% at 2 yr	0.10
ESPAC-1[60]	289	Observation Chemoradiotherapy	16.9 mo (median)† 13.9 mo	
		Fluorouracil Chemoradiotherapy plus fluorouracil	21.6 mo 19.9 mo	
CONKO-01[61]	368	Observation Gemcitabine	10.4% at 5 yr 20.7% at 5 yr	0.01
ESPAC 3[62]	1088	Fluorouracil Gemcitabine	23.0 mo (median) 23.6 mo	0.39
RTOG 9704[63]	451	Fluorouracil plus radiotherapy Gemcitabine plus radiotherapy	22% at 5 yr 18% at 5 yr	0.12
JASPAC-01[64]	378	S-1 (oral fluoropyrimidine) Gemcitabine	70% at 2 yr 53% at 2 yr	<0.001

* CONKO-01 denotes Charité Onkologie 01, EORTC European Organization for Research and Treatment of Cancer, ESPAC European Study Group for Pancreatic Cancer, GITSG Gastrointestinal Tumor Study Group, JASPAC-01 Japan Adjuvant Study Group of Pancreatic Cancer, and RTOG 9704 Radiation Therapy Oncology Group 9704.

† The estimated 5-year survival rate was 10% among patients who received chemoradiotherapy and 20% among patients who did not receive chemoradiotherapy (P=0.05). The 5-year survival rate was 21% among patients who received chemotherapy and 8% among patients who did not receive chemotherapy (P=0.009).

Ryan D et al. NEJM 2014

Adjuvant Gemcitabine After Complete Tumor Resection



- Statistically significant improvement in 5 and 10 year OS rates vs observation

5-year OS: 10.3% improvement (20.7% vs 10.4%)[a]

10-year OS: 4.5% improvement (12.2% vs7.7%)[b]

95% CI for gemcitabine and observation, respectively

[a](95% CI:14.7%-26.6%) vs (95% CI, 5.9%-15.0%)

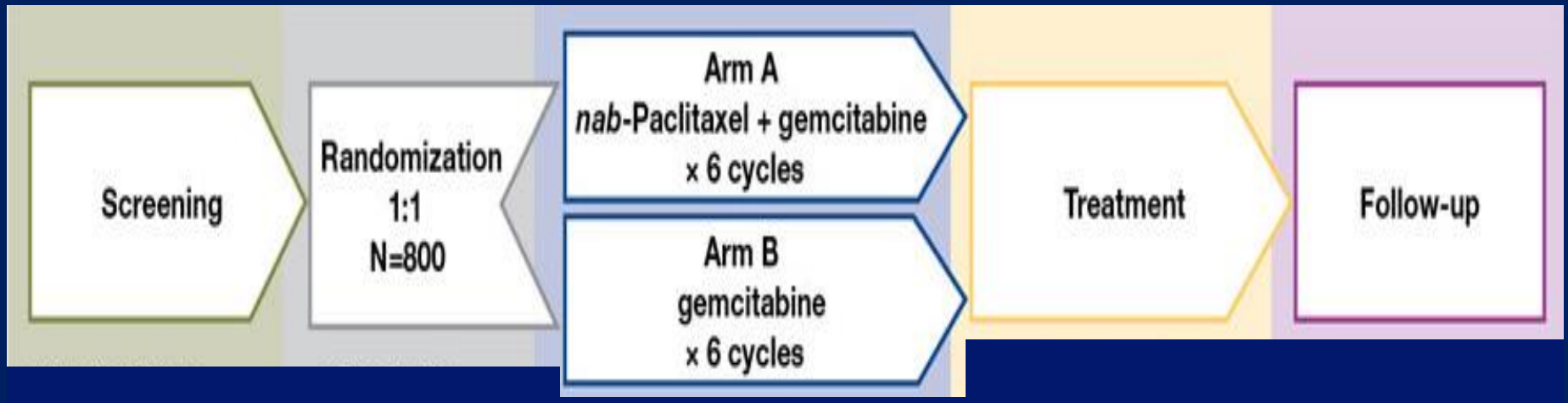
[b](95% CI: 7.3%-17.2%) vs (95% CI: 3.6%-11.8%)

Treatment with adjuvant gemcitabine for 6 months leads to 24% improvement in OS over observation

A phase III trial of *nab*-paclitaxel (*nab*-P) plus gemcitabine (Gem) vs Gem alone for resected pancreatic cancer (PC) is ongoing (APACT trial)[2]

Oettle H et al.. JAMA. 2013;310(14):1473-81. 2. Tempero MA et al. ESMO 2014 abstract

APACT:
Adjuvant Pancreatic Adenocarcinoma Clinical Trial



- **Nab-paclitaxel and Gemcitabine vs Gemcitabine Alone as Adjuvant Therapy for Patients With Resected Pancreatic Cancer[1]**
  - Primary endpoints: Disease Free Survival (DFS)
  - Secondary endpoints: OS, safety and tolerability
  - Exploratory endpoints: molecular profiling of tumours, QoL

1. https://clinicaltrials.gov/ct2/show/NCT01964430?term=nab-paclitaxel+and+pancreatic+cancer&rank=24

Pancreatic adenocarcinoma clinical grouping

- Metastatic disease
- Resectable disease

- **Borderline resectable disease: definition issues**
  - ✓ Neoadjuvant treatment
    - ✓ Chemotherapy
    - ✓ Chemoradiotherapy

- Locally advanced, but clearly not resectable disease

AHPBA (American Hepato-Pancreato-Biliary Association) Consensus Conference Refined the MDACC (MD Anderson) Criteria

- **Includes:**
  - **No distant metastases.**
  - **Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries,**
    - **or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction**

Callery M et al Ann Surg Oncol 2009

AHPBA Consensus Statement II

- **Continued**
  - **Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis**
  - **Tumor abutment of the SMA not to exceed 180° of the circumference of the vessel wall.**

- **Note: Method of assessment: Multidetector CT scan, 2 phases, with 3-dimensional reconstruction**

- **NCCN guidelines use this definition and ESDO accept these criteria**

Callery M, et al Ann Surg Oncol, 2009
Seufflerlein T, Van Cutsem et al, Ann Oncol 2014

Differing Criteria for Borderline Resectable may Produce Different Results

- Recent study of FDR gemcitabine + capecitabine as neoadjuvant therapy (no XRT)
  - Local criteria used: 33 borderline resectable patients and 10 unresectable patients
  - NCCN criteria used: 18 borderline resectable, 25 unresectable
  - By local criteria, 15 BR went to surgery, 13 R0 resections and 1 of 2 UR who went to surgery had R0 resection
  - By NCCN criteria, 11 BR went to surgery, 9 R0 resections and 5 of 6 UR who went to surgery had R0 resection

Lee J-L, et al Surgery 2012, epub ahead of print, June 6

3 Principle Goals of Neoadjuvant Therapy

- Response
  - This may not be RECIST response
  - Needs to “sterilize” the margins
  - Needs to shrink away from the vessels if possible
- Margin free resection
  - All data suggests that margin + resections result in poorer survival outcomes
- Not interfering with surgical outcome
  - Treatment should not cause increased morbidity/increased post-operative complications
  - Treatment should not cause fibrosis/scarring that make the operation more difficult

Combined Analysis of Published Data Shows Low Response Rates

	CR	PR	SD	PD
All patients (n = 330)	1.8%	18.8%	59.2%	18.9%
Resectable (n = 196)	0.8%	9.5%	73.9%	17%
Borderline/unresectable (n =134)	4%	31.8%	40.9%	21.8%

54.2% of all patients underwent resection
65.8% of resectable patients underwent resection
80.6% of these were R0
31.6% of borderline/unesectable patients underwent resection
62.2% of these were R0
All patients received chemo, 85% had chemoxrt

Mura Assifi, et al Surgery 150:466-73, 2011

Combined Analysis Shows We Can Achieve RO Resection

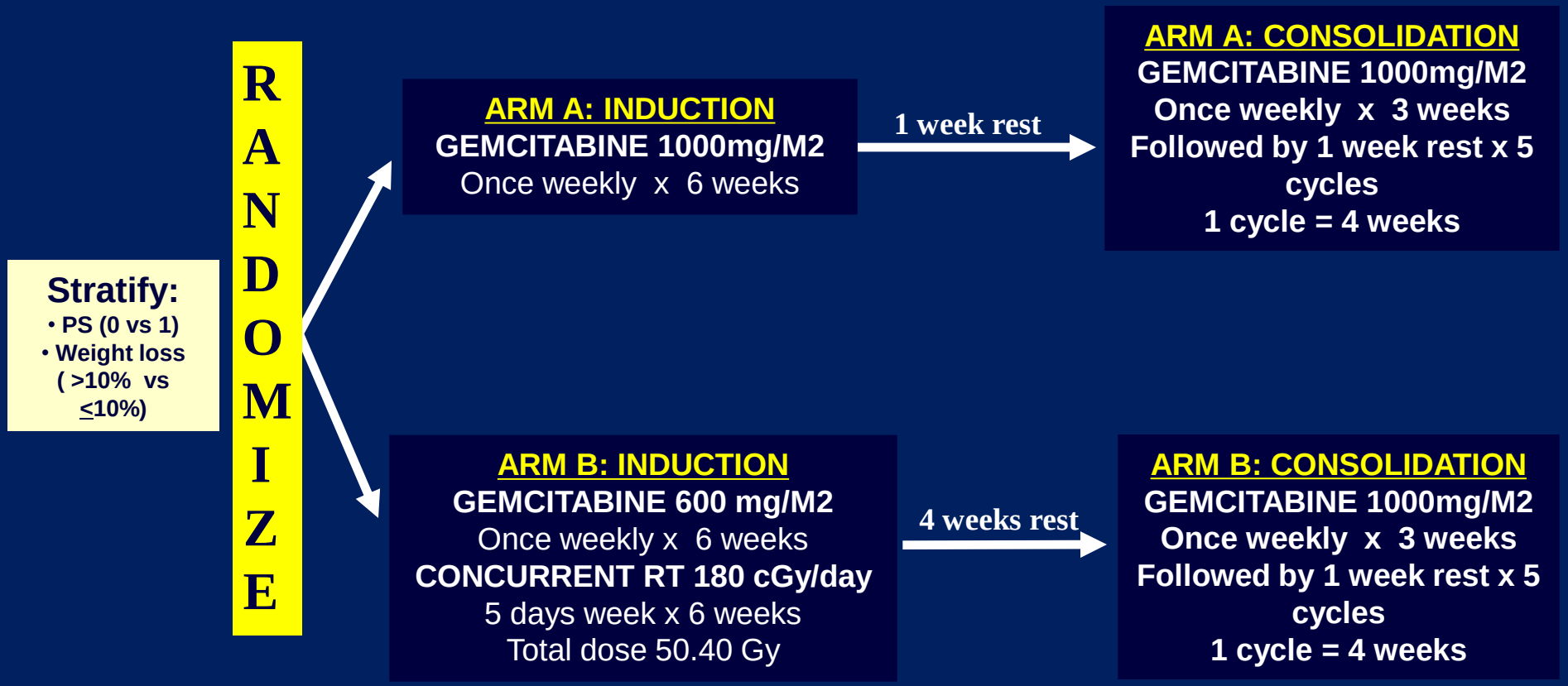
- Suggests that neoadjuvant therapy leads to high R0 resection rate
  - These studies had differing definitions of resectable, borderline and unresectable
  - Intriguingly, borderline and unresectable patients who had resection had the same survival (22.3months) as resectable patients (23 months)
    - Does this suggest our definitions of borderline resectable are just bad on these studies?
  - Did not differentiate chemo from chemoradiation

Mura Assifi, et al Surgery 150:466-73, 2011

Does chemoradiation have a higher response rate than chemo alone?

- Very little evidence of this
- Even in the combined analysis, the definitions of response varied over the years
- Primary pancreatic cancers
  - Appear less responsive than metastases
  - Are difficult to measure even with high quality scans

E4201: Locally Advanced pancreatic Cancer Trial Schema



E4201: Response is the Same for Chemo and ChemoXRT

	GEM alone N = 35	GEM plus XRT N = 34
Partial Resp.	5%	6%
Stable Disease	35%	68%
Progression	16%	6%
Inevaluable*	46%	21%

*** Clinical "progression' without confirmation scans or scans performed outside of scheduled times**

Slide from J Berlin

E4201: But ChemoXRT has More Stable Disease

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Partial Resp.	5%	6%
Stable Disease	35%	68%
Progression	16%	6%
Inevaluable*	46%	21%

*** Clinical "progression' without confirmation scans or scans performed outside of scheduled times**

Slide from J Berlin

E4201: ChemoXRT May Decrease Incidence of Local Relapse

	GEM alone	GEM plus XRT
Local	41%	23%
Distant	14%	23%
Local and Distant	5%	9%
Not documented*	41%	44%

*** Clinical "progression' without confirmation scans or scans performed outside of scheduled times**

Slide from J Berlin

E4201: Conclusions

- Despite no improvement in response or PFS
  - This study appeared to show a modest survival benefit (time was equal to the time patients spent getting radiated)
  - While response was not higher for XRT, local relapse appeared modestly less likely when XRT was used
  - Does not give conclusive evidence of anything as it was underpowered due to poor accrual

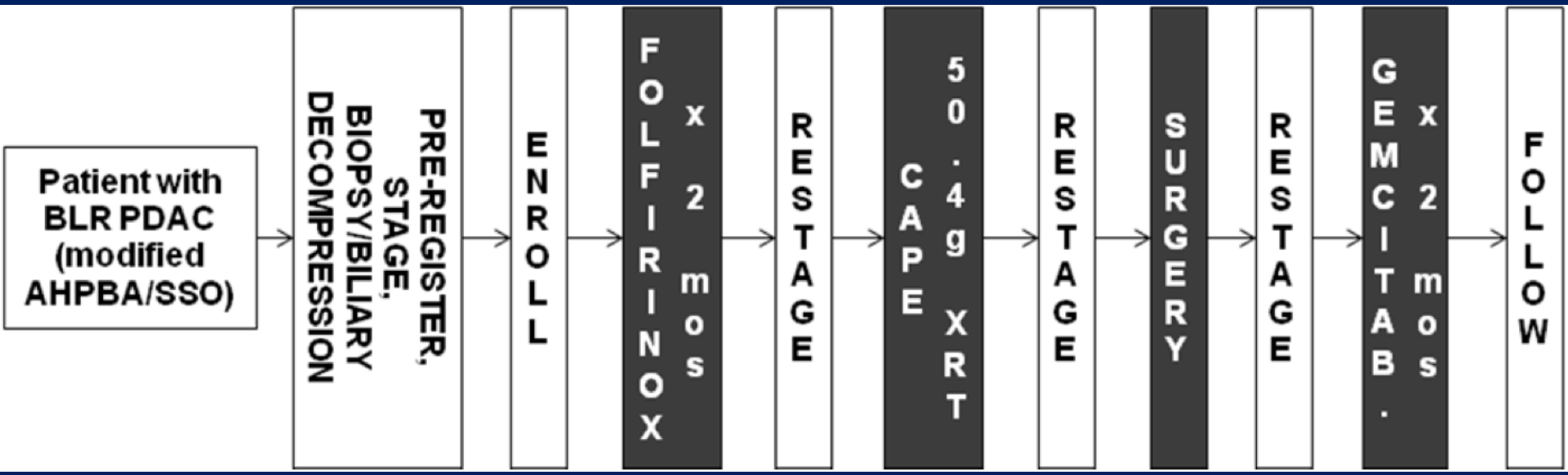
Slide from J Berlin

Can Chemotherapy Before ChemoXRT Provide Better Outcomes?

- 70 patients with borderline (n = 24), or unresectable (n = 46) disease treated with chemoXRT
  - Two strategies
    - ChemoXRT with 50.4Gy (53% unresectable pre-treatment)
    - Chemo (gem based) followed by ChemoXRT if no PD after chemo (83% unresectable pre-treatment)
    - 20% in both strategies had resection
  - The patients who underwent chemo followed by chemoradiation had an improved OS (18.7 vs 12.4 months, p =0.02) compared to chemoXRT alone

Arvold ND, et al Cancer 2012

Alliance A021101 Protocol



Pre-Registration allows for
Biliary decompression
Central review of staging scans (restaging also reviewed centrally)

Alliance A021101 Protocol

- **Endpoints**
  - **Primary:**
    - **Estimate the 1-year overall survival (OS) rate**
  - **Secondary:**
    - **To estimate the rate of treatment-related toxicity during preoperative therapy.**
    - **To estimate the R0 resection rate following preoperative therapy.**
    - **To estimate the rate of radiographic and histopathologic response to preoperative therapy.**
    - **To estimate the time to locoregional and distant recurrence following completion of treatment.**

Treatment For Borderline Resectable or Locally Advanced Unresectable Pancreatic Cancer

Regimen	Stage	Study Design	N	ORR, %	Resection rate, %	R0 resections, %	1-year PFS, %
FOLFIRINOX[1,a]	BL or unresectable	Retro-spective	18	---	39	28	83
FOLFIRINOX[2,a]	laPC	Retro-spective	16	50	---	---	---
FOLFIRINOX[3,a]	laPC or BL	Registry	23	34	---	---	75
FOLFIRINOX[4,a]	laPC or BL	Retro-spective	43	---	54	42	---
FOLFIRINOX[5,a]	BL or unresectable	Phase II	32	37	41	---	---
FOLFIRINOX[6,a]	laPC	Phase II[b]	8	63	37	---	---
Nab-paclitaxel + gemcitabine[7]	BL or resectable	Phase II	16	31[c]	56[d]	89[e]	---

[a]Oxaliplatin-Irinotecan Based Chemotherapeutic Regimen
[b]Sequential regimen including FOLFIRINOX and *nab*-paclitaxel plus gemcitabine
[c]1 complete pathological response and 4 near complete responses (few (<5%) residual tumor)
[d]At the time of the analysis [e]Of patients who had been operated on at the time of the analysis

BL: borderline
laPC: locally advanced pancreatic cancer

1. Hosein PJ et al. *BMC Cancer*. 2012;12: 199 2.Gunturu KS et al. *Medical Oncology*. 2013;30(1): 361 3.Peddi PF et al. *Journal of the Pancreas*. 2012;13(5): 497–501 4. Blazer MA, Wu C, and Goldberg R. *J Clin Oncol* . 2014;32(3): (suppl; abstr 275) 5. Vasile E, de Lio N, and Cappelli C. *J Clin Oncol* . 2013: 31:(suppl; abstr 4062) 6. Kunzmann V et al. *J Clin Oncol* , 2013; 31:(suppl; abstr e15193) 7. Alvarez-Gallego et al. *J Clin Oncol* 2012;30: (suppl; abstr 4040)

ESMO–ESDO Clinical Practice Guidelines

- The only curative treatment of pancreatic cancer is surgical resection[1,2]
- This approach is mainly suitable for patients with early stage of disease mainly stage I and some stage II.[1]
- For borderline resectable disease, neoadjuvant chemotherapy or CRT is recommended, if R0 resection is possible[2]
- Multidisciplinary approach is paramount in assessing resectability[2]
  - Surgeon, radiologist, oncologist, gastroenterologist and radiotherapist

1. Seufferlein T…V an Cutseml. Annals of Oncology 2012 2.Seufferlein T …Van Cutsem E. Annals of Oncology 2014;25(2):ii1-ii4

Borderline Resectable Conclusions

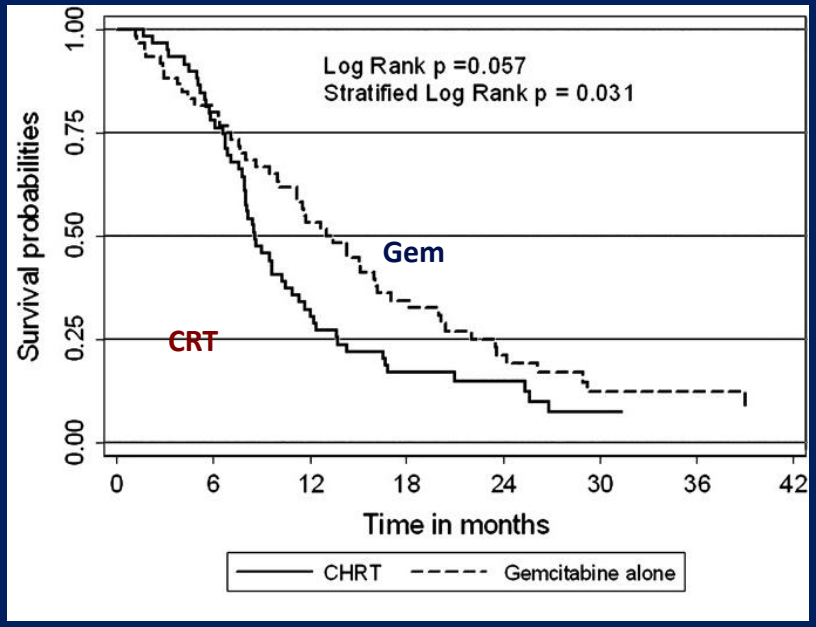
- We need to establish more standards for this category
  - Pathology
  - Surgery
  - Radiology
  - Treatment choice
- These definitions need to truly separate borderline unresectable from truly unresectable patients
- Standard of care is not clearly defined
  - More intense chemotherapy or chemoradiotherapy

Pancreatic adenocarcinoma clinical grouping

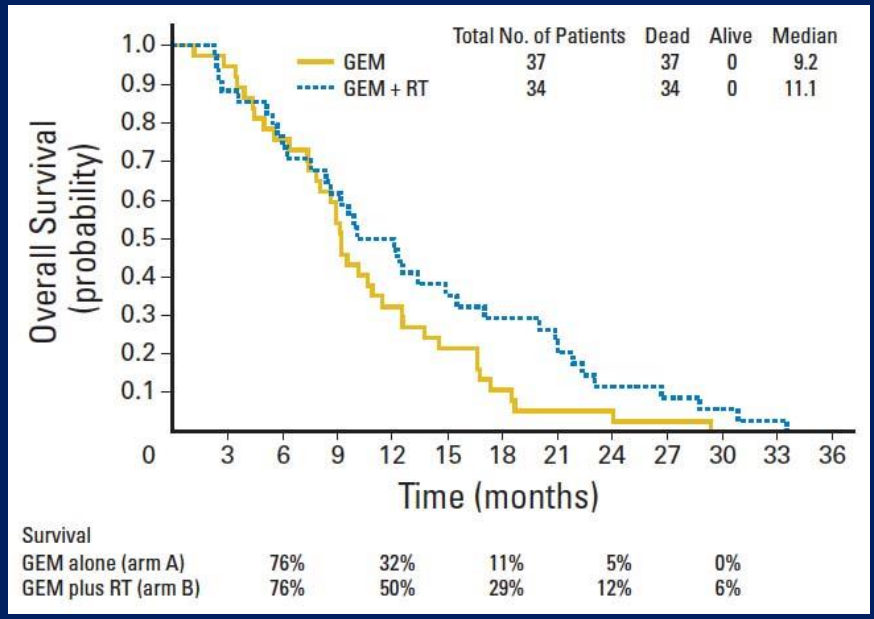
- Metastatic disease
- Resectable disease
- Borderline resectable disease

- Locally advanced, but clearly not resectable disease

Frontline CRT versus chemotherapy in LAPC



Chauffert B et al. Ann Oncol 2008

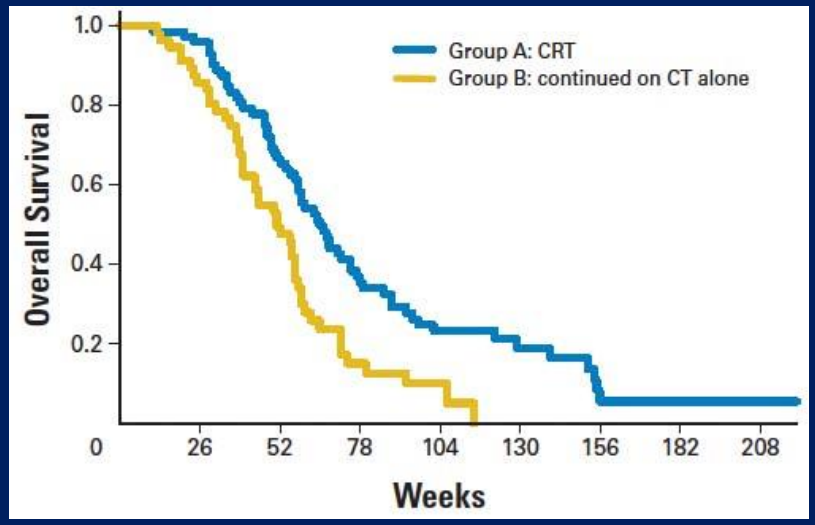


Loehrer P et al. J Clin Oncol 2011

→ **Contradictory** results

Induction CT followed by CRT in LAPC

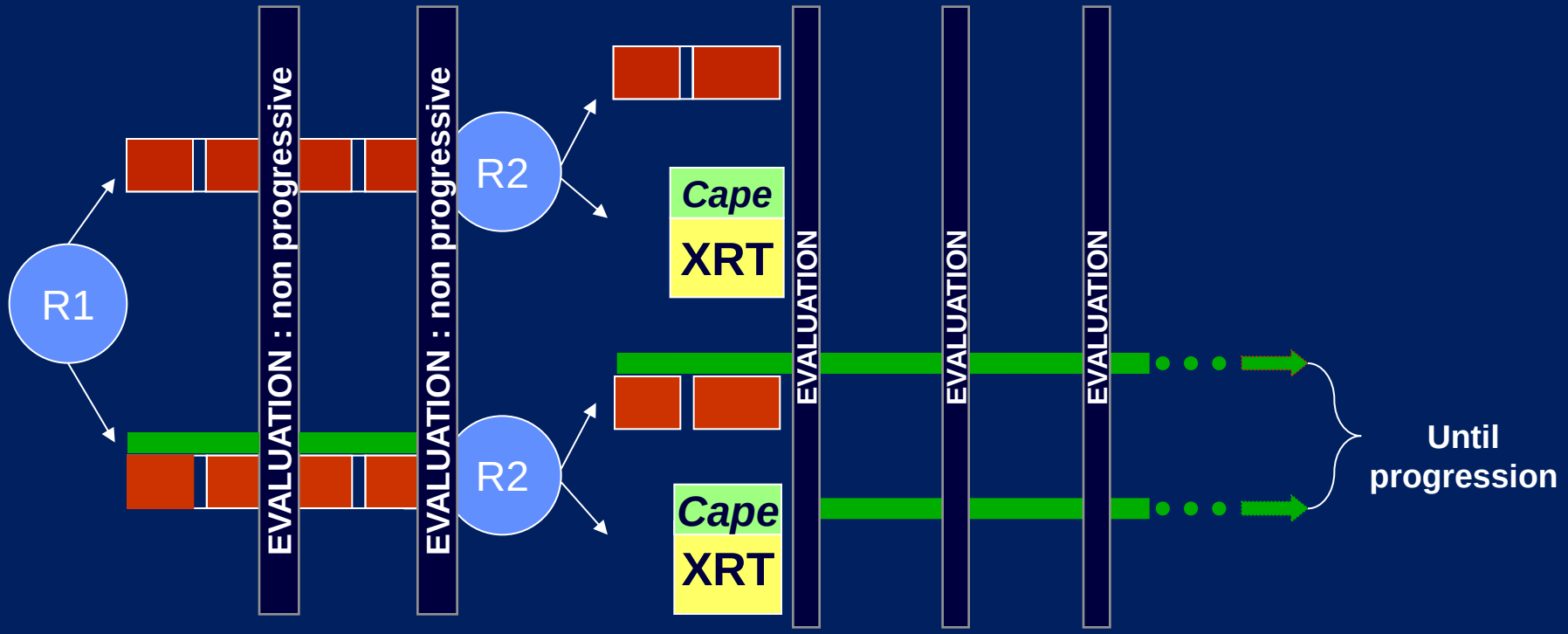
CRT after 3 months of induction chemotherapy



Huguet F et al, J Clin Oncol 2007

→ **Promising** strategy

LAP07 study



1 month = Gemcitabine (1000 mg/m²)/wkX3

Erlotinib : 100 mg/d with gem
150 mg/d as single agent

Cape
XRT

Capecitabine plus radiation
Quality assurance

Secondary surgery allowed at any time

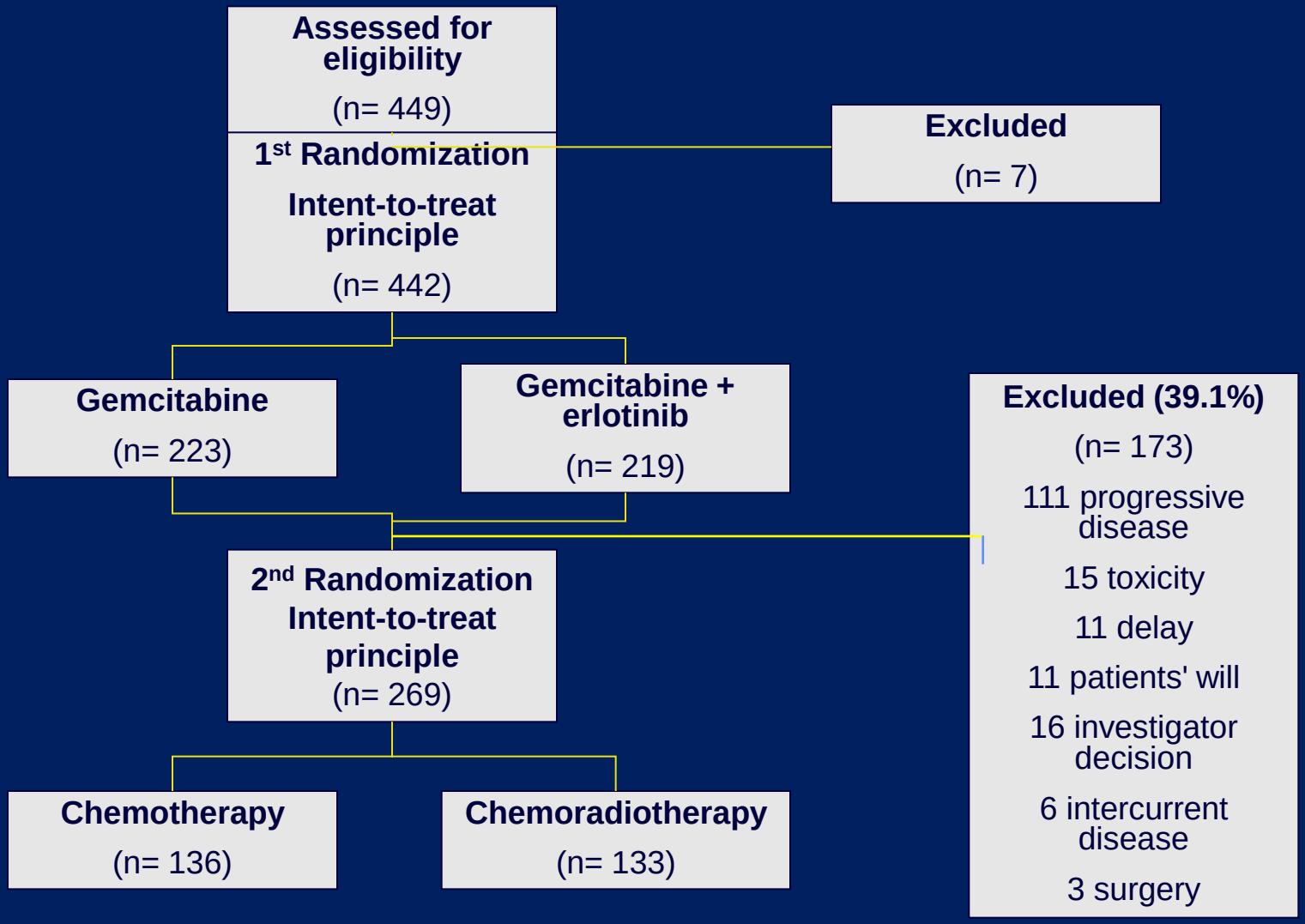
Objectives of LAP07 study

- **Primary objective**: to assess whether administering CRT increases overall survival in patients whose tumor is controlled after 4 months of induction chemotherapy

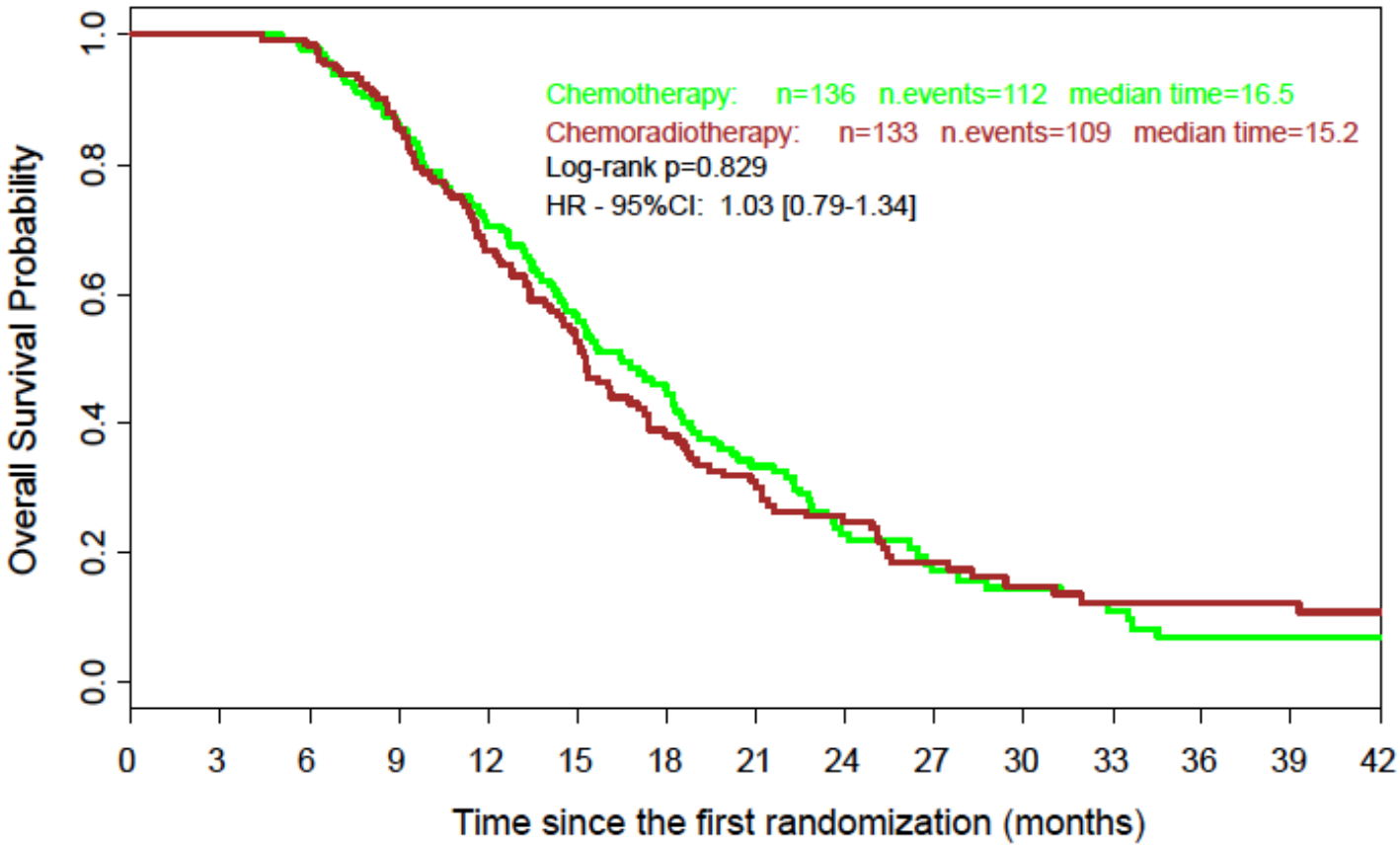
- **Secondary objectives:**
  - Role of erlotinib
  - Progression free survival (PFS)
  - Tolerance
  - Impact of Radiation Therapy Quality Assessment (RTQA)[1]
  - Predictive molecular markers, circulating tumor cells[2]

[1] Huguet F et al. ASTRO 2013; [2] Bidard FC et al. Ann Oncol 2013

LAP 007: Flow Chart



LAP 007: Overall Survival



N at risk

Chemotherapy	136	136	133	117	94	70	55	39	24	14	12	8	4	4	4
Chemoradiotherapy	133	133	131	113	87	66	45	34	26	18	12	9	9	8	6

LAP-007: Site of progression

- **R2 patients**:

236/269 patients (88%) with tumor progression

93 with local progression only (39.4%)

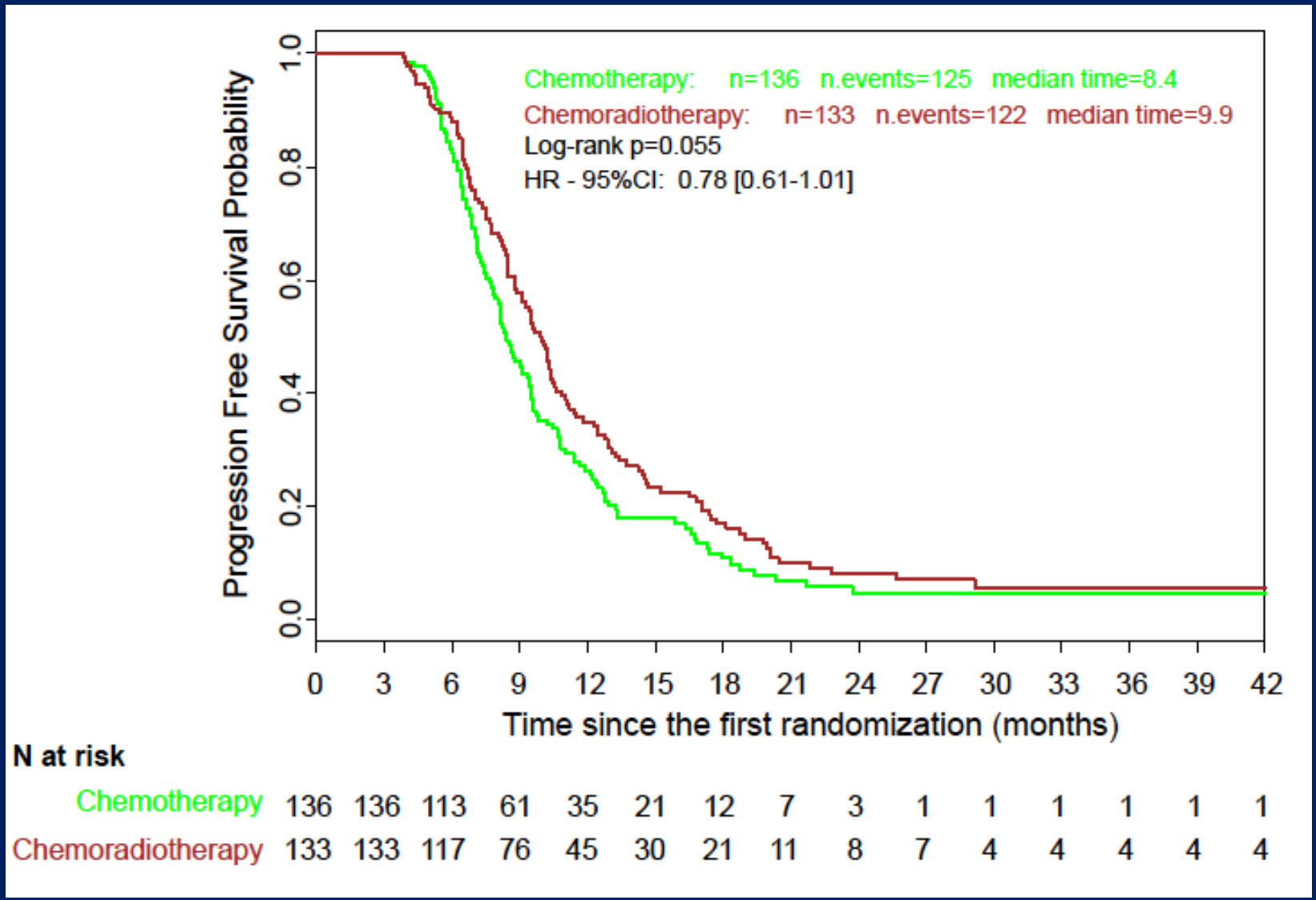
122 with metastatic (± local) progression (51.7%)

21 unknown (8.9%)

	Chemotherapy (n= 125)	Chemoradiation (n= 111)
LA	58 (46%)	35 (32%)
M+	55 (44%)	67 (60%)
unknown	12 (10%)	9 (8%)

p=0.035

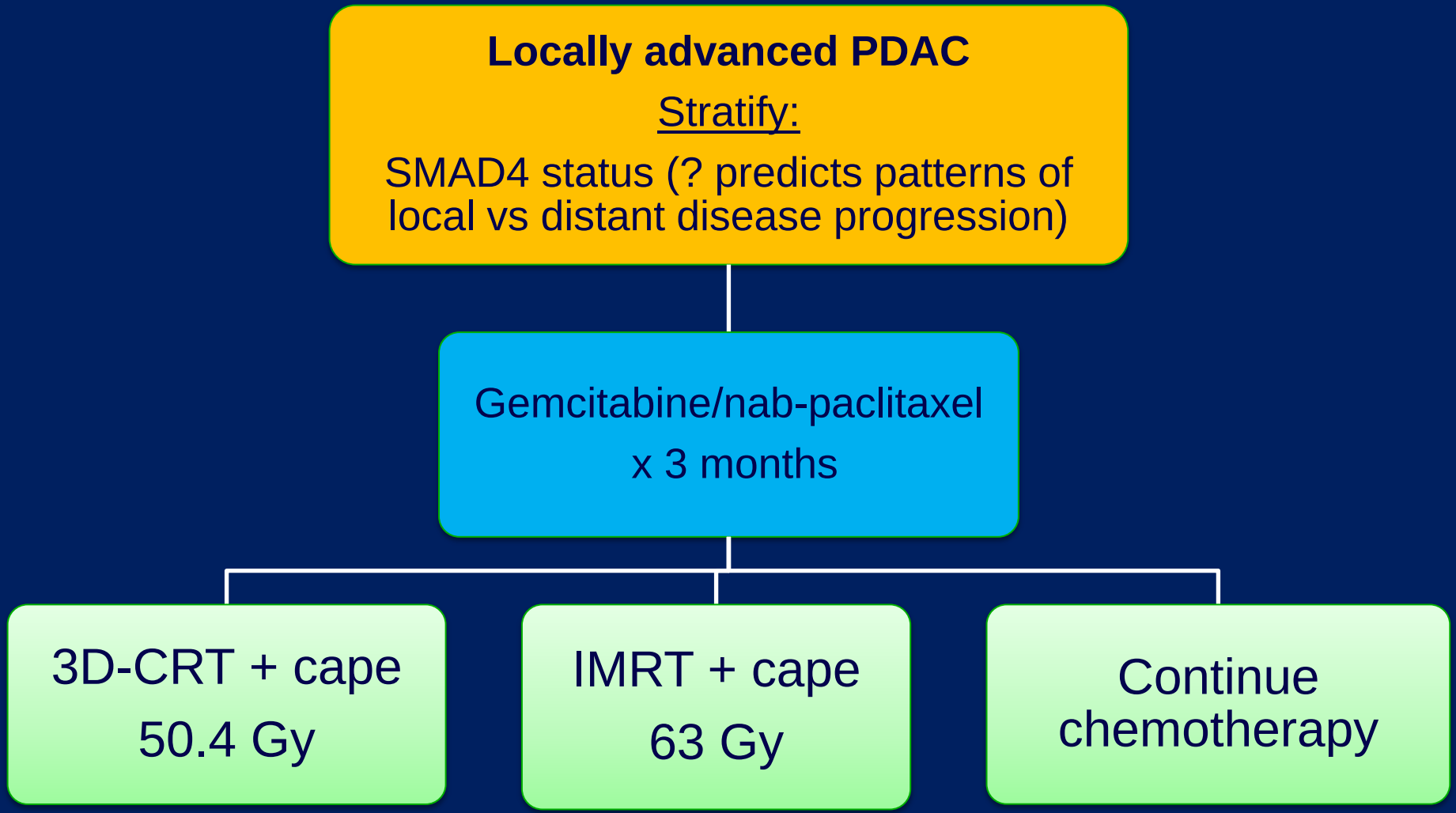
LAP-007: Progression Free Survival



LAP07 Conclusions

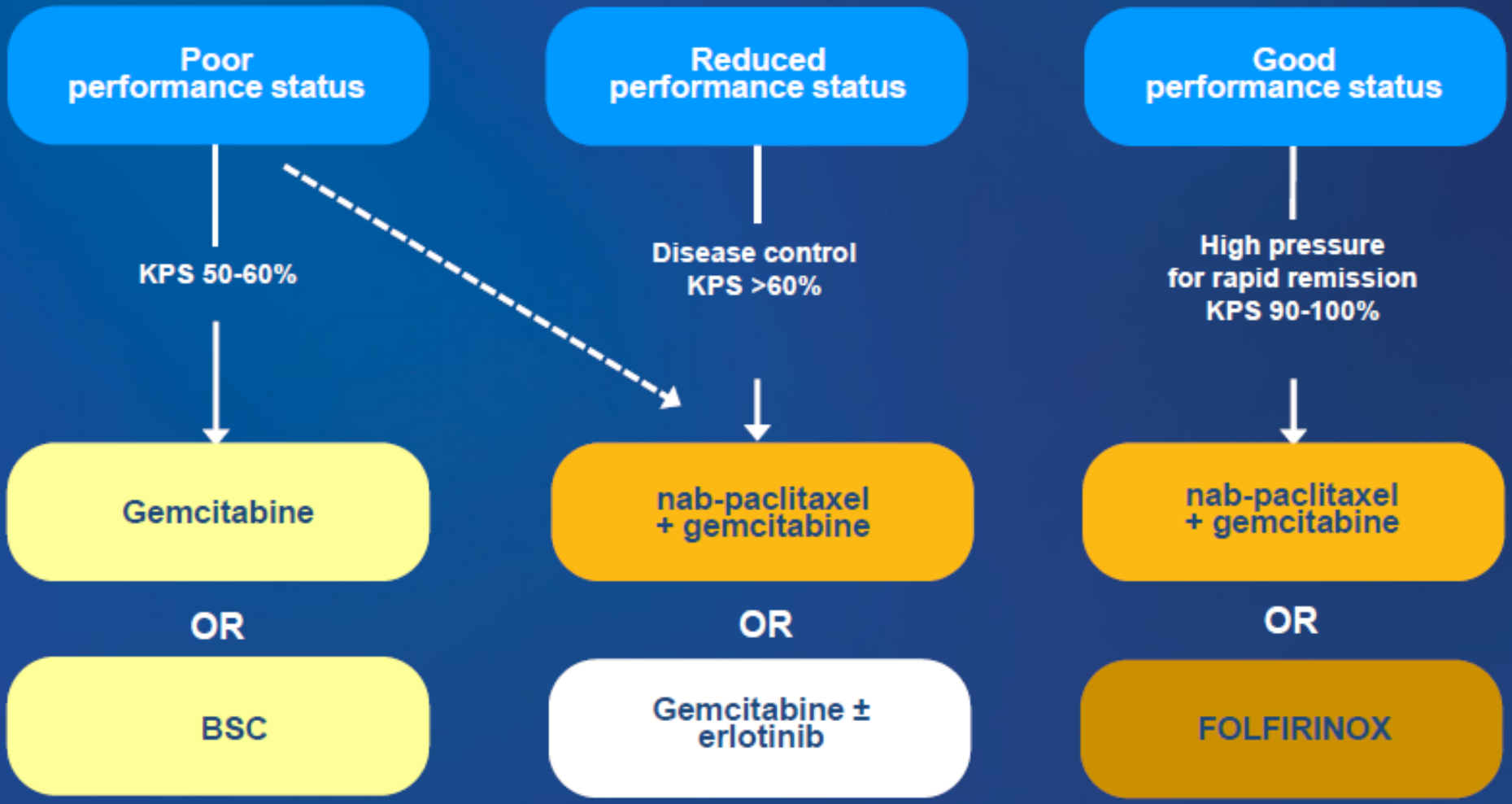
- LAP07 prospectively confirmed the value of frontline chemotherapy in LAPC patients
- Overall survival in CRT arm is not superior to chemotherapy arm in LAPC patients with tumor controlled after 4 months of chemotherapy
- However, trend for PFS in favor of CRT
- In the CRT arm, patients had a significantly less local tumor progression and a longer period without chemotherapy

RTOG 1201 will help address the question of whether more effective chemotherapy impacts the role of radiation in locally advanced disease



(P.I.: Christopher Crane, MD Anderson)

Suggested treatment algorithm for metastatic pancreatic cancer



Pancreatic adenocarcinoma clinical grouping

- Metastatic disease
- Resectable disease
- Borderline resectable disease
- Locally advanced, but clearly not resectable disease

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