Pancreas Cancer: Borderline/Advanced

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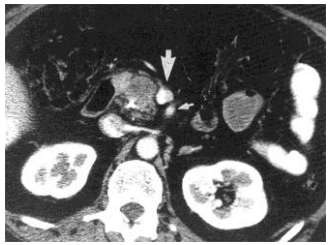
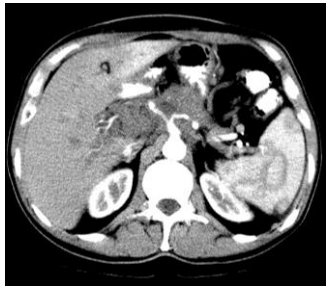
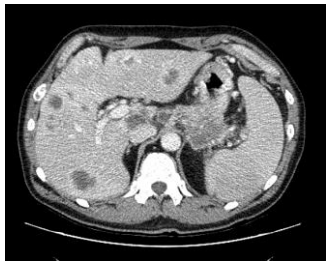
Questions

- Patient Selection
- How often are we missing occult micrometastatic disease at the time of initial diagnosis?
- Role of staging laparoscopy.
- What systemic agents should be used (before/during/after radiation)?

Pancreatic Cancer by Stage (SEER Database)

Stage Classification	Proportion	5-Yr Survival
Resectable 	18%	22%
Borderline or unresectable 	27%	9%
Metastatic 	53%	2%

Siegel R, et al. CA Cancer J Clin. 2012;62:10-29.

Role of Laparoscopy

Occult Mets in Locally Advanced Disease

Upstage by laparoscopy:

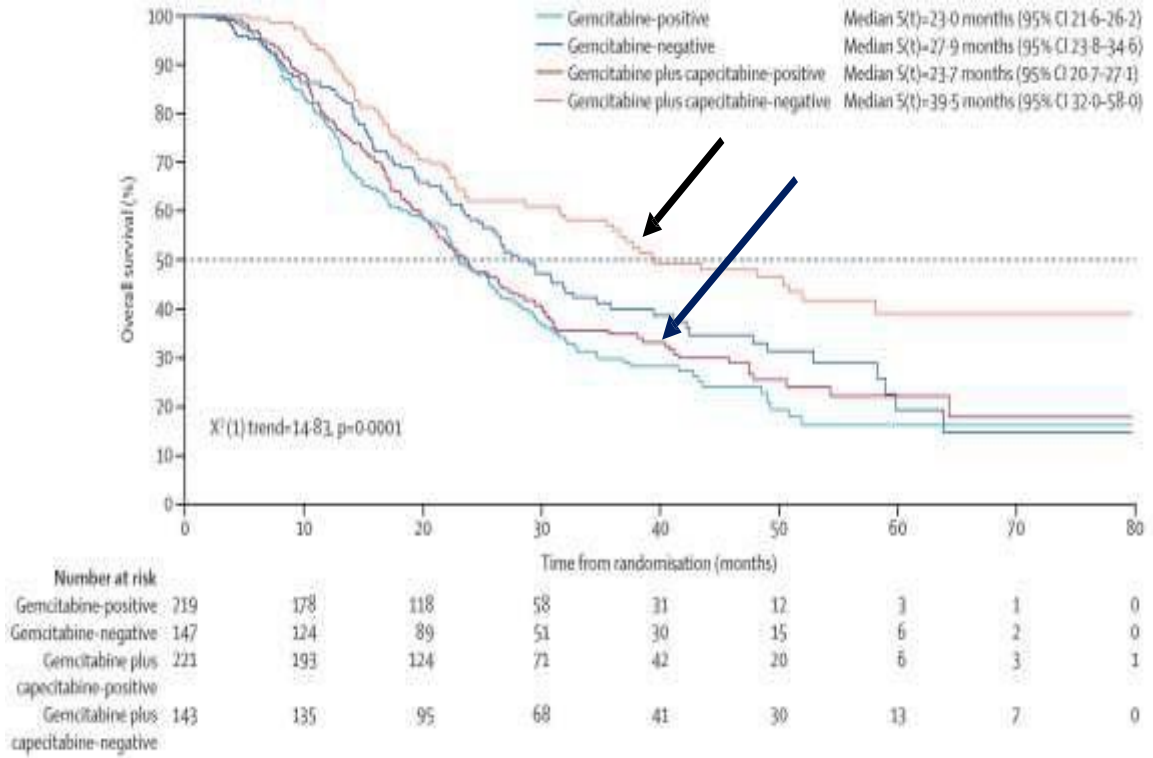
Author/ year	n LAD radiology	Laparoscopy: + Mets
Shoup/ 2004	100	37%
Liu/ 2005	70	34%
White/2001	55	24%

About 30% of pts diagnosed with LAD have mets by laparoscopy

M. Shoup. J Gastrointest Surg 8(8):1068-71, 2004
R. Liu. Surg Endosc 19:638-642, 2005
R. White. J Gastrointest Surg 6: 626-633, 2001

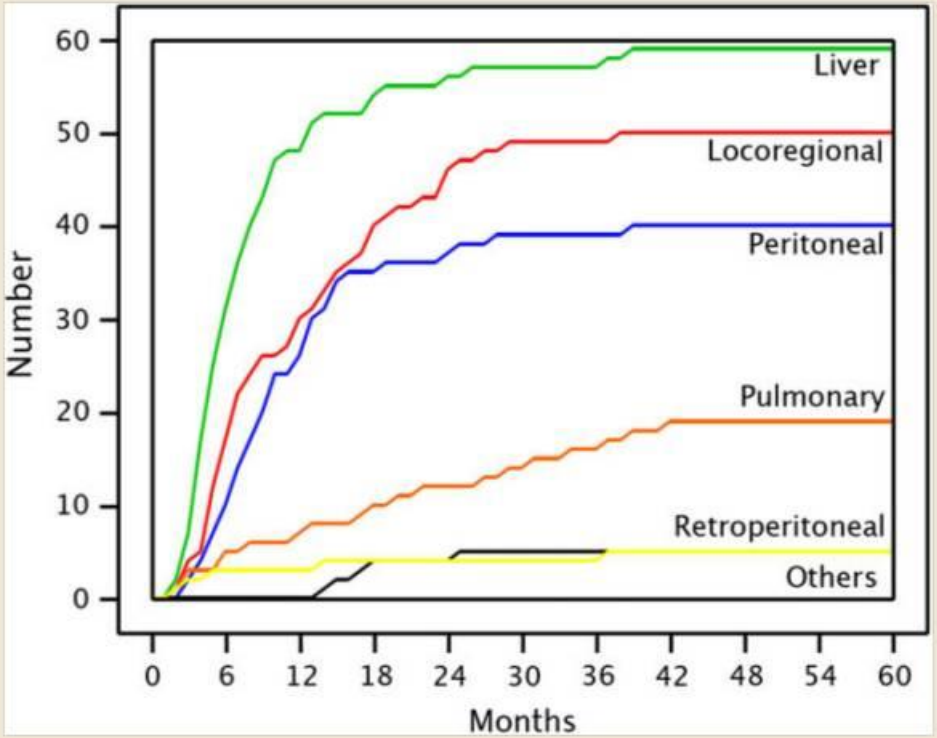
R-STATUS AND SURVIVAL

- Adjuvant combination chemotherapy performs less well in patients with positive resection margins
- Downsizing as a strategy



Neoptolemos et al., The Lancet 2017

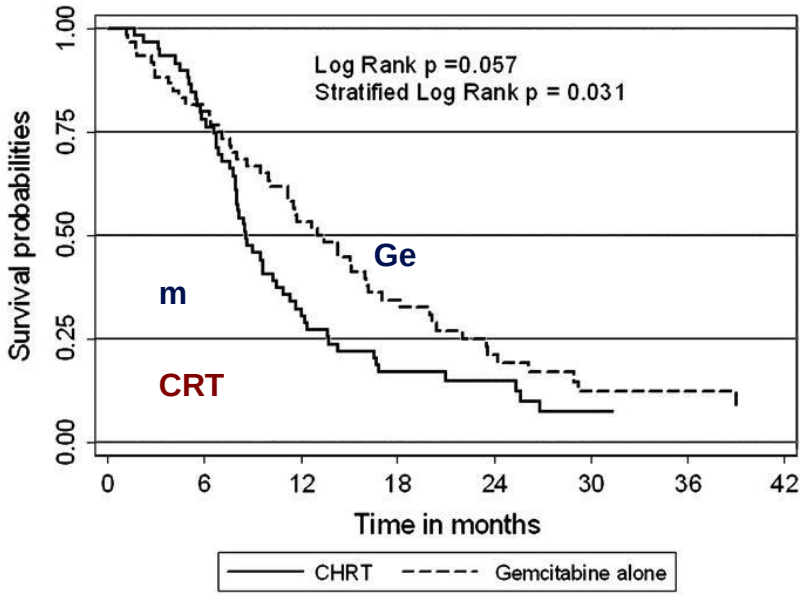
Occult Microscopic Disease



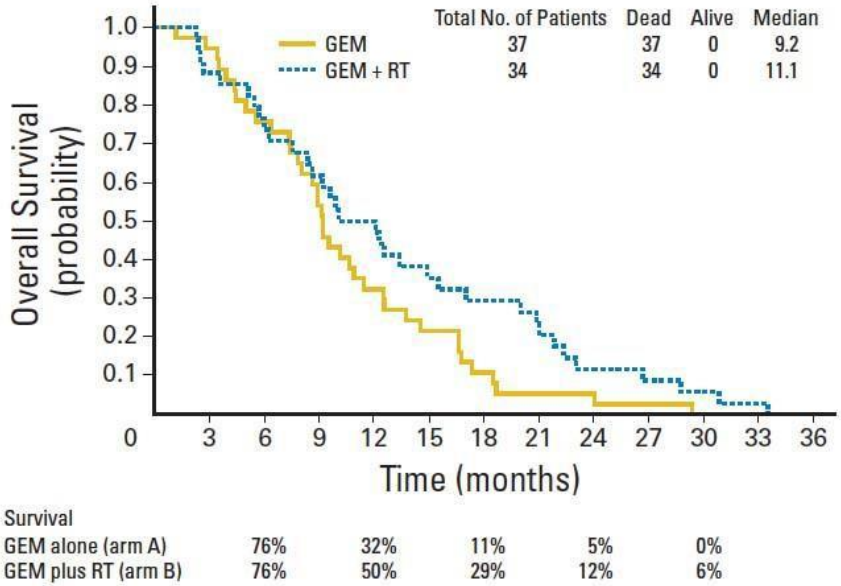
80% of patients recur – even those s/p R0 resection

Van den Broeck, E J Surg Onc 2009

Frontline CRT versus chemotherapy in LAPC



Chauffert B et al. Ann Oncol 2008



Loehrer P et al. J Clin Oncol 2011

→ **Contradictory** results

CT-CRT IN ADVANCED PAN CA

Authors	Treatment	N pts	PFS (months)	OS (months)	1-year survival (%)
Huguet (retrosp)	CT	181	7.4	11.7	47.5
	CT then CRT		10.8	15	65.3
Krishnan (retrosp)	CRT	323	4.2	8.5	-
	CT then CRT		6.4	11.9	
Brunner (retrosp)	CRT	172	-	7.6	21
	CRT then CT			13.5	65
Ko (phase 2)	CT then CRT (32% PD after CT)	25	10.5 (12.7)	13.5 (17)	62
Schneider (phase 2)	CT - CRT - CT	18	-	12.8	-

Concurrent chemotherapy

SCALOP
(phase 2)

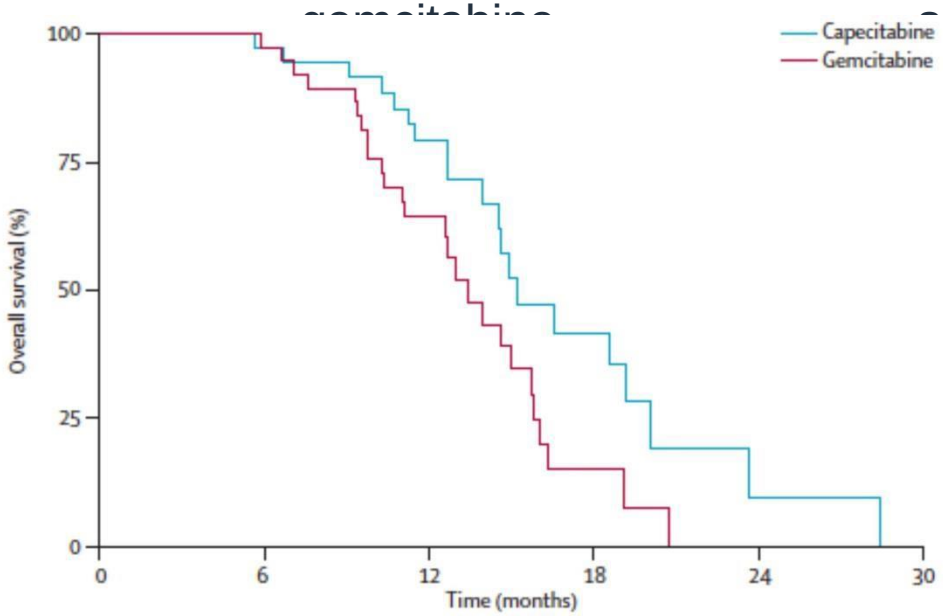
74 pts

Gem-Cap x 3

R

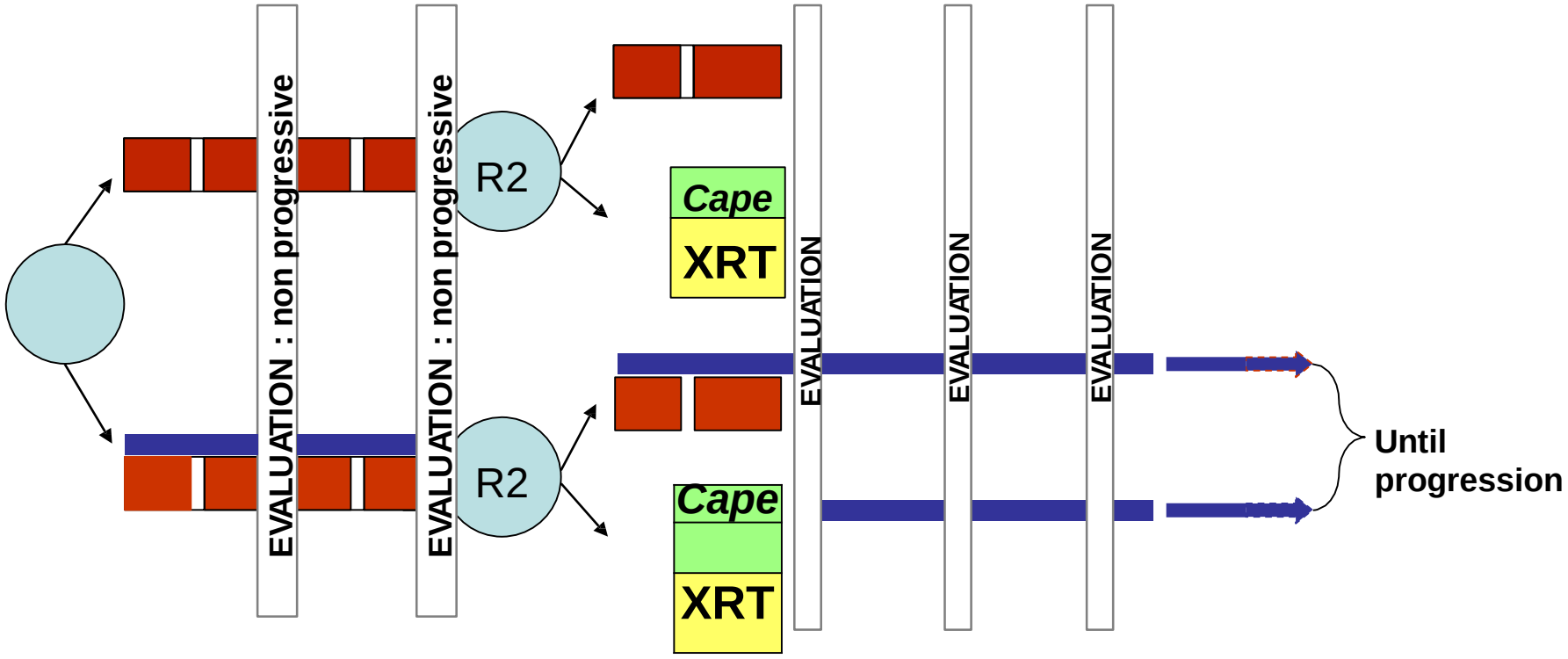
- CRT 50.4 Gy with capecitabine — 15.2 months
- CRT 50.4 Gy with [illegible] — 13.4 month[illegible]

p= 0.01



Mukherjee S *et al.* Lancet Oncol 2013

LAP07 study



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

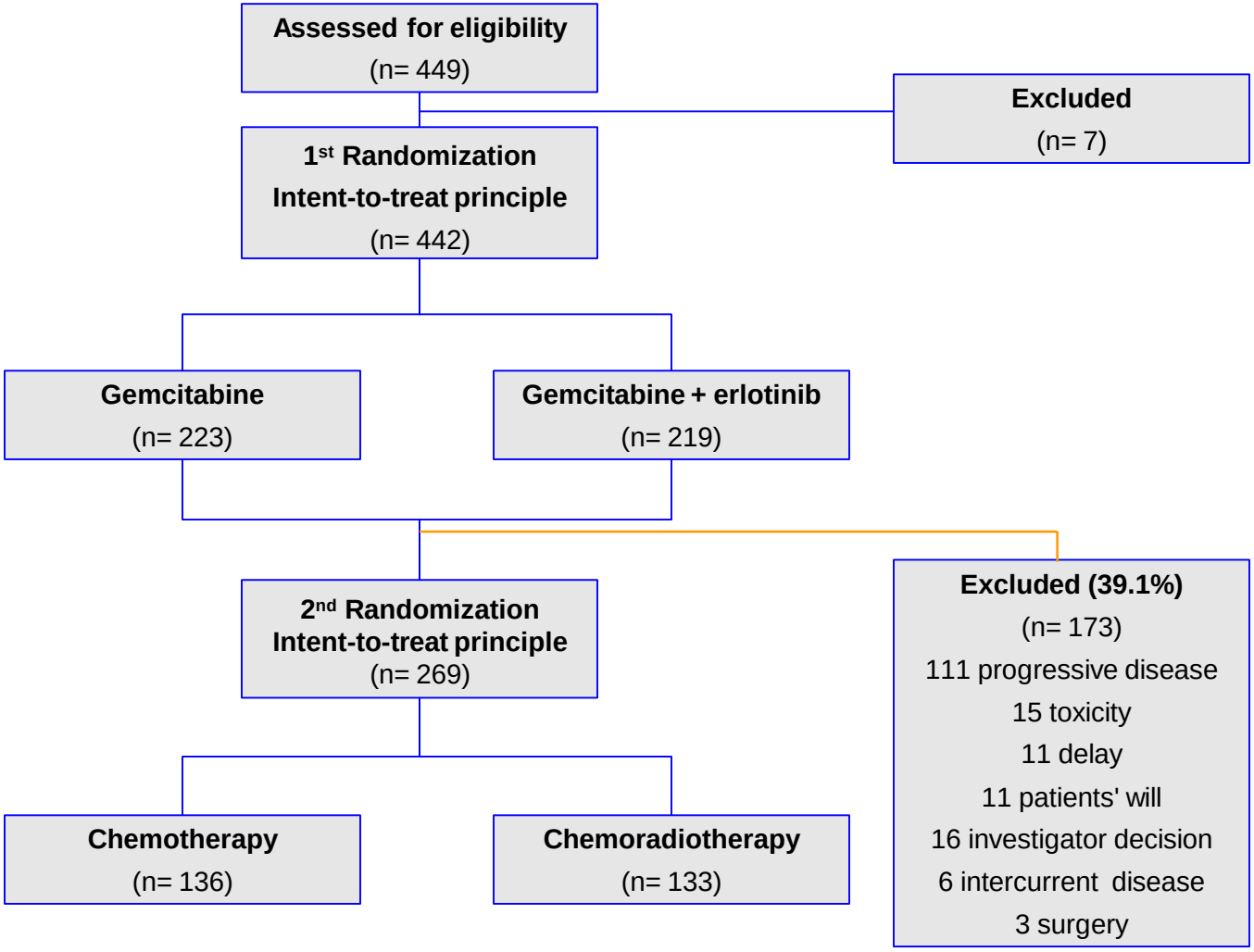
Erlotinib : 100 mg/d with gem
150 mg/d as single agent

Cape
XRT

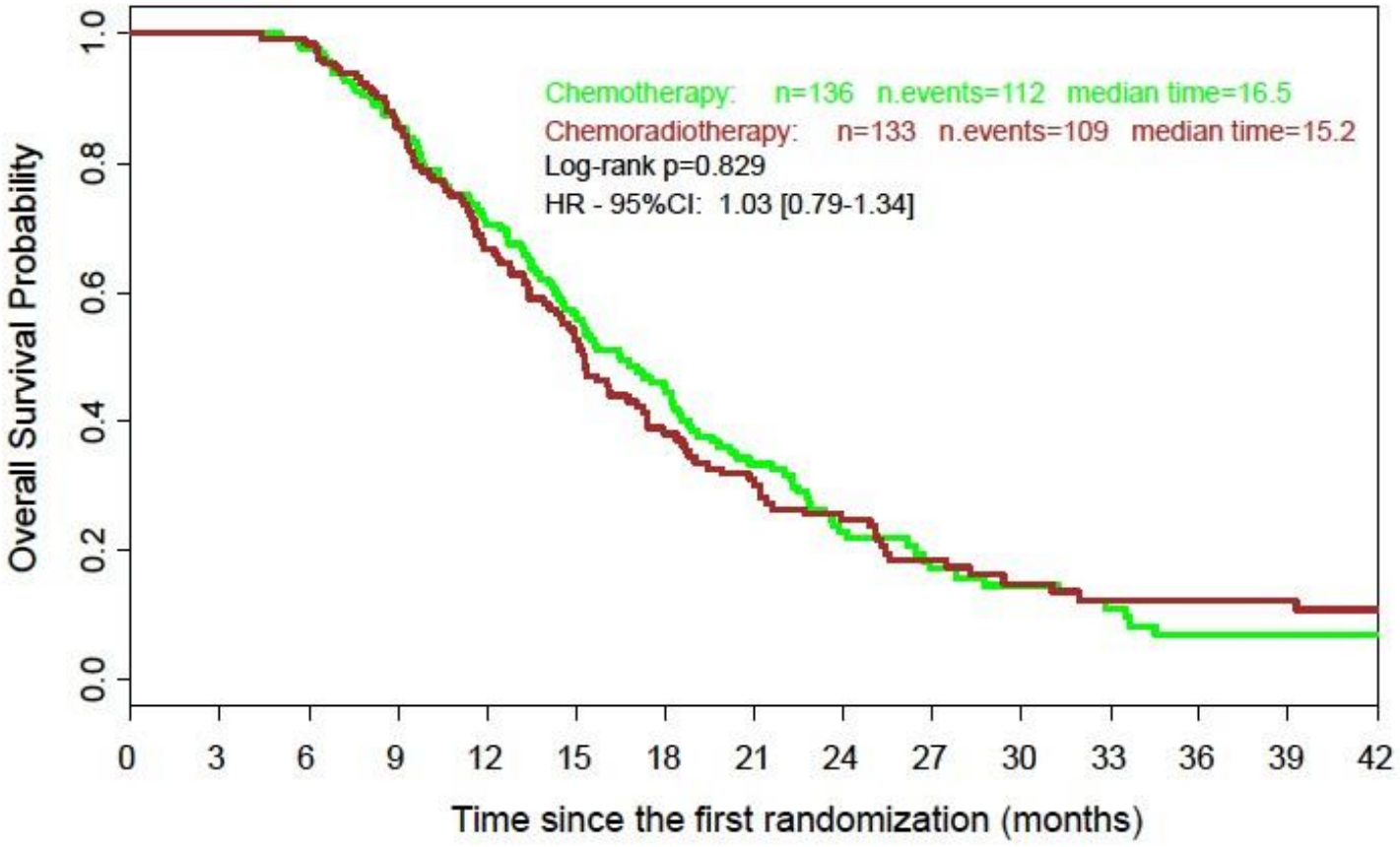
Capecitabine plus radiation
Quality assurance

Secondary surgery allowed at any time

LAP07study
Flow Chart



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

Site of progression

- **R2 patients**:

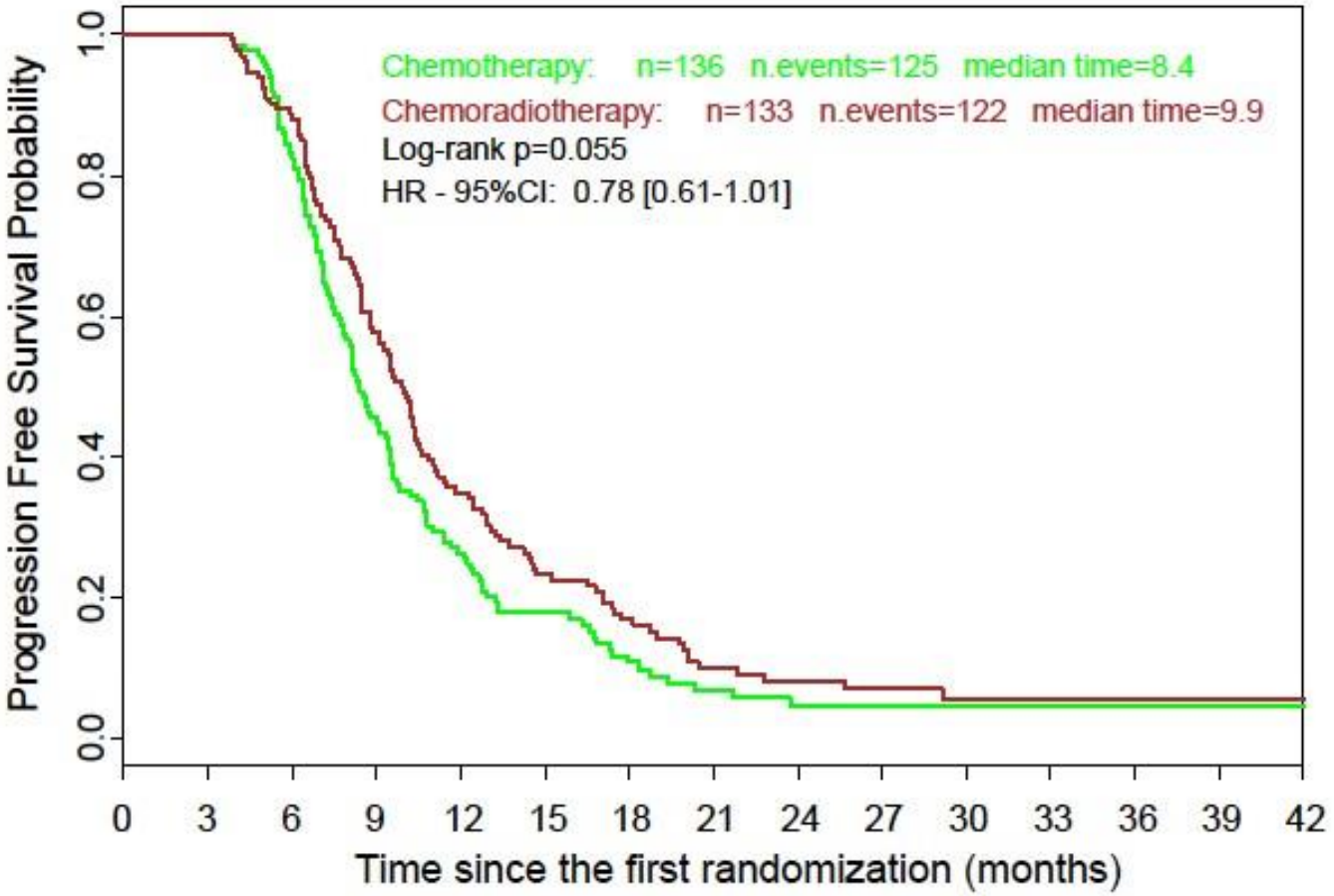
  236/269 patients (88%) with tumor progression 93 with local progression only (39.4%)

  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

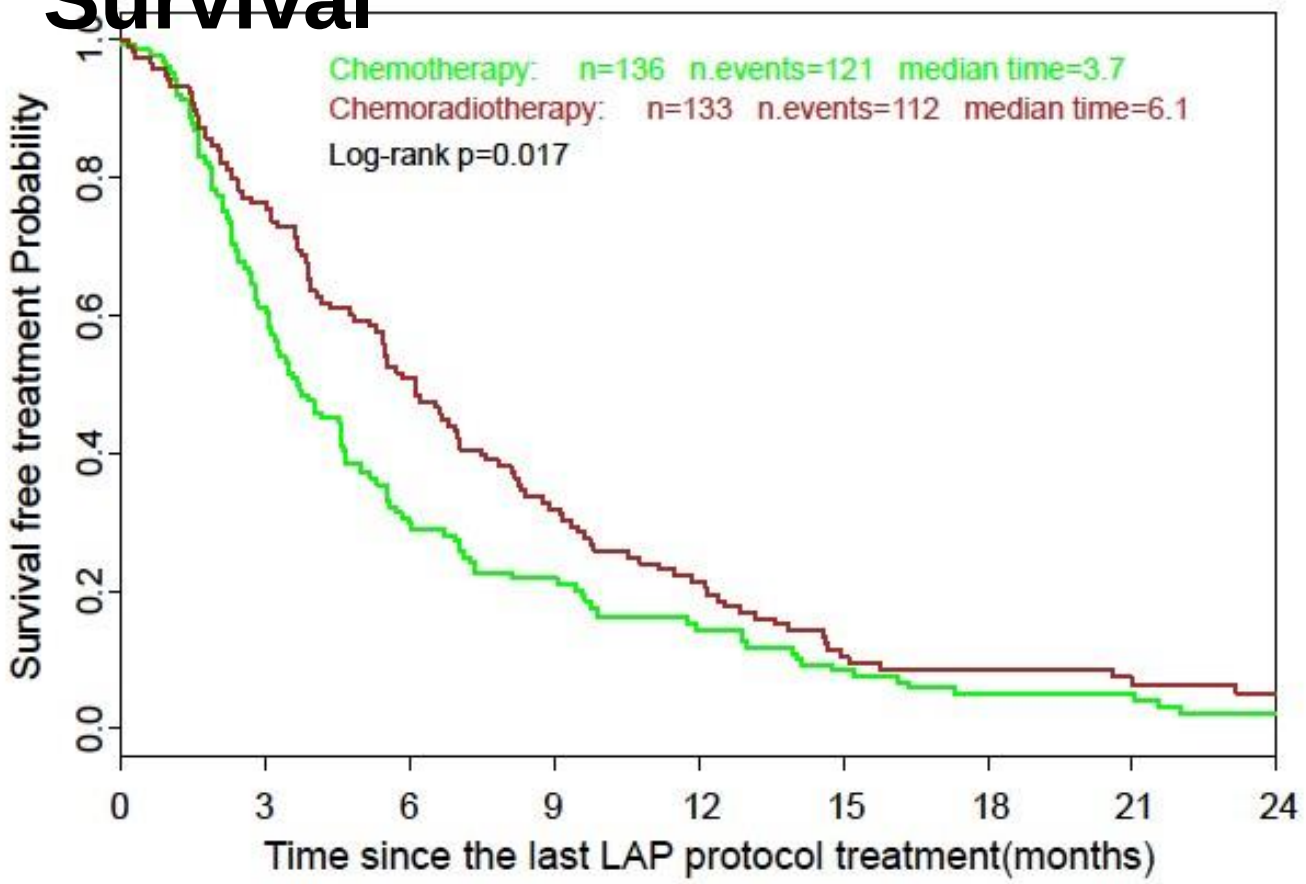
Progression Free Survival



N at risk

Chemotherapy	136	136	113	61	35	21	12	7	3	1	1	1	1	1	1
Chemoradiotherapy	133	133	117	76	45	30	21	11	8	7	4	4	4	4	4

Treatment Free Survival

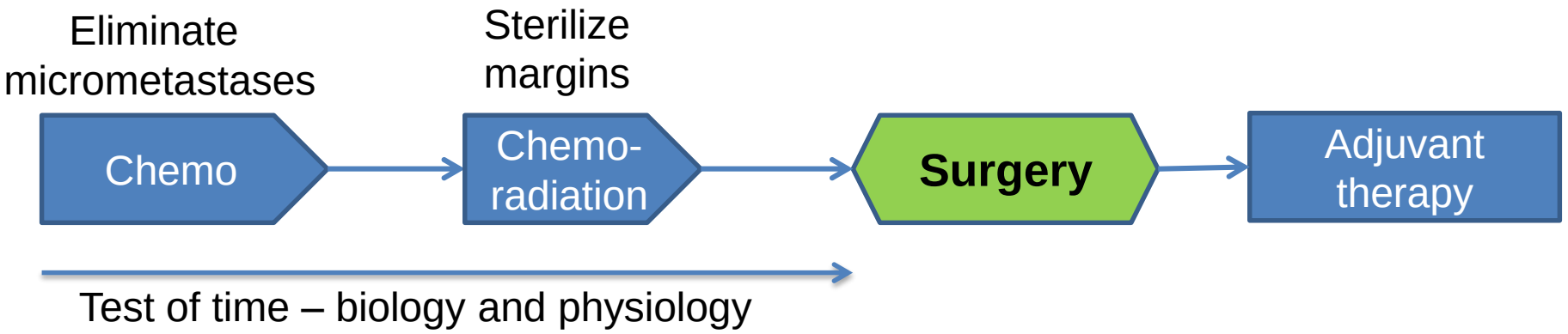


N at risk

Chemotherapy	136	75	37	27	17	10	6	6	2
Chemoradiotherapy	133	89	60	37	24	11	8	6	5

LA and Borderline Resectable Pancreatic Cancer

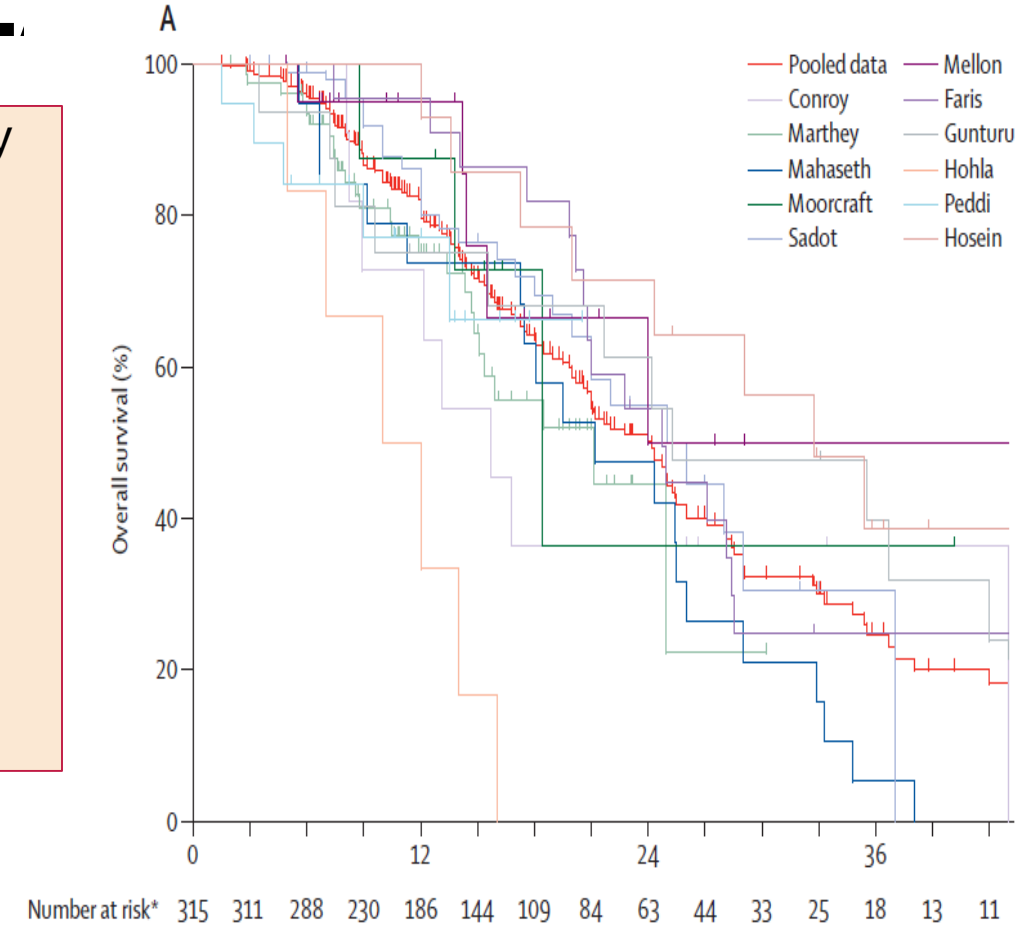
Current treatment paradigm based on limited data
Institutional approaches vary depending on local preferences and consensus opinion
Usual approach:



Katz MH, *et al. J Clin Oncol* 2015; 33(suppl); abstr 4008

FOLFIRINOX FOR LAPC

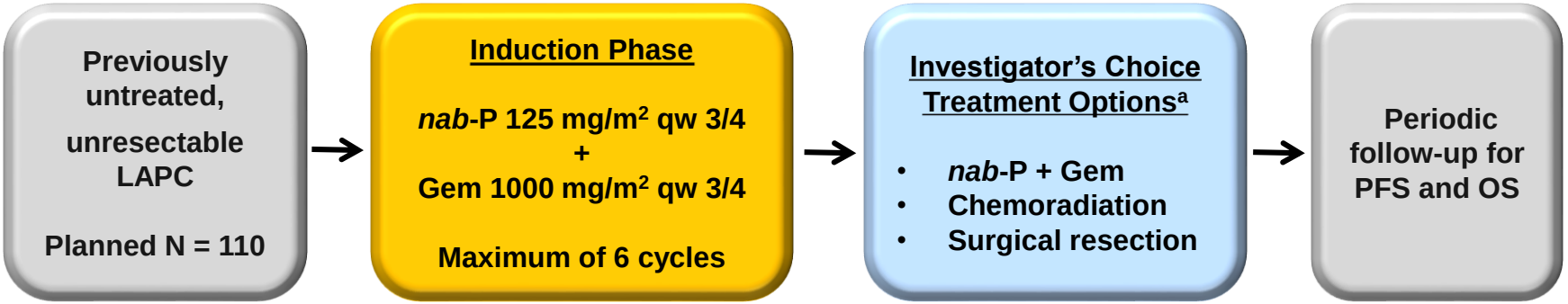
- Meta-analysis with 11 studies finally included
  - 315 patients with LAPC
  - **mOS 24.2 mo**
  - **mPFS 15 mo**
- Partly RT/RCT after FOLFIRINOX
- Secondary resectability: 25.9%
- Supports the concept of „neoadjuvant“ treatment in LAPC



Suker et al., The Lancet 2016

nab-P + Gem in Pts with LAPC: Efficacy, safety, and qol

study design[1,2]



Surgical intervention was allowed prior to completing 6 cycles of *nab*-P + Gem if deemed operable

Chemoradiation = concurrent Cape or Gem plus radiation

lapact™
Locally Advanced Pancreatic Adenocarcinoma Clinical Trial
albumin-bound paclitaxel (ABI-007) + gemcitabine followed by investigator choice

LAPC
- Unresectable pancreatic cancer:[b]
  - Occlusion, thrombosis, or encasement of the superior mesenteric vein and portal vein
  - Tumor abutment > 180° or thrombosis of superior mesenteric artery
  - Abutment or encasement of the celiac axis
  - Lymph node involvement

Key Exclusion Criteria
- Endocrine/mixed-origin pancreatic tumors
- Prior anticancer therapy for pancreatic carcinoma
- Borderline resectable disease

- **Primary Endpoint:** Time to treatment failure: time from first dose of study therapy to treatment failure[c]
- **Secondary Endpoints:** DCR (after 6 cycles of therapy; CR, PR, and SD), ORR, PFS, OS, safety, and QoL (EORTC QLQ-C30 and QLQ-PAN26)

Objective [Interim Analysis]: To assess preliminary efficacy, safety, and QoL data after all patients had completed or discontinued the induction phase of *nab*-P + Gem

[a] For patients without disease progression or unacceptable toxicity after induction. [b] According to radiographic criteria (MRI or CT) or exploration. [c] Treatment failure is defined as discontinuation of study therapy due to disease progression, death by any cause, or the start of a non–protocol-defined anticancer therapy.

1. Philip PA, et al. Poster at ESMO 2017 [poster 622PD]. 2. Portales F, et al. Poster at ESMO 2017 [poster 730P].

nab-P + Gem in Pts with LAPC: Efficacy, safety, and qol *Grade ≥ 3 TEAE in ≥ 5% of patients*

Grade ≥ 3 TEAEs in ≥ 5% of Patients During Induction

TEAE, n (%)	*nab*-Paclitaxel + Gemcitabine (n = 106)	
	All-Grade	Grade ≥ 3
Patients with ≥ 1 adverse event	105 (99.1)	85 (80.2)
Neutropenia[a]	61 (57.5)	43 (40.6)
Anemia	50 (47.2)	12 (11.3)
Fatigue	53 (50.0)	11 (10.4)
Asthenia	37 (34.9)	8 (7.5)
Hyperglycemia	12 (11.3)	7 (6.6)
Thrombocytopenia[b]	44 (41.5)	7 (6.6)
Alanine aminotransferase increased	20 (18.9)	6 (5.7)

- Other relevant TEAEs (all-grade; grade ≥ 3) included diarrhea (45%; 4%), peripheral sensory neuropathy (24%; 4%), peripheral neuropathy (22%; 0%), and febrile neutropenia (5% for both)
- No patients experienced grade 4 peripheral sensory neuropathy

[a] Neutropenia includes preferred terms “neutropenia” and “neutrophil count decreased.”
[b] Thrombocytopenia includes preferred terms “thrombocytopenia” and “platelet count decreased.”

Philip PA, et al. Poster at ESMO 2017 [poster 622PD].

nab-P + Gem in Pts with LAPC: Efficacy, safety, and qol *best response during induction phase*

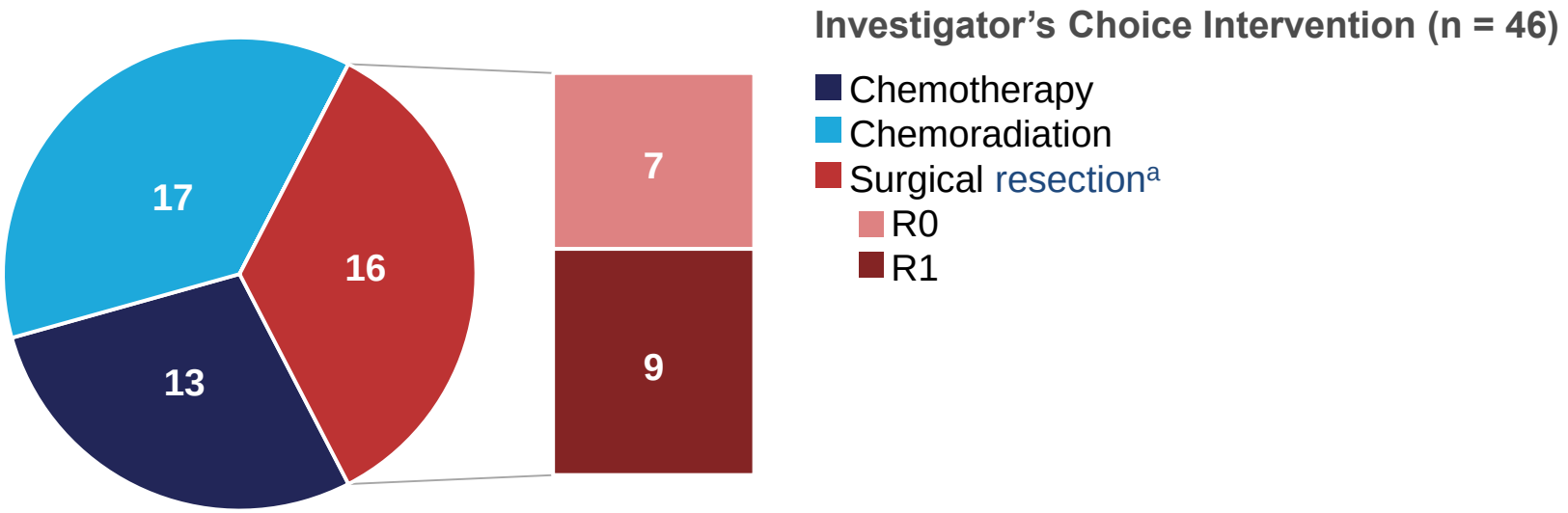
Best Response by RECIST v1.1, n (%)	ITT Population (N = 107)
Complete response	0
Partial response	36 (33.6)
All stable disease	61 (57.0)
SD ≥ 16 weeks	47 (43.9)
SD ≥ 24 weeks	35 (32.7)
Disease control rate, [90% CI]	
SD ≥ 16 weeks + CR + PR	83 (77.6 [70.3 - 83.5])
SD ≥ 24 weeks + CR + PR	71 (66.4 [58.5 - 73.4])
Progressive disease	5 (4.7)
Not evaluable	1 (0.9)
No postbaseline assessment	4 (3.7)

- DCRs based on SD ≥ 16 weeks and SD ≥ 24 weeks were both > 66%

Philip PA, et al. Poster at ESMO 2017 [poster 622PD].

nab-P + Gem in Pts with LAPC: Efficacy, safety, and qol

investigator's choice



- After induction, 46 (43.0%) patients received an Investigator's Choice of therapy
- Sixteen patients (15.0%) had surgical tumor resection after *nab*-P + Gem induction:
  - 7 (6.5%) had R0 resection
  - 9 (8.4%) had R1 resection

[a] Includes patients who received surgery during the induction phase.

Philip PA, et al. Poster at ESMO 2017 [poster 622PD].

nab-P + Gem in Pts with LAPC: Efficacy, safety, and qol *time to improvement/resolution*

Dimension[a]	Median Time to Improvement, days (n = 98)	Complete Resolution, n/n[b] (%)
Constipation	29.5	35/50 (70.0)
Pain interfering with daily activity	30.0	32/49 (65.3)
Depression	29.0	26/41 (63.4)
Anxiety		
Tense	32.0	43/69 (62.3)
Worry	32.5	36/83 (43.4)
Pain	31.0	45/74 (60.8)
Lacked appetite	57.0	37/64 (57.8)
Insomnia	33.0	37/66 (56.1)
Physical condition or medical treatment		
Interfered with family life	33.0	22/41 (53.7)
Interfered with social activities	37.0	20/52 (38.5)

- The majority (> 60%) of patients experienced ≥ 1 complete resolution of anxiety (tense) constipation, depression, or pain with median times to improvement ≈ 30 days

[a] The most common (n ≥ 40 patients) dimensions experienced during induction and assessed at baseline and ≥ 1 postbaseline time point.
[b] Patients who had ≥ 1 complete resolution of the limitation/patients who experienced the limitation.

Portales F, et al. Poster at ESMO 2017 [poster 730P].

nab-P + Gem in Pts with LAPC: Efficacy, safety, and qol *time to improvement/resolution (cont)*

Dimension[a]	Median Time to Improvement, days (n = 98)	Complete Resolution, n/n[b] (%)
Irritability	31.5	24/48 (50.0)
Need to stay in bed or chair during day	43.0	19/41 (46.3)
Limited in pursuing hobbies or leisure	31.0	19/49 (38.8)
Limited in work or other daily activity	33.0	18/49 (36.7)
Weakness	34.0	19/67 (28.4)
Fatigue	33.0	13/80 (16.3)
Trouble taking long walks	30.0	9/57 (15.8)
Need to rest	46.5	10/72 (13.9)
Trouble doing strenuous activity	30.0	7/54 (13.0)
Overall health	35.0	Not applicable

[a] The most common (n ≥ 40 patients) dimensions experienced during induction and assessed at baseline and ≥ 1 postbaseline time point.
[b] Patients who had ≥ 1 complete resolution of the limitation/patients who experienced the limitation.

Portales F, et al. Poster at ESMO 2017 [poster 730P].

nab-P + Gem in Pts with LAPC: Efficacy, safety, and qol

authors' conclusions

- Interim efficacy and safety[1]
  - This interim analysis suggests a tolerable safety profile for *nab*-P + Gem
    - Most patients (59%) completed the induction phase
    - Overall, 60% and 48% of patients received 5 and 6 cycles of induction treatment, respectively
  - A total of 34% of the ITT population had a PR to induction therapy
  - The DCR of 78% for SD ≥ 4 months was promising and indicative of antitumor activity in patients with LAPC
  - All patients were identified as having locally advanced unresectable disease at baseline, yet 15% were resectable after the *nab*-P + Gem induction phase
    - All of these patients underwent R0 or R1 resection
- Interim QOL[2]
  - These results indicate that QoL was generally maintained during *nab*-P + Gem induction in patients with LAPC
  - The scales with the greatest rates of stability/improvement were nausea and vomiting, financial difficulties, pain, and constipation, and items with the greatest complete resolution rates were constipation and pain interfering with daily life
  - Majority of the most commonly experienced global, functional, and symptom items improved within approximately 1 month

1. Philip PA, et al. Poster at ESMO 2017 [poster 622PD]. 2. Portales F, et al. Poster at ESMO 2017 [poster 730P]..

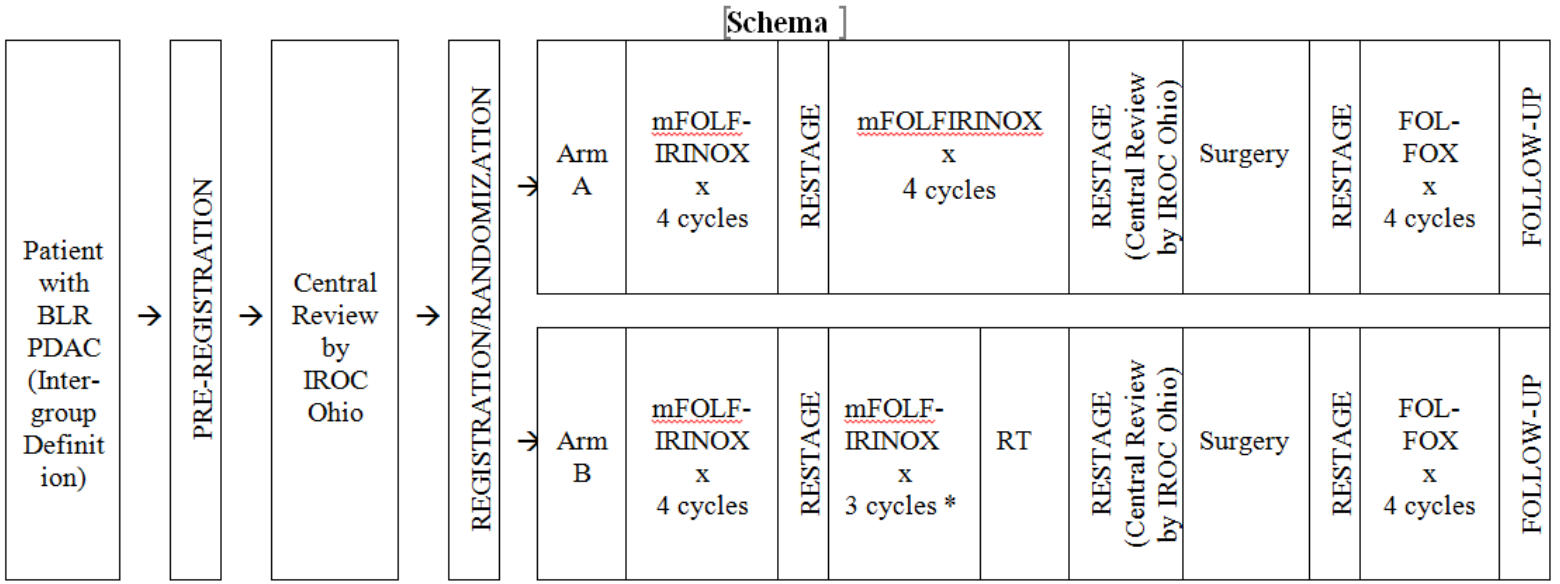
Pancreas SBRT

- Patient convenience
- Shorter time away from full dose chemo (e.g. FOLFIRINOX)
- Prospective multicenter study showed SBRT safe and improves pain/QoL in LAPC
- Retrospective single institution data (e.g. Moffitt, Hopkins) suggests SBRT for BR PDAC:
  - Does not compromise potential surgical option
  - Does not increase postoperative complications
  - Is associated with high rate of R0 resection
  - Is very well tolerated

Pancreas SBRT

- Local control with as few as 5d XRT then surgery.
  - 30Gy/10 compatible with local control and favorable OS in resectable Pancreas Cancer (Evans 2008)
  - 25Gy/5 safe and favorable local control after surgery in resectable Pancreas Cancer (Hong 2014)
  - 33Gy/5 SBRT following induction chemo for BLR: 56% resected, 97% R0 resections (Chuong 2013)

Pancreas SBRT, A021501 Schema



Pancreas Cancer: NeoAdjuvant Therapy:

Stage	Preoperative Therapy	Goal
Resectable	Optional	Cure
Borderline Resectable	Reccomended	Cure
Unresectable	Unlike to convert	Palliation

Summary

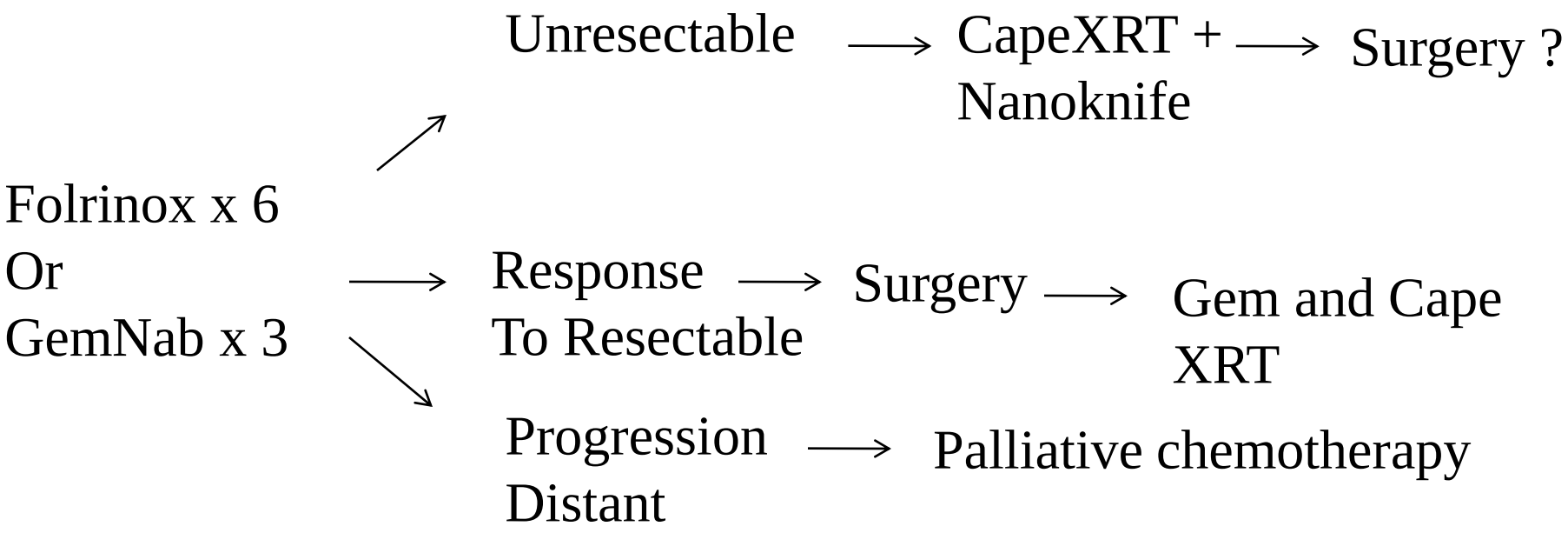
Only chance for curative treatment of pancreatic cancer remains surgery

Results with FOLFIRINOX or Gem/Nab are more attractive than historical control.

We need:

Randomized controlled trials comparing neoadjuvant to adjuvant treatment in the setting of resectable disease.

Gibbs LAD/Borderline Strategy



OBRIGADO!