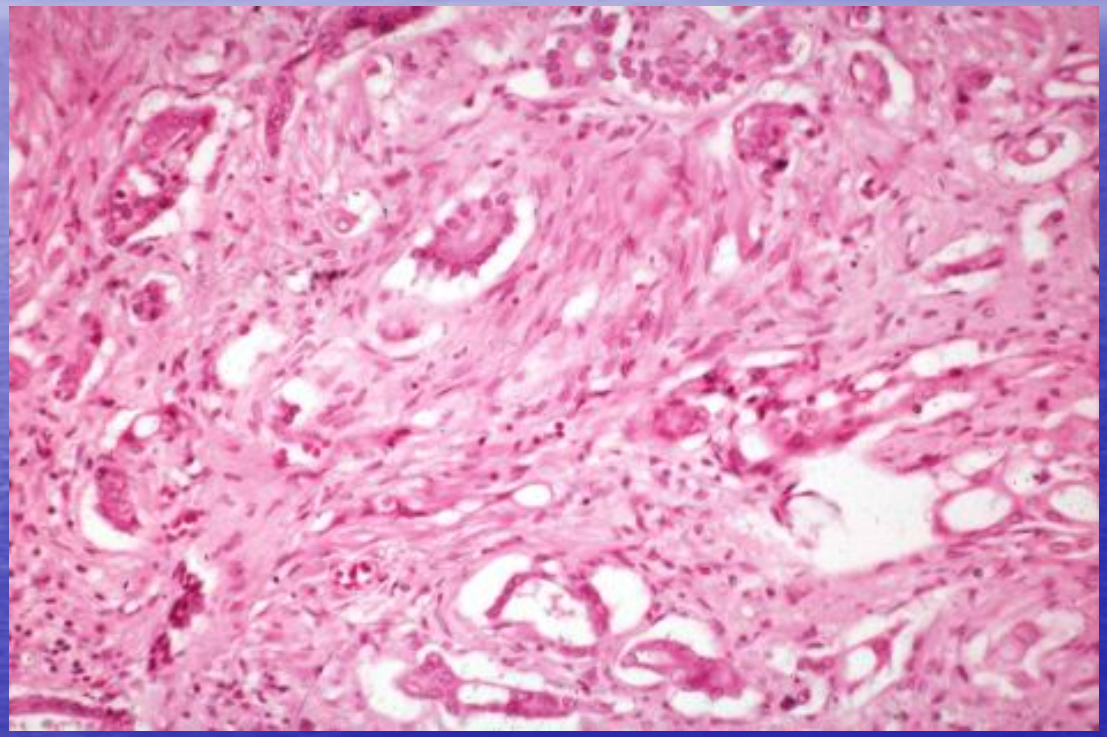
Oncological treatment of pancreatic cancer



Morten Ladekarl
Department of Oncology
Aarhus University Hospital
Denmark

Denmark

Cancerregisteret
1991-95

1 year survival rate	5 year survival rate
10%	2%

Storm & Engholm: www.cancer.dk

US

Gem-treated patients
1995-96

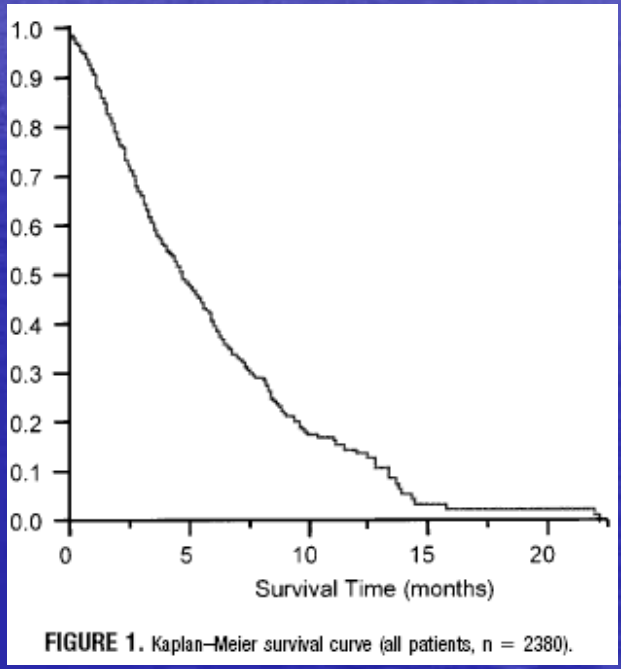


FIGURE 1. Kaplan–Meier survival curve (all patients, n = 2380).

Storinolo et al., Cancer 1998

Disease stage	5-year survival (%)
Localized	15.2
Regional	6.8
Distant	1.8

SEER Cancer Statistics Review 1975-2001

Resectable disease

- Adjuvant or neoadjuvant chemotherapy
- Adjuvant or neoadjuvant chemoradiotherapy (CRT)

Adjuvant chemotherapy vs. observation

Table 1. Randomized trials comparing adjuvant chemotherapy with observation

Study	Year	No. of patients	Treatment arms	Duration of treatment (months)	Median OS (months)	5-year OS (%)
Bakkevold [12]	1993	30	AFM regimen every 3 weeks for 6 cycles	4.5	23[b]	4
		31	Observation		11	8
Takada [14]	2002	81	Mitomycin C + 5-FU → oral 5-FU	0.75[a]	NA	11.5
		77	Observation			18.0
Kosuge [13]	2006	45	5-FU + cisplatin every 4–8 weeks for two cycles	2–4	12.5	26.4
		44	Observation		15.8	14.9
ESPAC-1 [15]	2004	147	5-FU/FA	6	20.1	21
		142	No chemotherapy		15.5[c]	8
CONKO-001 [16]	2007	179	Gemcitabine weekly ×3 every 4 weeks for six cycles	6	22.8[d]	21
		177	Observation		20.2	9

AFM, doxorubicin + 5-fluorouracil + mitomycin C; FA, folinic acid; 5-FU, 5-fluorouracil;. NA, data not available; OS, overall survival.

[a]Intravenous therapy only.

[b]$P = 0.02$.

[c]$P = 0.009$.

[d]$P = 0.005$.

Heinemann & Boeck, Ann. Oncol. 2008

Meta-analysis, effect on median survival

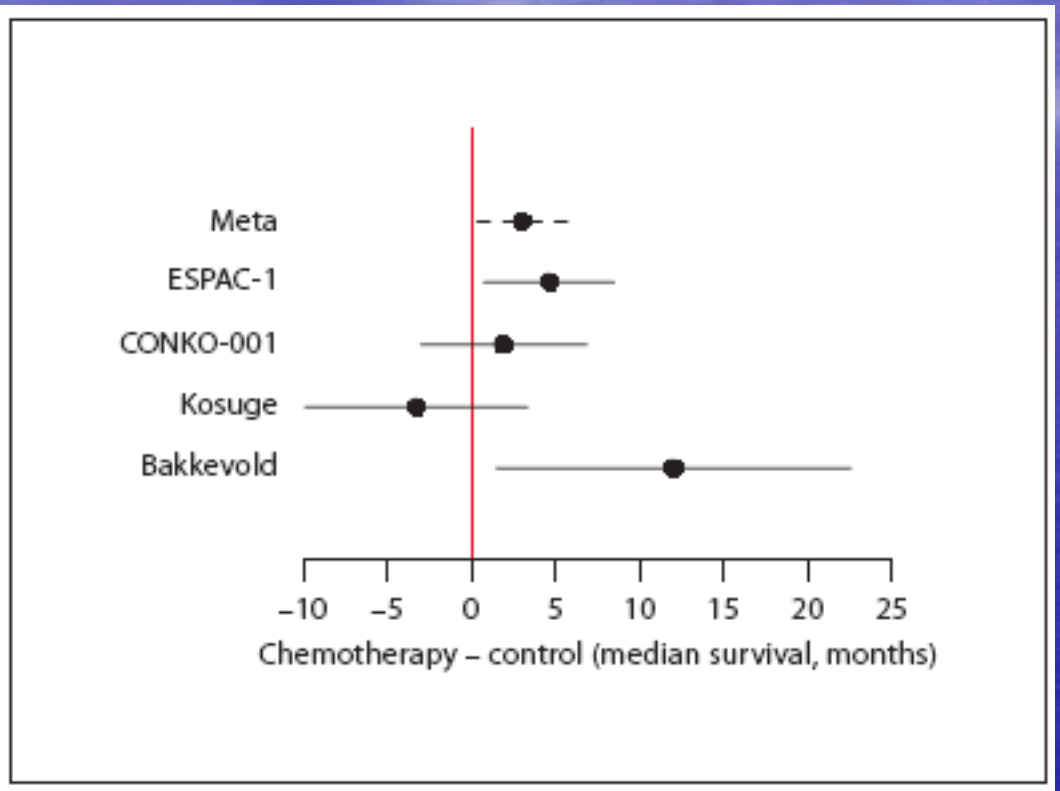
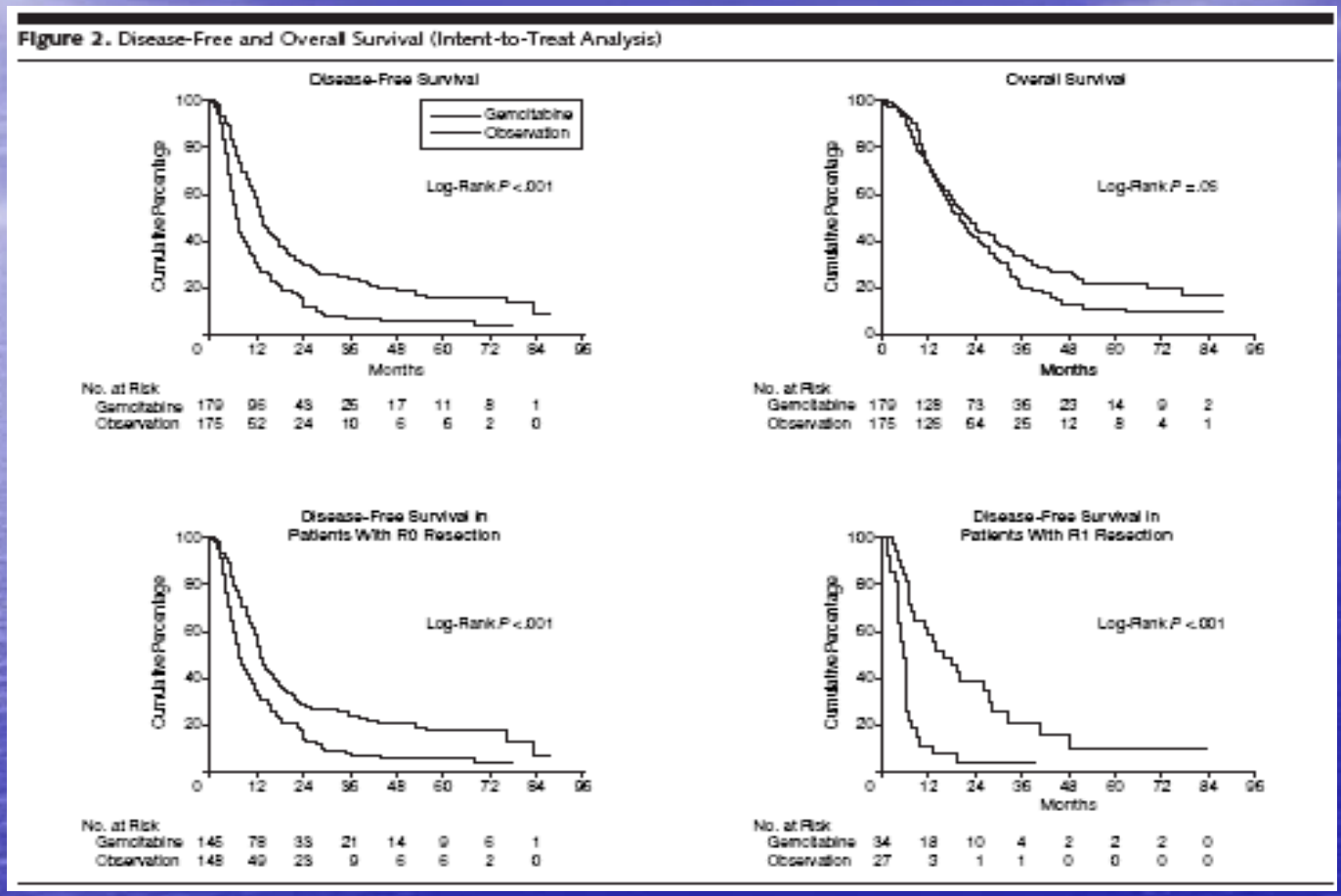


Fig. 2. Differences in median survival time between chemotherapy and control groups and CI among the 4 studies included in the meta-analysis. Studies are ordered by length of CI (uncertainty in estimates).

Boeck et al., Oncology 2007

CONKO-001, Gem vs observation



Significant increase in DFS from 7 to 13 months
Significant increase in median survival from 20 to 23 months
Increase in est. 5-year survival rate from 9% to 21%
Beneficial effect in all subgroups

Neuhaus et al., ASCO 2008 Oettle et al., JAMA 2007

Adjuvant chemoradiotherapy

Table 2. Randomized trials investigating adjuvant chemoradiation

Study	Year	No. of patients	Treatment arm	OS (months)	5-year OS (%)
GITSG [20]	1985	21	[a]CRT/5-FU → 5-FU maintenance for 2 years	20.0*	19
		22	Observation	10.9	5
EORTC [21]	1999	60	[b]CRT/ 5-FU (no maintenance)	17.1	20
		54	Observation	12.6	10
ESPAC-1 [15]	2004	145	[a]CRT/5-FU ± 5-FU/FA bolus ×6 cycles	15.9	10
		144	No chemoradiation	17.9	20
RTOG 9704 [22] Pancreatic head only	2006	187	Gem 3 weeks → CRT/5-FU → Gem 3 months	20.5**	31 (3-year OS)
		194	5-FU 3 weeks → CRT/5-FU → 5-FU 3 months	16.9	22 (3-year OS)
RTOG 9704 [22] All patients	2006	221	Gem 3 weeks → CRT/5-FU → Gem 3 months	18.8	NA
		221	5-FU 3 weeks → CRT/5-FU → 5-FU 3 months	16.9	NA

FA, folinic acid; 5-FU, 5-fluorouracil; OS, overall survival; Gem, gemcitabine; NA, data not available.

[a]CRT: 20 Gy + 5-FU bolus days 1–3 ×2.

[b]CRT: 20 Gy + 5-FU continuous infusion ×2

*$P = 0.035$; **$P = 0.09$.

Heinemann & Boeck, Ann. Oncol. 2008

Neoadjuvant chemotherapy,

Gem vs. Gem + cisplatin, a randomized phase II-study

TABLE 3. *Patient outcome data*

Characteristic	Gem (n = 24)		Gem + Cis (n = 26)	
Resectability				
Pancreatic resection	9 (38%)		18 (70%)	
Bypass	14 (58%)		4 (15%)	
No surgery	1 (4%)		4 (15%)	
	Resection	Bypass	Resection	Bypass
Tumor type (n)				
Adenocarcinoma	7	13	14	3
Other malignancy	1	0	2	0
No evidence of malignancy	1	0	2	1
No histology	0	1	0	0
Posterior resection margins[a]				
Positive	2 (25%)		4 (25%)	
Negative	6 (75%)		12 (75%)	
Lymph nodes[a]				
Disease positive	6 (75%)		9 (56%)	
Disease negative	2 (25%)		7 (44%)	

Resection rate improved from 38% to 70%

1-year survival improved from 46% to 61%

Palmer et al., Ann. Surg. Oncol. 2007

Neoadjuvant CRT,
Gem-based CRT, a phase II-study

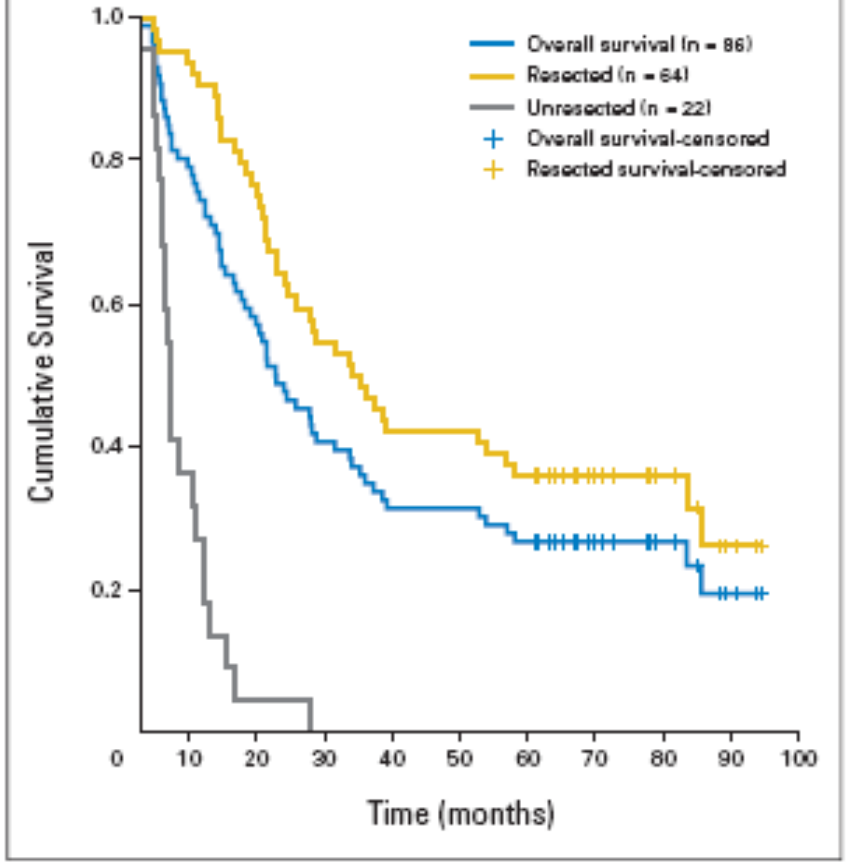


Fig 3. Survival curve for all 86 patients and survival curves for the patients who underwent pancreaticoduodenectomy (PD; n = 64) versus those who did not undergo PD (n = 22).

Evans et al., JCO 2008

Conclusions, adjuvant and neoadjuvant treatment

- Adjuvant Gem is a standard of care
  - Relative effect of 5FU?
    - ESPAC-3: 5FU/FA vs Gem
  - Combination chemotherapy and molecular therapy?
  - Treatment of R1-resected pts?
- Adjuvant CRT is another standard, but evidence is debatable
    - EORTC-trial: Gem vs Gem-based CRT
- Neoadjuvant chemotherapy or CRT is experimental

Locally advanced disease

- Chemotherapy
  - Gem
  - Gem in combinations
- Chemoradiotherapy

Overall survival on Gem

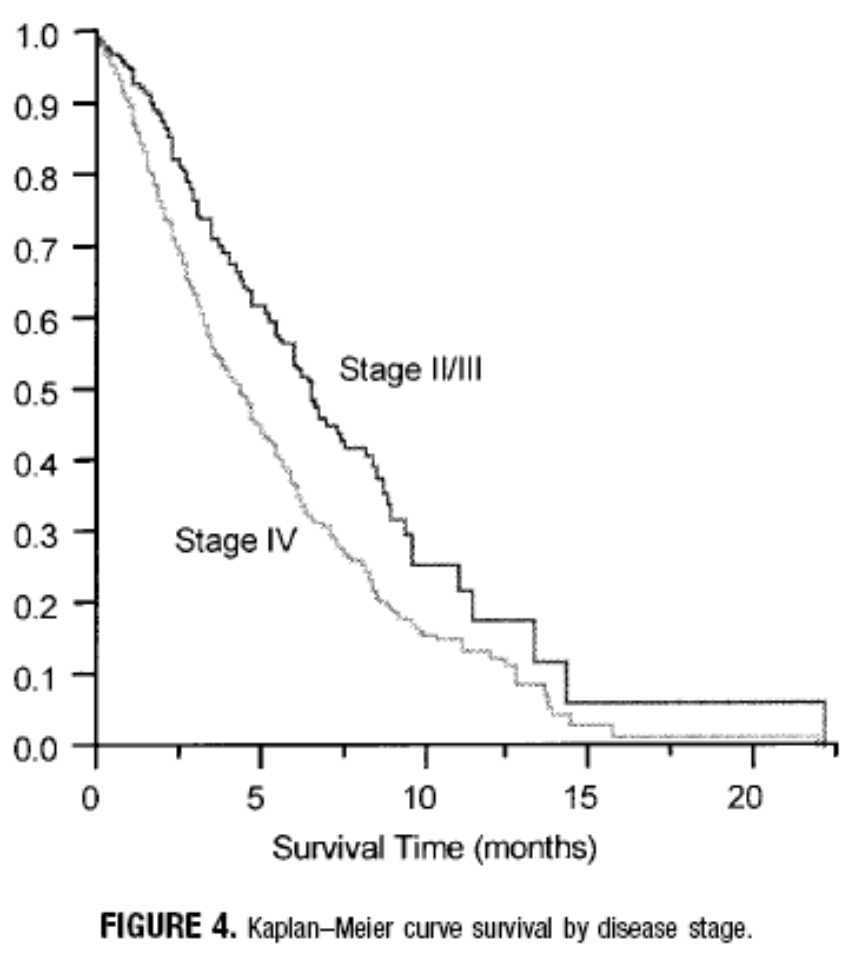
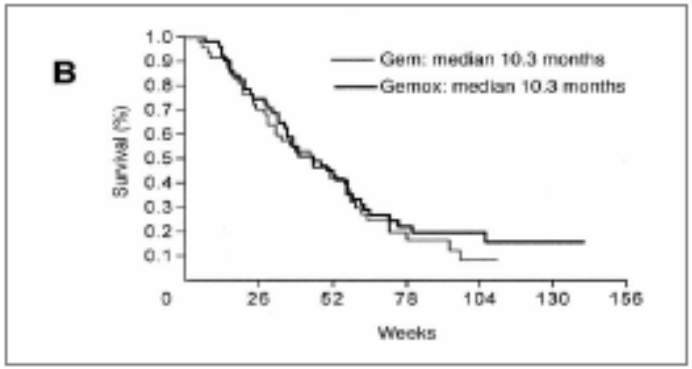


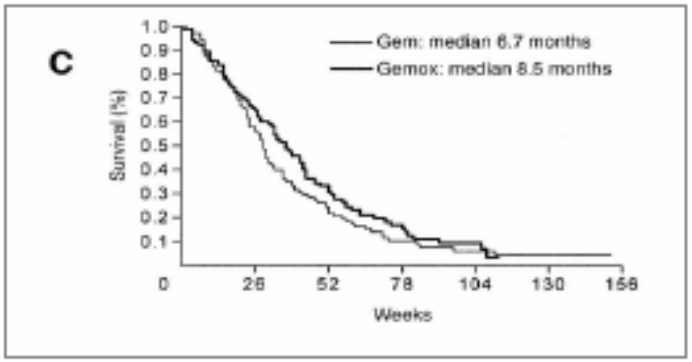
FIGURE 4. Kaplan–Meier curve survival by disease stage.

Storinolo et al., Cancer 1998

Effect of Combination Chemotherapy in LAPC



LAPC



metastatic

No benefit from GemOx in LAPC patients

Louvet JCO 2005

CRT in locally advanced disease

- studies are heterogeneous and difficult to compare

- Prolongation of survival vs. “down sizing”
- Lack of randomized studies using modern treatment
- Lack of clear definition of locally advanced disease
- Indications for operation after CRT are not standardized

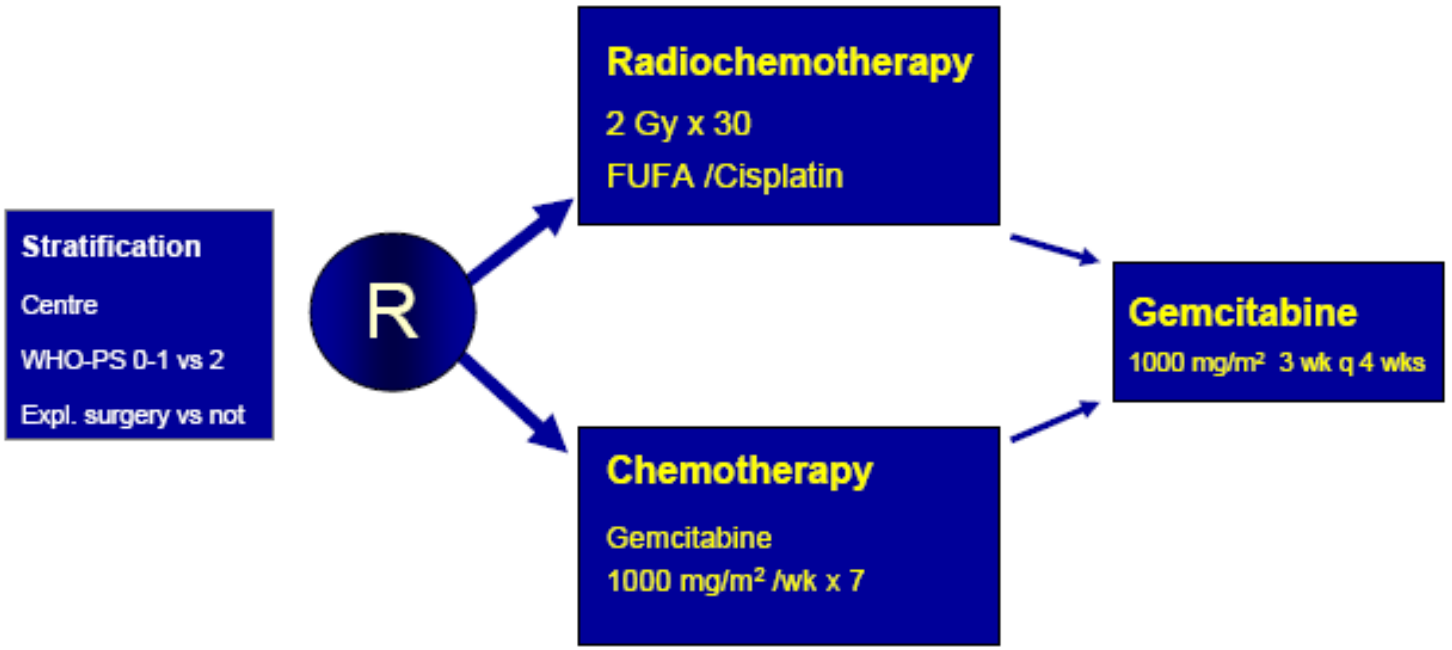
Massucco et al., Ann. Surg. Oncol. 2005

Chauffert et al.,

Phase III-study of Gem +/- 5FU/cisplatin-based CRT

Chemoradiotherapy vs Chemotherapy

in locally advanced pancreatic cancer

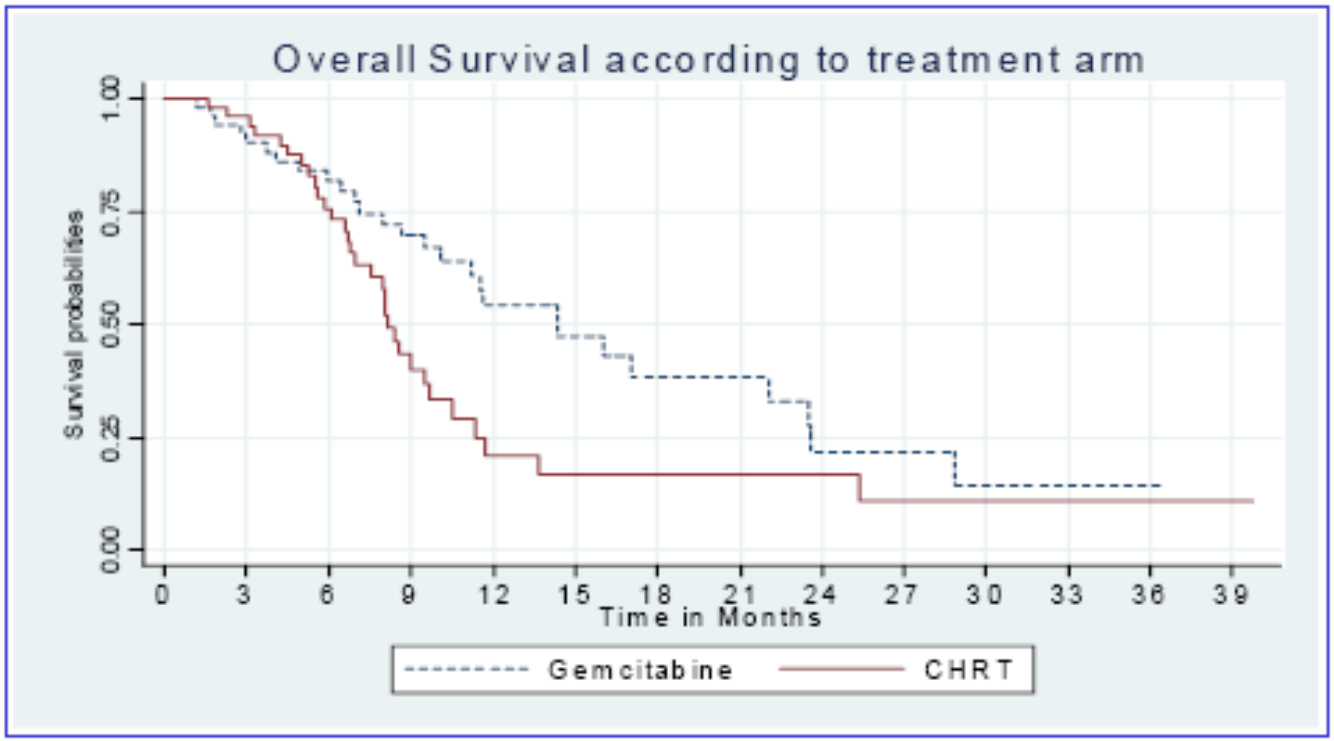


recruitment
planned: 176 pts
stop after: 119 pts

Chauffert et al. ASCO 2006

RCT (5-FU/Cisplatin) → Gemcitabine versus Gemcitabine

109 patients included, median follow-up : 16 months [1 – 60]



Median survival
CRT (5-FU/Cis): 8 mo
Gemcitabine: 14 mo

1-yr-survival :
CRT (5-FU/Cis): 24%
Gemcitabine: 51%

Chauffert. ASCO 2006, # 4008

Chauffert et al.,

Phase III-study of Gem +/- 5FU/cisplatin-based CRT

RCT (5-FU/Cisplatin) → Gemcitabine versus Gemcitabine

Analysis of Grade 3-4 Toxicity

	Initial CHRT	Initial Gem	P
	n=59	n=60	
Overall toxicities	**31 (53%)**	**15 (25%)**	**≤0.001**
Hematologic toxicities	28 (47%)	11 (18%)	≤0.001
Neutropenia	14 (24%)	5 (8%)	≤0.001
Febrile neutropenia	1 (2%)	0 (0%)	NS
Anemia	16 (27%)	2 (3%)	≤0.001
Thrombocytopenia	7 (12%)	6 (10%)	NS

Chauffert et al. ASCO 2006

Cumulative dose of gemcitabine

	RCT→Gem	initial Gem	p
Cumulative dose of gemcitabine	3500 mg/m^2	6900 mg/m^2	0.01
Number of infusions	4 (0-33)	9 (0-44)	0.01

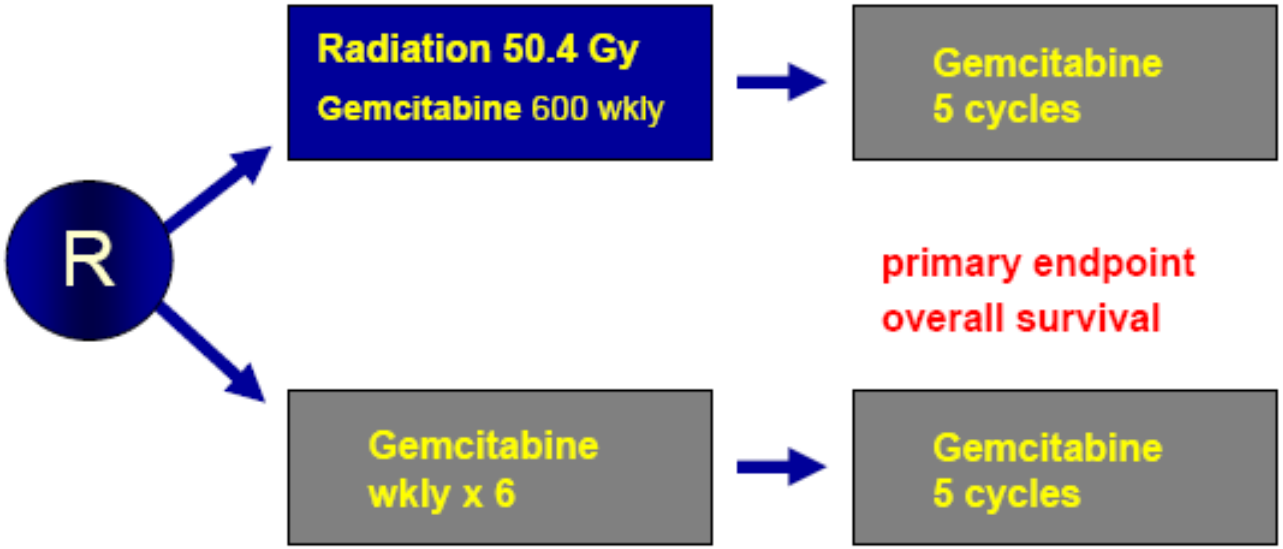
Chauffert et al. ASCO 2006

No data on resection rate

Loehrer et al.,

Phase III-study of Gem +/- Gem-based CRT

E4201 Study: Phase III in LAPC



3D conformal radiation

central review of treatment dose volume

recruitment

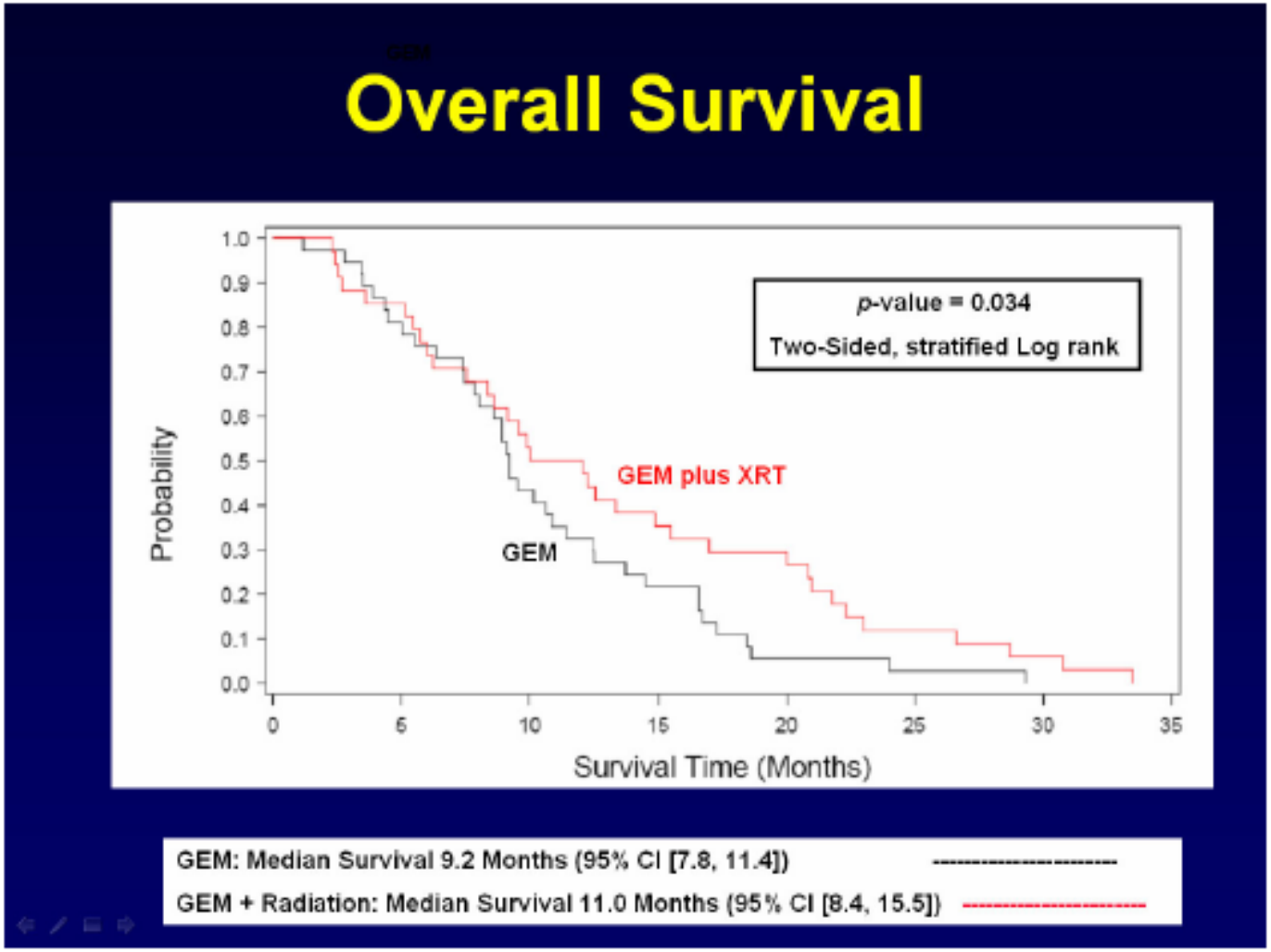
planned: 316 pts

stop after: 74 pts

Loehrer et al. ASCO 2008, #4506,.

Loehrer et al.,

Phase III-study of Gem +/- Gem-based CRT

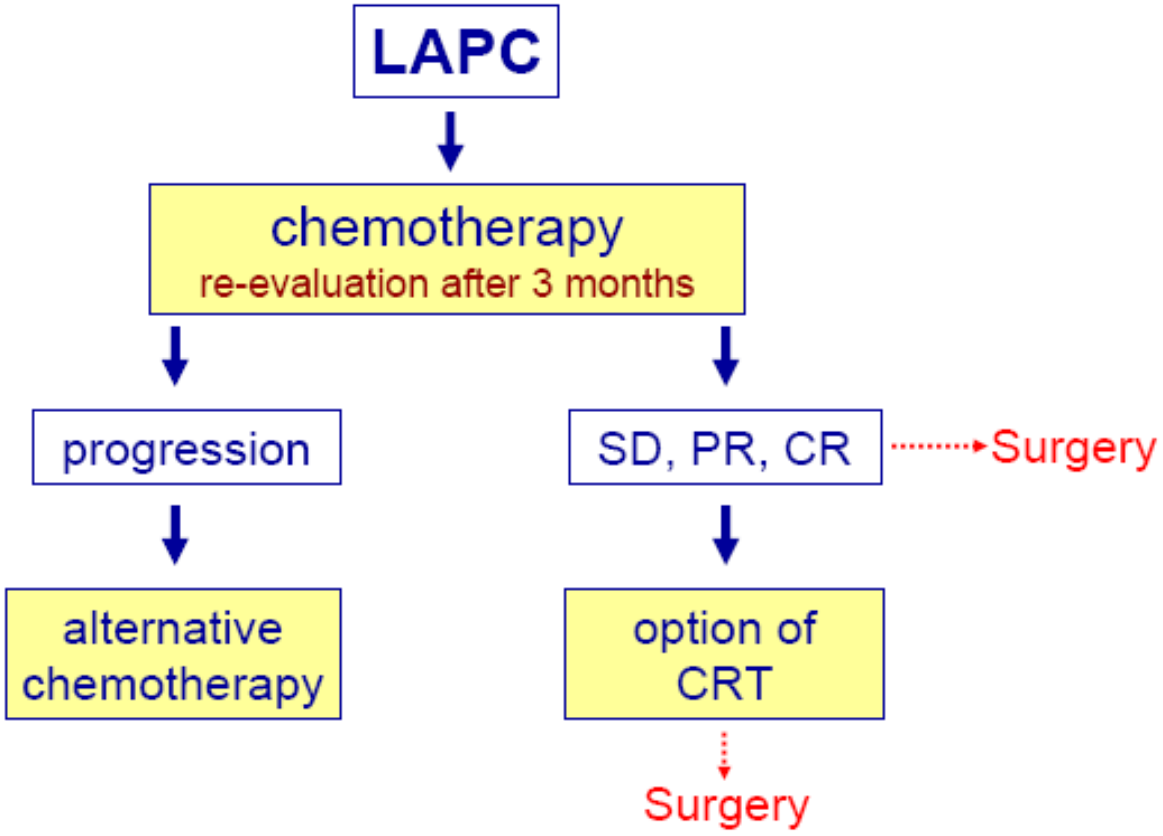


Loehrer et al. ASCO 2008, #4506,.

Conclusions,
Oncological treatment of locally advanced disease

- Current evidence that CRT prolongs overall median survival compared to Gem is scarce
  - Negative effect of Cis-5FU-based CRT followed by Gem
  - Effect of Gem-based CRT, but study underpowered
- Phase II-studies indicate that CRT may induce down sizing and R0-resection in some patients
  - Selection of candidates
  - Detrimental effect in unresectable patients?

Treatment Algorithm in LAPC



Herrmann 2008

Advanced disease

- Median survival 3-4 months
- Primary goals of treatment
  - Prolongation of survival
  - Improvement in QoL

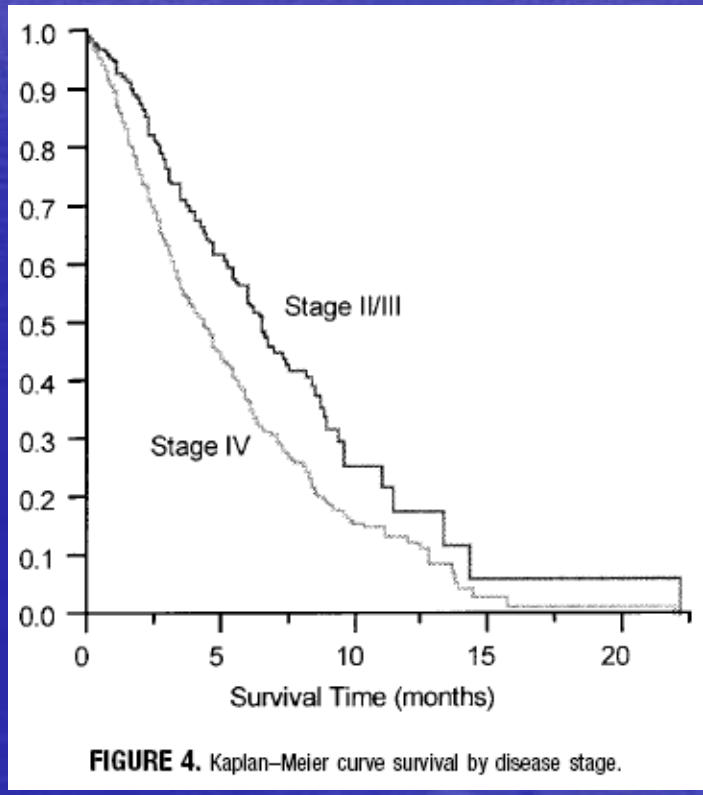


FIGURE 4. Kaplan–Meier curve survival by disease stage.

Storinolo et al., Cancer 1998

Gem vs. 5-FU

	Gemcitabine	5-FU	*P*
Clinical benefit response*	24%	5%	0.002
Median survival (months)	5.7	4.4	0.002
Time to progression (months)	2.1	0.9	0.001
6-month survival	46%	31%	
1-year survival	18%	2%	
Partial response	5.4%	0%	
Stable disease	39.3%	19%	

*Composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight

Burris H, et al. *JCO* 1997

Survival of Gem-treated patients according to performance status

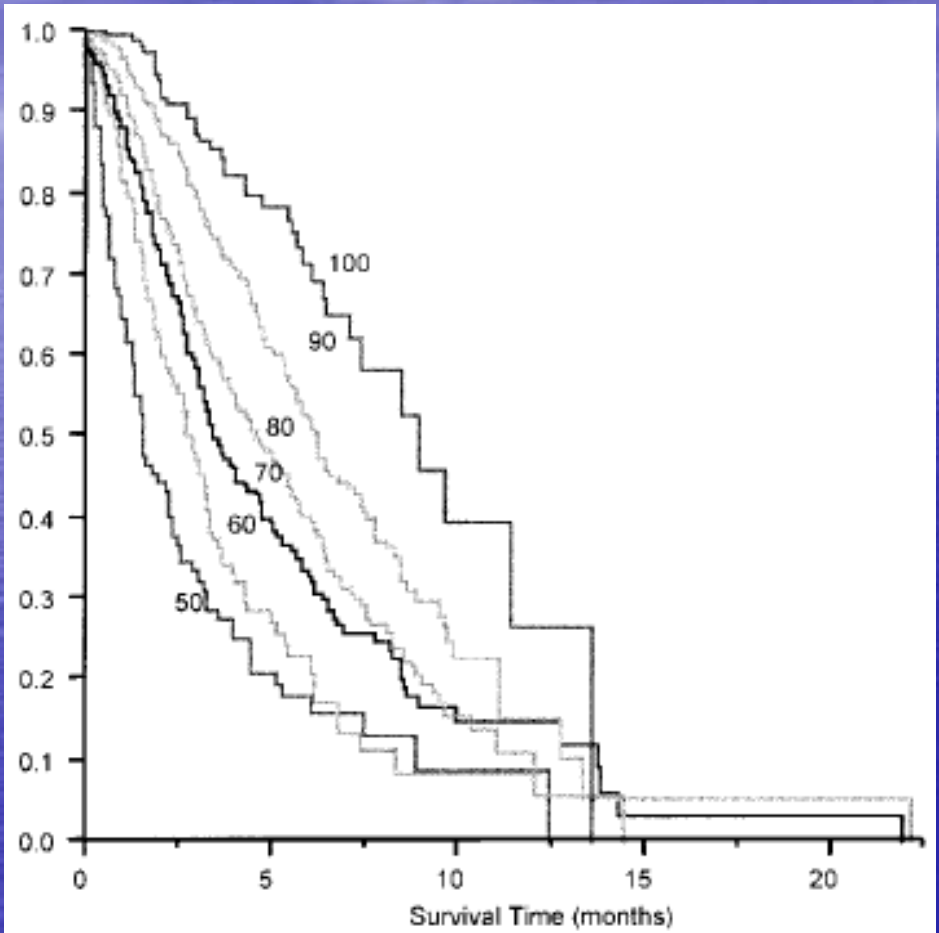
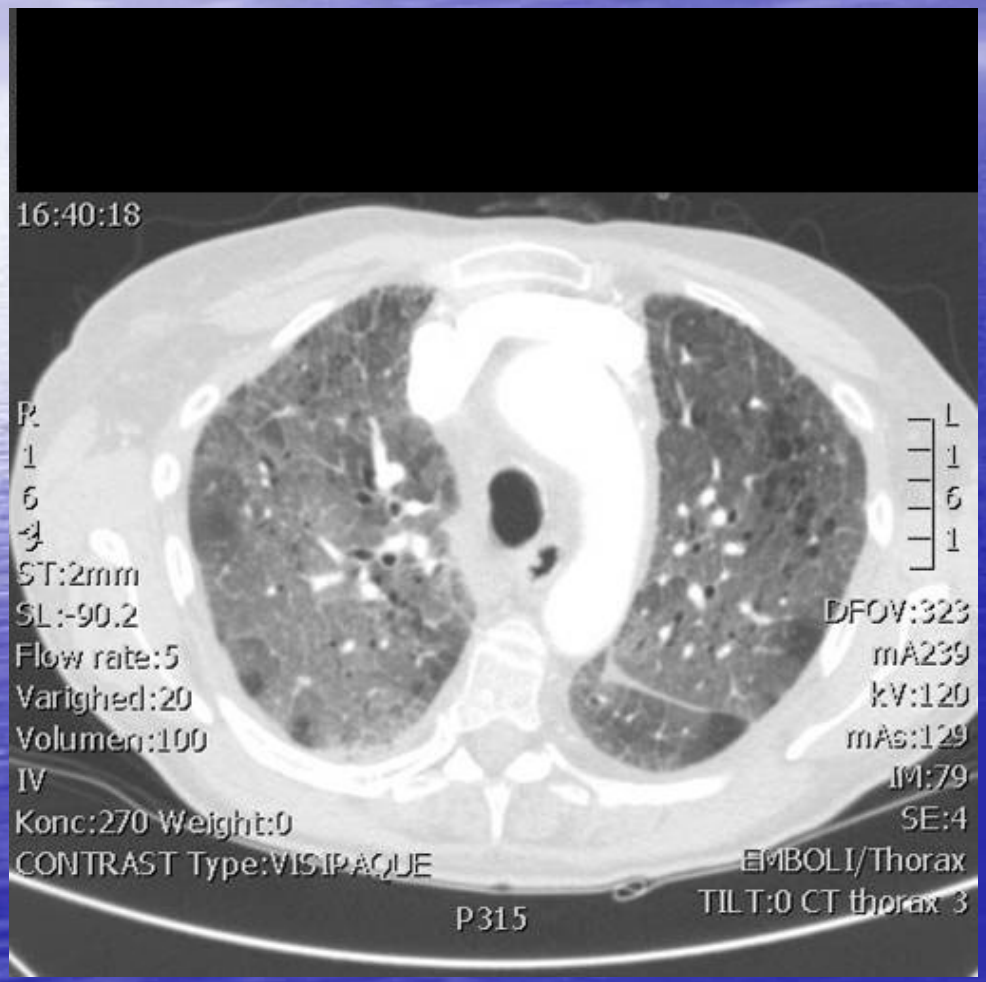


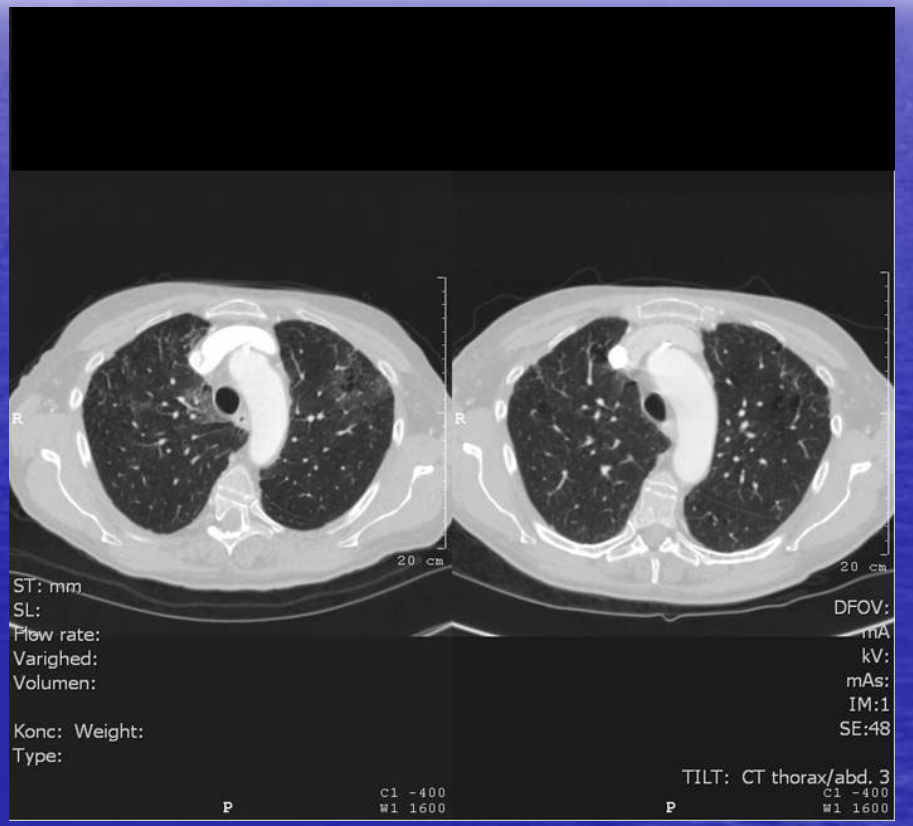
FIGURE 3. Kaplan–Meier curve survival by baseline Karnofsky performance status.

Storinolo et al., Cancer 1998

Case,
Fatal interstitial pneumonitis due to Gem



One day before death



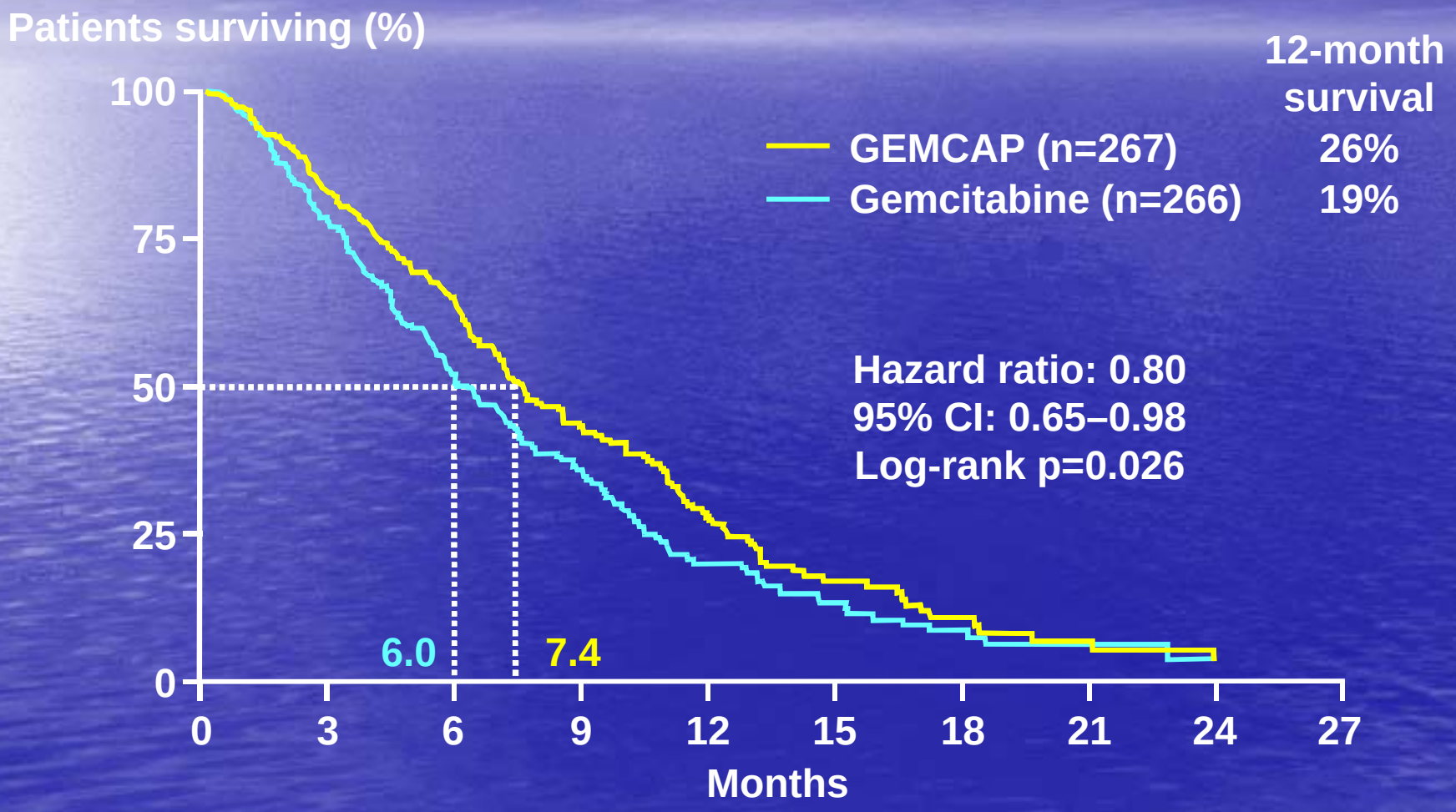
One week before

One month before

Negative phase III 1st-line Gem combination chemotherapy trials

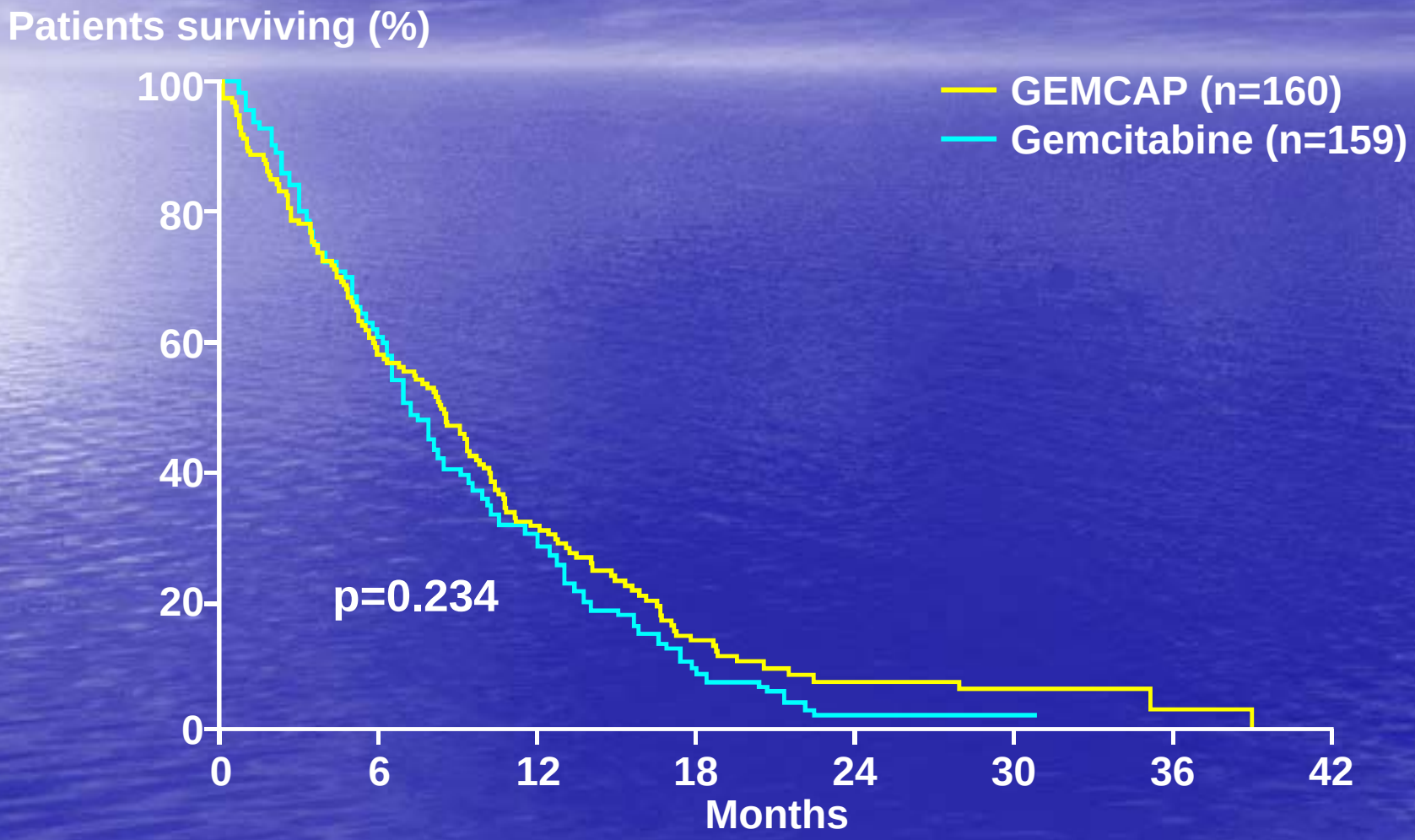
- Gemcitabine vs gemcitabine + 5-FU (n=316)
  - **Berlin J, et al. *J Clin Oncol.* 2002;20:3270-3275**
- Gemcitabine vs gemcitabine + irinotecan (n=360)
  - **Rocha Lima C, et al. *J Clin Oncol.* 2004;22:3776-3783**
- Gemcitabine vs gemcitabine + oxaliplatin (n=326)
  - **Louvet C, et al. *Proc ASCO.* 2004;22:14S (Abs. 4008)**
- Gemcitabine vs gemcitabine + pemetrexed (n=565)
  - **Richards D, et al. *Proc ASCO.* 2004;22:14S (Abs. 4007)**
- Gemcitabine vs gemcitabine + exatecan (n=349)
  - **O'Reilly E, et al. *Proc ASCO.* 2004;22:14S (Abs. 4006)**
- Gemcitabine vs gemcitabine + cisplatin + epirubicin + 5-FU (n=104)
  - **Reni M, et al. *Proc ASCO.* 2004;22:316S (Abs. 4010)**

UK NCRI
Gem-capecitabine vs Gem phase III study



Cunningham D et al. Eur J Cancer Suppl 2005

SAKK
Gem-capecitabine versus Gem phase III study



Herrmann R et al. Eur J Cancer Suppl 2005

Combination chemotherapy and effect according to performance status

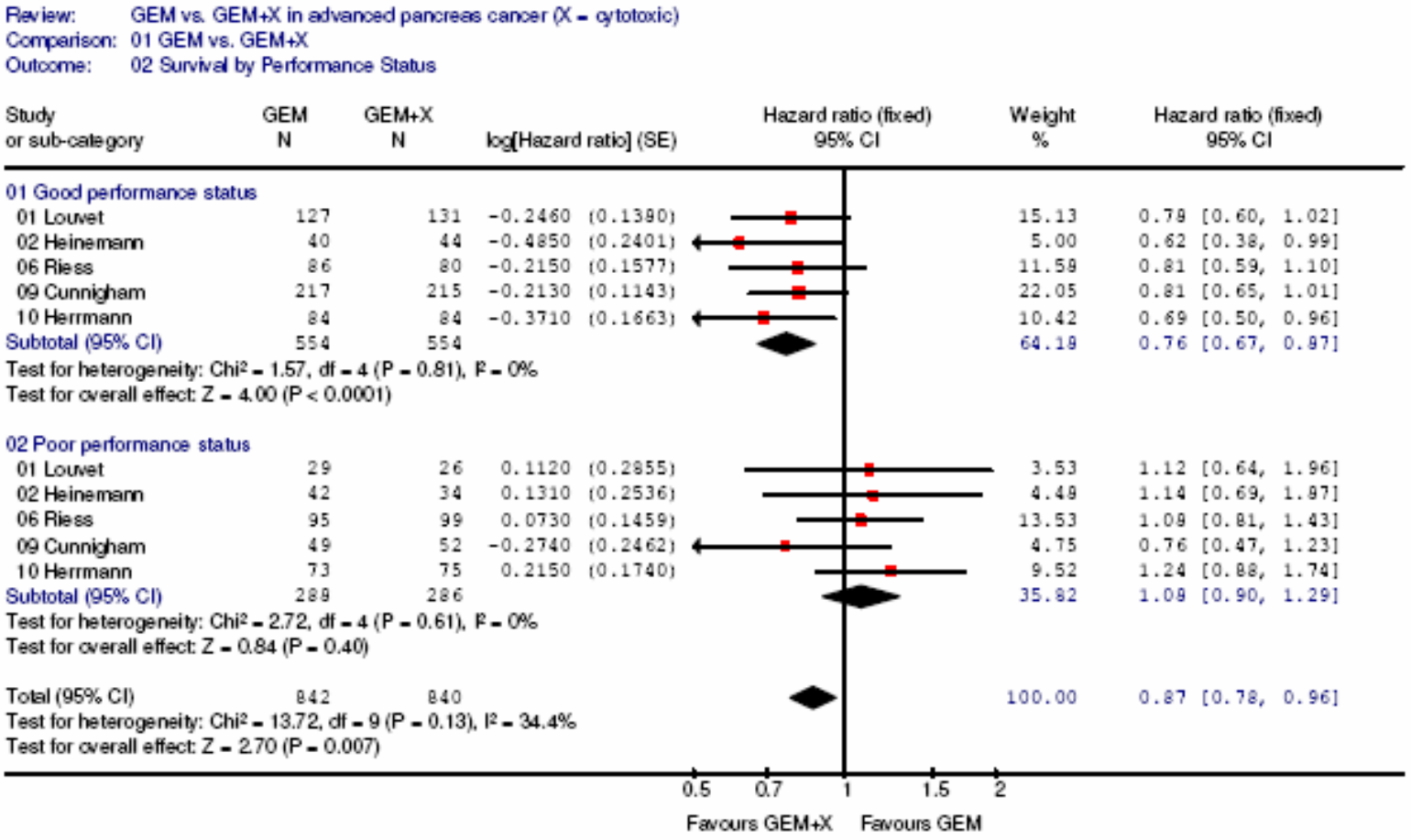


Figure 2
Meta-analysis for combination chemotherapy in advanced pancreatic cancer – overall survival with regard to performance status.

Heinemann et al., BMC Cancer 2008

Negative phase III trials of Gem vs. Gem + biological agents

Ras-farnesyltransferase inhibitors

- Gemcitabine vs gemcitabine + tipifarnib
  - **Van Cutsem E, et al. *J Clin Oncol.* 2004;22:1430-1438**

Matrix metalloproteinase inhibitors

- Gemcitabine vs gemcitabine + marimastat
  - **Bramhall S, et al. *Br J Cancer.* 2002;87:161-167**
- Gemcitabine vs BAY 12-9566
  - **Moore M, et al. *J Clin Oncol.* 2003;21:3296-3302**

Vaccines

- Gemcitabine vs gemcitabine + G17DT
  - **Aphton Corporation press release**
- Gemcitabine vs GW1001 + Gemcitabine at PD
  - **Pharmexa press release, 2008**

Negative phase III trials of Gem vs. Gem + biologic agents, cont.

Angiogenesis inhibitors

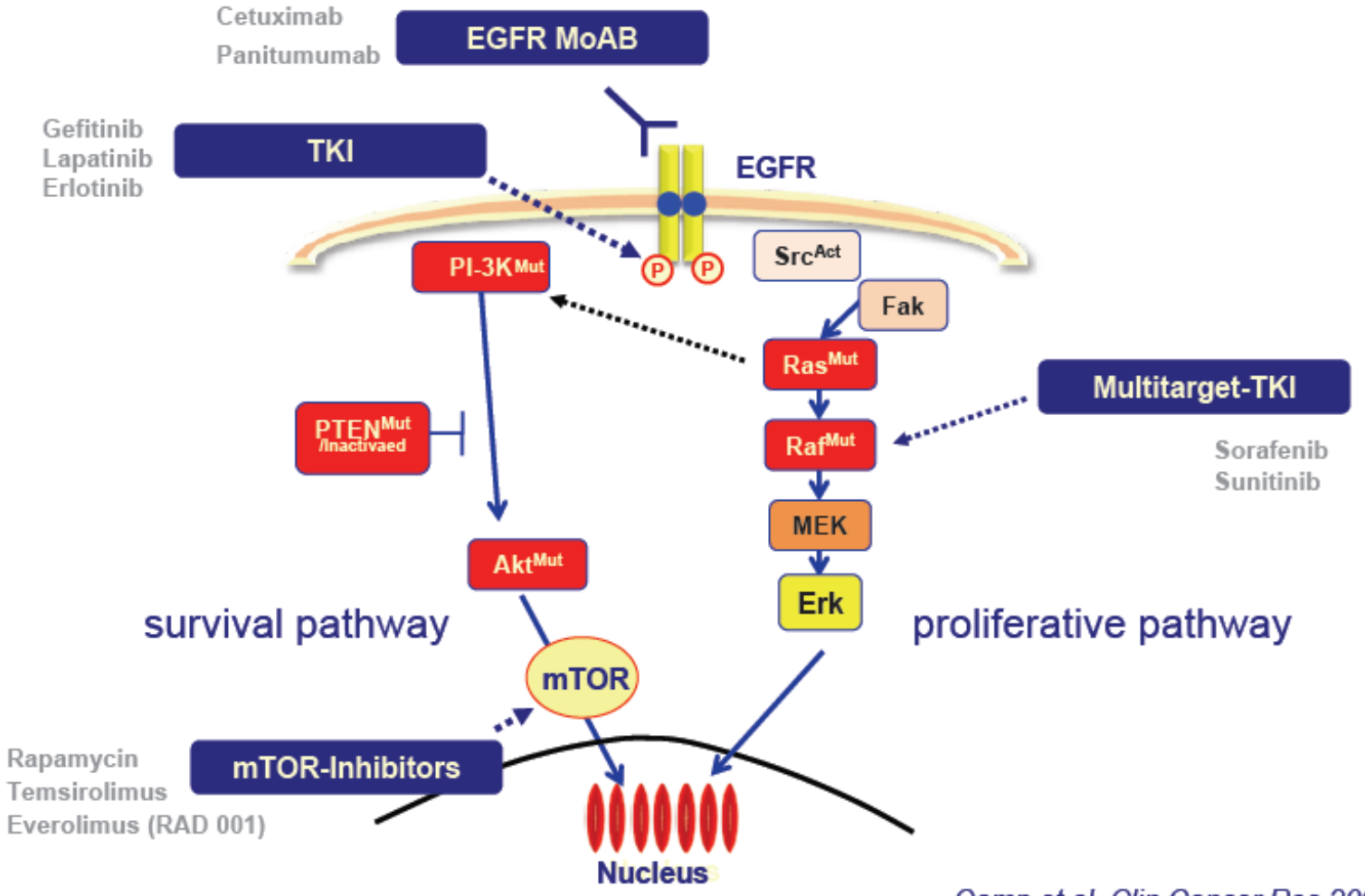
- Gemcitabine vs gemcitabine + bevacizumab
  - **Kindler, ASCO 2007**

- Gemcitabine + erlotinib vs gemcitabine + erlotinib + bevacizumab
  - **Vervenne, ASCO 2008**

Epidermal Growth Factor Receptor inhibitors

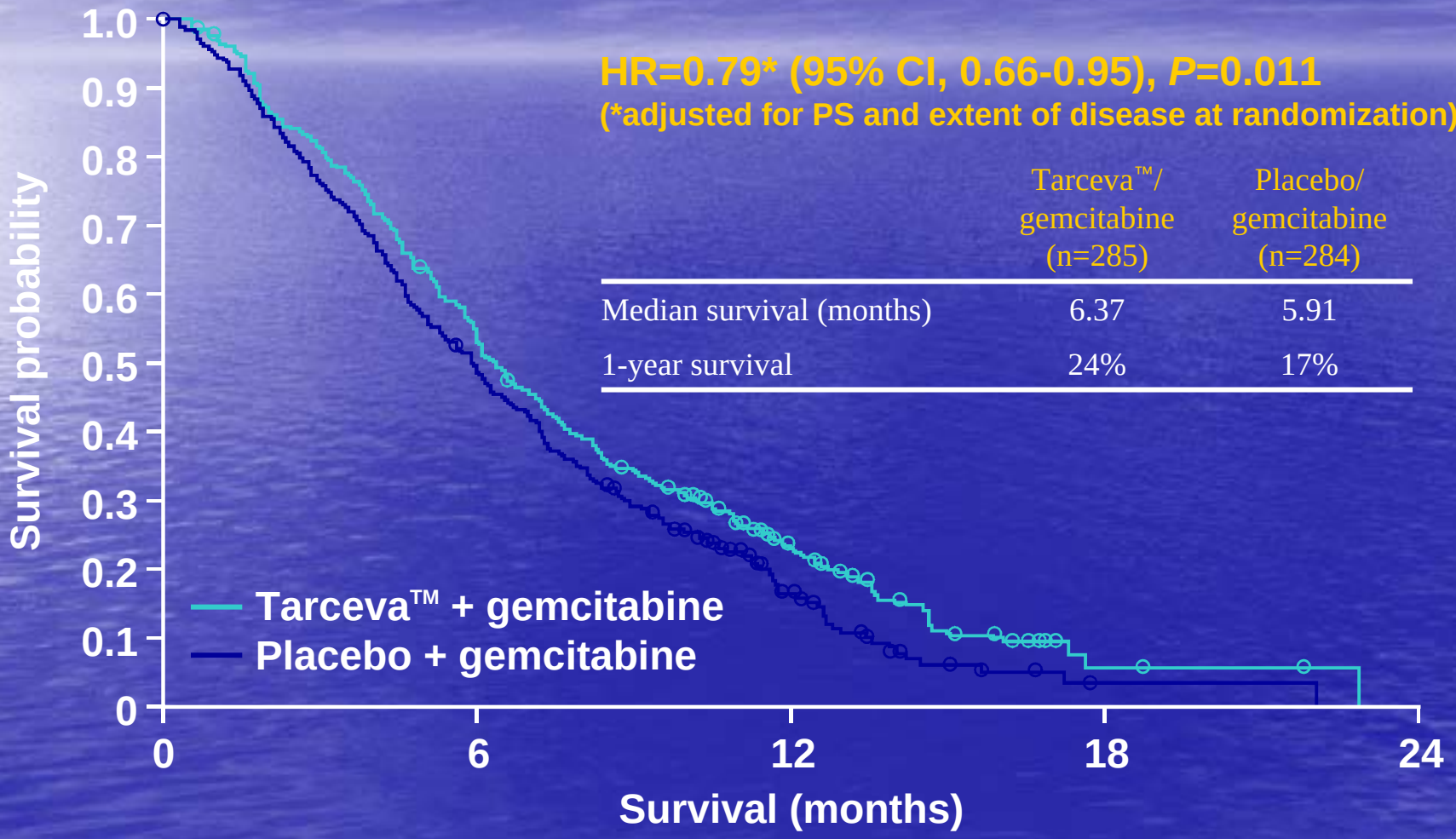
- Gemcitabine vs gemcitabine + cetuximab
  - **Philip, ASCO 2007**

EGFR-mediated signal transduction



Camp et al, Clin Cancer Res 2005

PA.3 study, Gem + erlotinib vs Gem + placebo



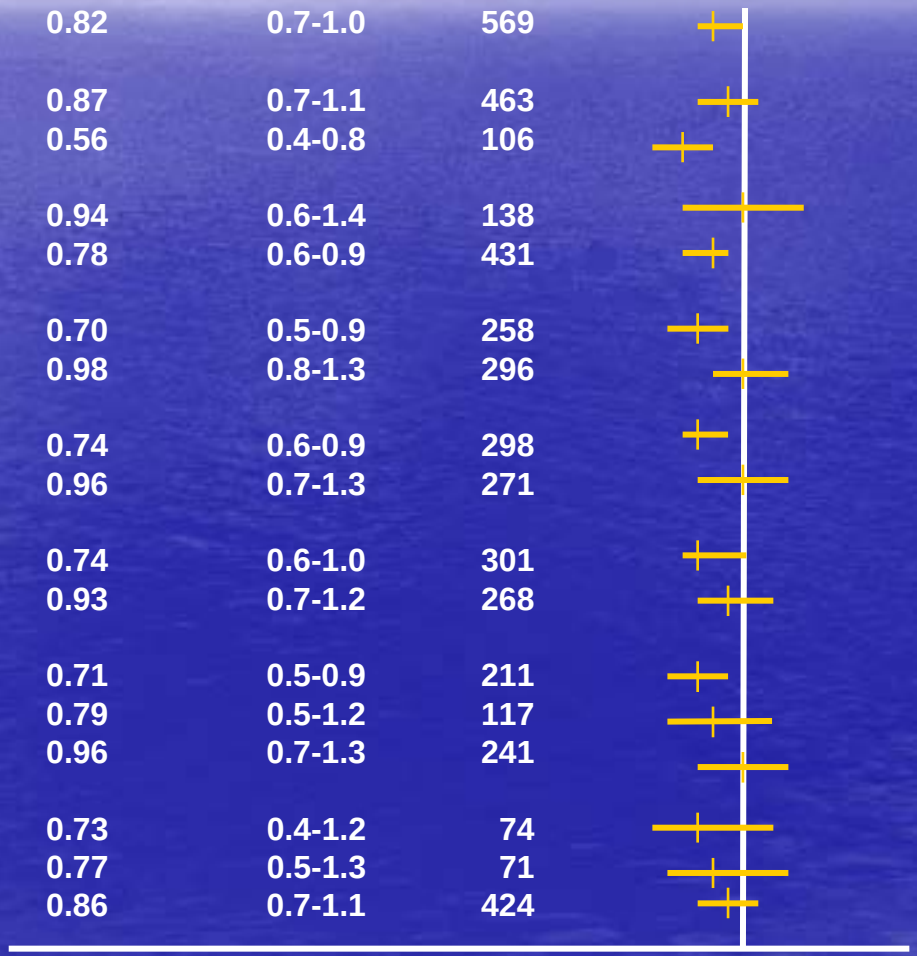
HR=0.79* (95% CI, 0.66-0.95), *P*=0.011
(*adjusted for PS and extent of disease at randomization)

	Tarceva™/ gemcitabine (n=285)	Placebo/ gemcitabine (n=284)
Median survival (months)	6.37	5.91
1-year survival	24%	17%

Moore et al., JCO 2007

PA.3 study, Hazard ratios for survival

Factors	HR	95% CI	n
Tarceva:placebo	0.82	0.7-1.0	569
Performance status 0-1	0.87	0.7-1.1	463
Performance status 2	0.56	0.4-0.8	106
Locally advanced	0.94	0.6-1.4	138
Distant metastasis	0.78	0.6-0.9	431
Pain ≤20	0.70	0.5-0.9	258
Pain >20	0.98	0.8-1.3	296
Male	0.74	0.6-0.9	298
Female	0.96	0.7-1.3	271
Age <65	0.74	0.6-1.0	301
Age ≥65	0.93	0.7-1.2	268
United States	0.71	0.5-0.9	211
Canada	0.79	0.5-1.2	117
Rest of World	0.96	0.7-1.3	241
HER1/EGFR positive	0.73	0.4-1.2	74
HER1/EGFR negative	0.77	0.5-1.3	71
HER1/EGFR unknown	0.86	0.7-1.1	424



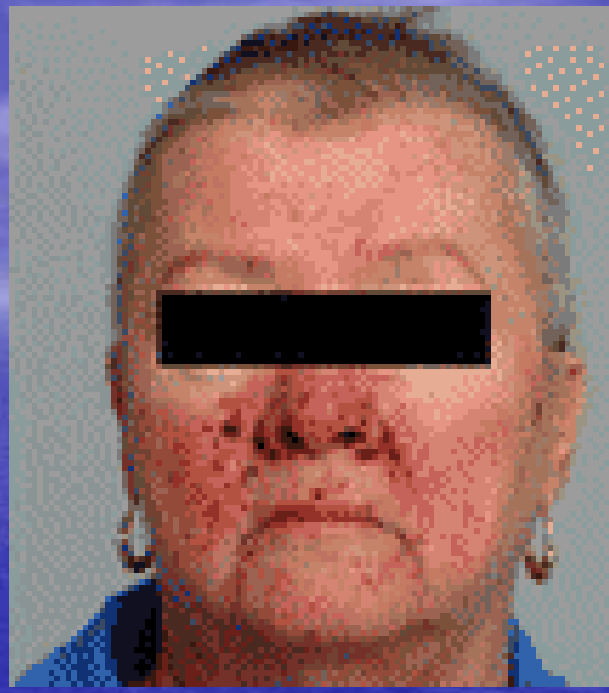
Moore et al., JCO 2007

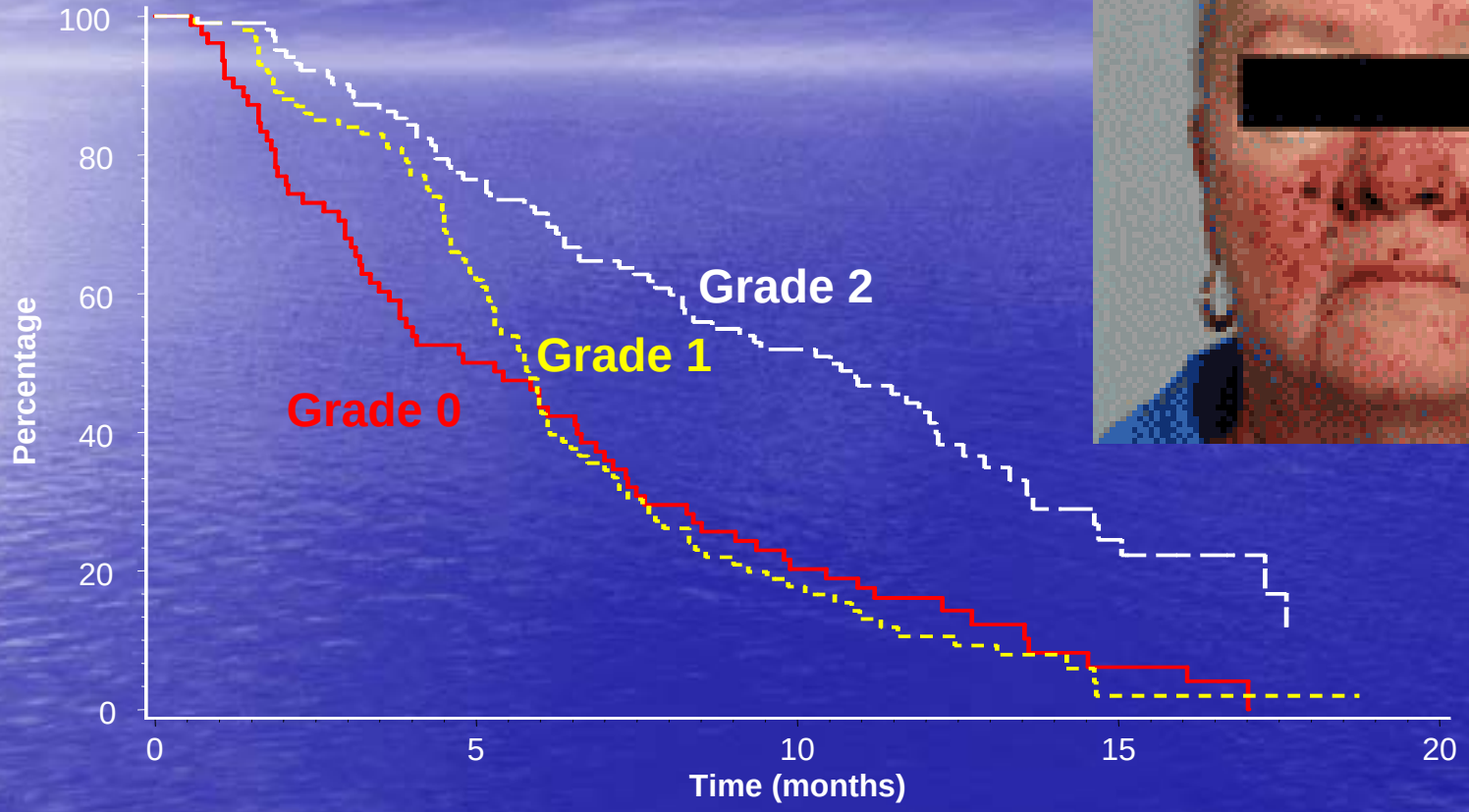
PA.3 study, Adverse events

	Tarceva (%) n=282		Placebo (%) n=280	
Events	Any	Grade 3,4	Any	Grade 3,4
Rash	72	6	29	1
Diarrhoea	56	6	41	2
Infection	43	17	34	16
Stomatitis	23	<1	14	0
Pneumonitis	2	2	1	<1
Fatigue	89	15	86	15

Moore et al., JCO 2007

PA.3 study,
Rash vs survival





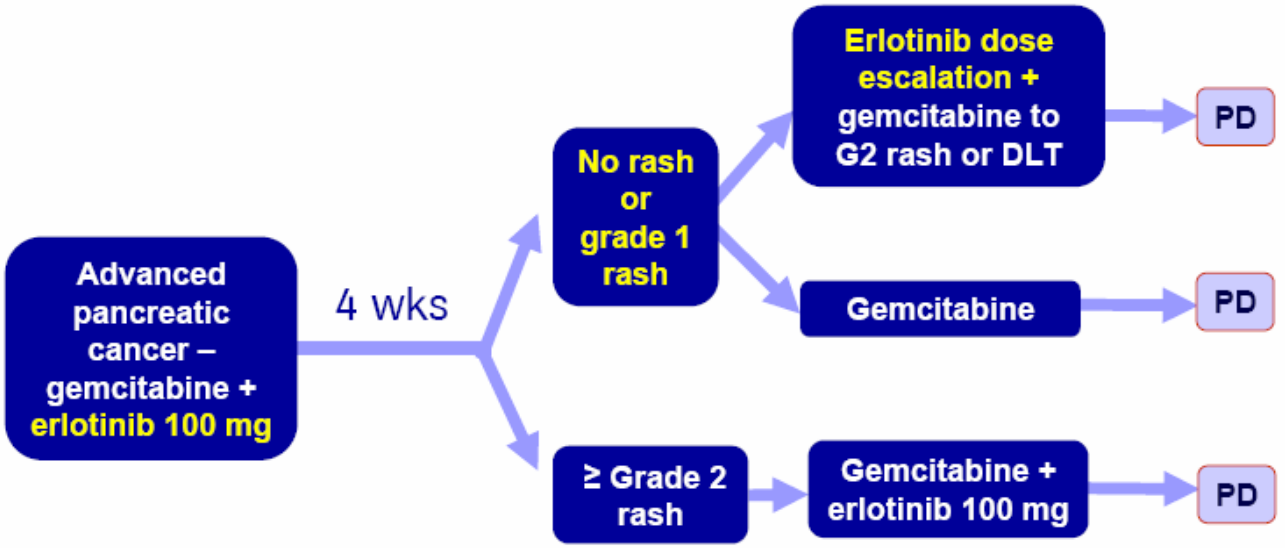
HR [Rash]= 0.71

p<0.0001

Moore et al., JCO 2007

Further studies to identify subset of pts who benefit from erlotinib or to increase effect

Can dose escalation of erlotinib improve outcome?



- Primary endpoint: OS
- Mandatory tissue collection
- Secondary endpoints: PFS, disease control, safety, correlation of EGFR-related biomarkers with outcome (EGFR, EGF, TGFα, K-ras, pAKT, pMAPK)

2nd-line treatment?

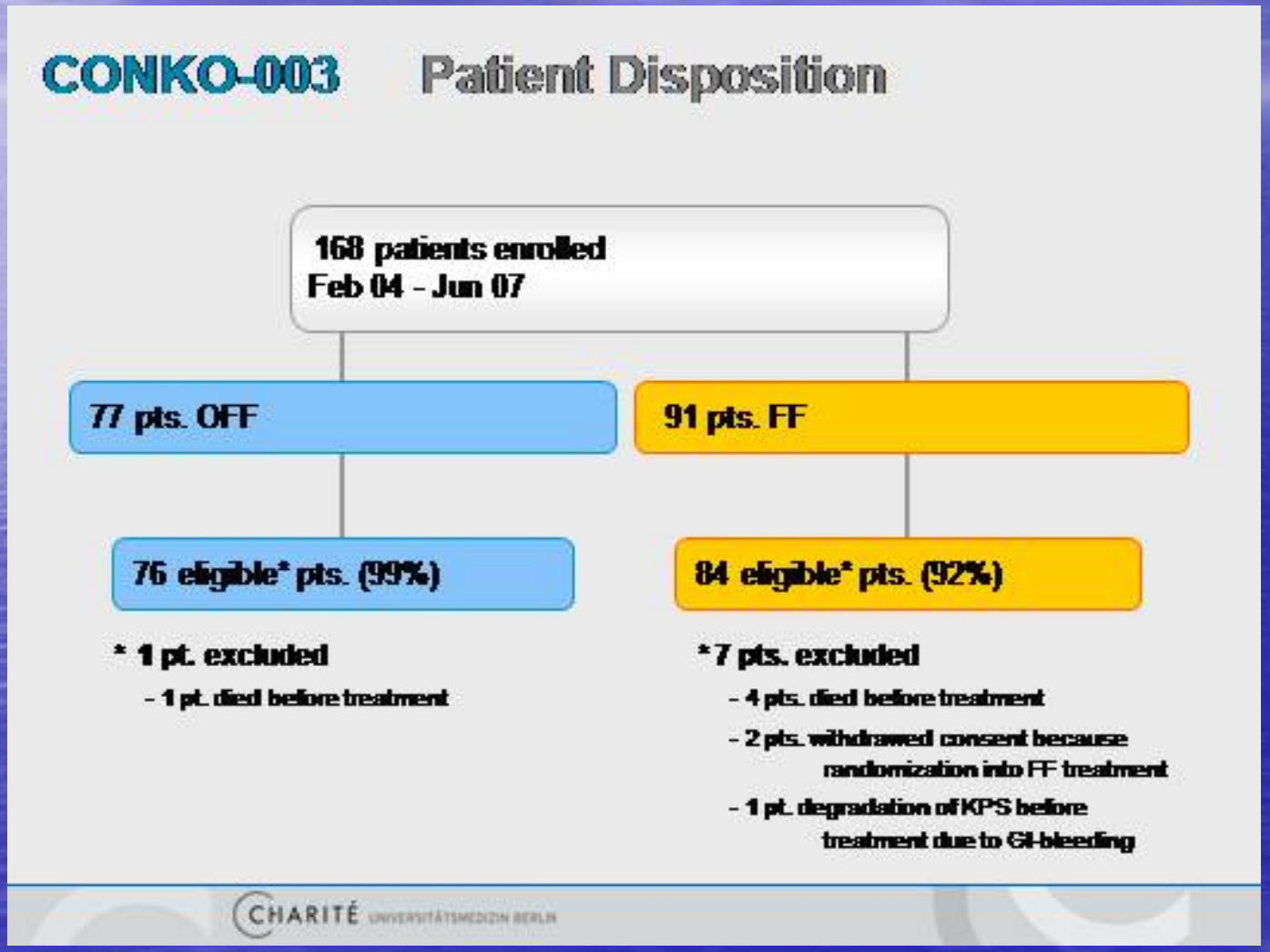
2nd-Line After Failure of Gemcitabine

Agent	n	PFS	OS
Pemetrexed	52	1.6	4.7
Capecitabine	39	2.3	7.6
Capecitabine + Oxaliplatin	39	na	5.8
5-FU/FA + Oxaliplatin	30	5.1	5.8
Gemcitabine + Oxaliplatin	33	4.2	6.0
Gemcitabine + Cisplatin	24	na	4.0
Capecitabine + Erlotinib	30	3.4	6.5
Irinotecan + Oxaliplatin	30	4.1	5.9

PFS 1.6 – 5.1 months
OS 4.7 – 7.6 months

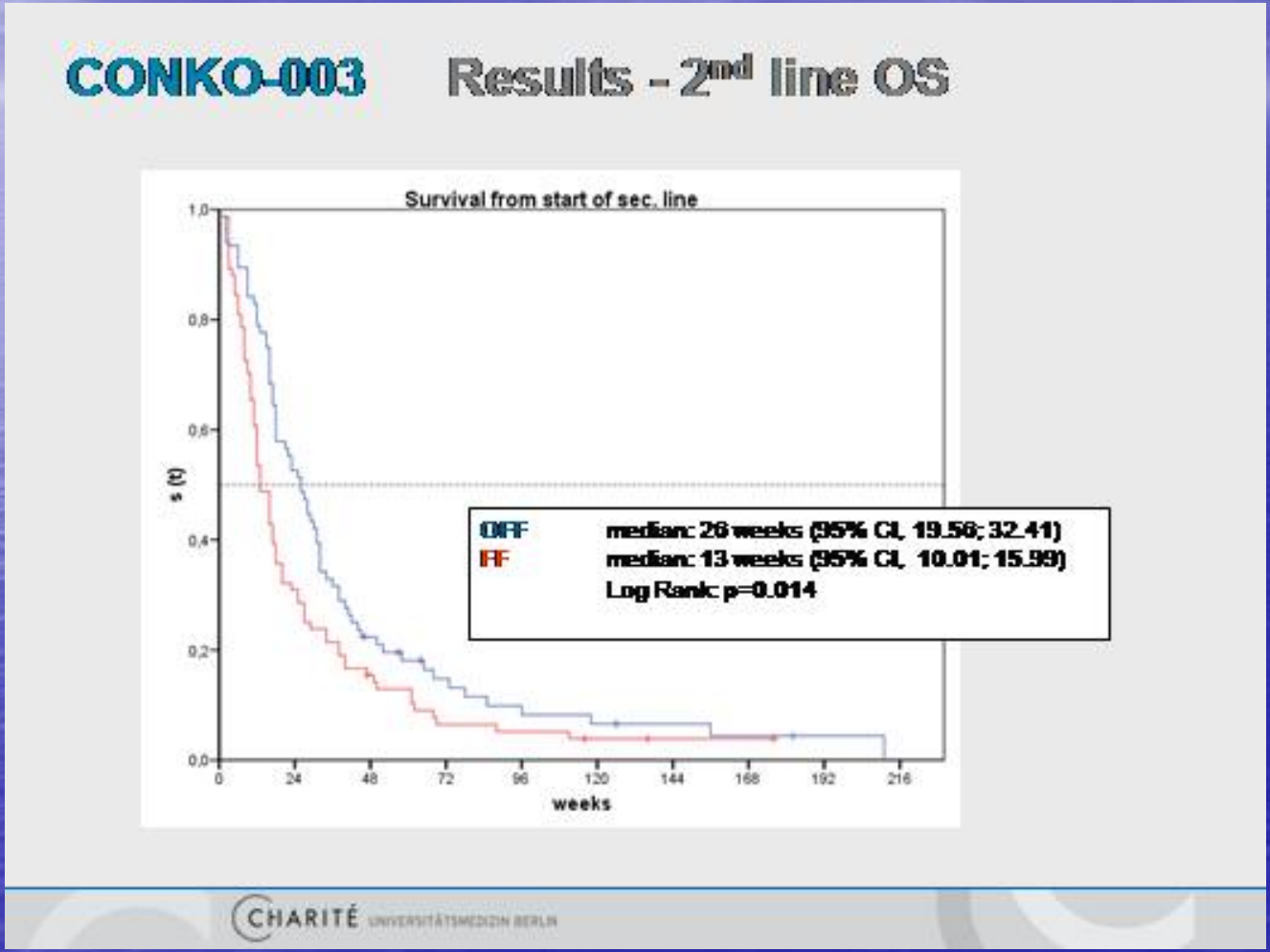
Boeck S, Heinemann V, Future Oncology 2008

CONKO-003,
Phase III-study of oxaliplatin-5FU vs. 5FU



Pelzer et al., ASCO 2008

CONKO-003,
Phase III-study of oxaliplatin-5FU vs. 5FU



Pelzer et al., ASCO 2008

Current acceptable choises of palliative treatment of advanced disease

1st-line

- Gem alone or combined with either erlotinib, capecitabine or oxaliplatin/cisplatin for good PS patients
- Gem or Gem + erlotinib for intermediate PS patients
- BSC for poor PS patients
- Protocols

2nd-line

- BSC
- Treatment preferably in protocols
- Oxaliplatin-5FU should be considered for fit patients, especially those with long TTP on 1st-line