Modern treatment of pancreatic cancer 2009 update

Resectable disease
Locally advanced disease
Advanced disease

Supportive care
Pancreatic neuro-endocrine tumours

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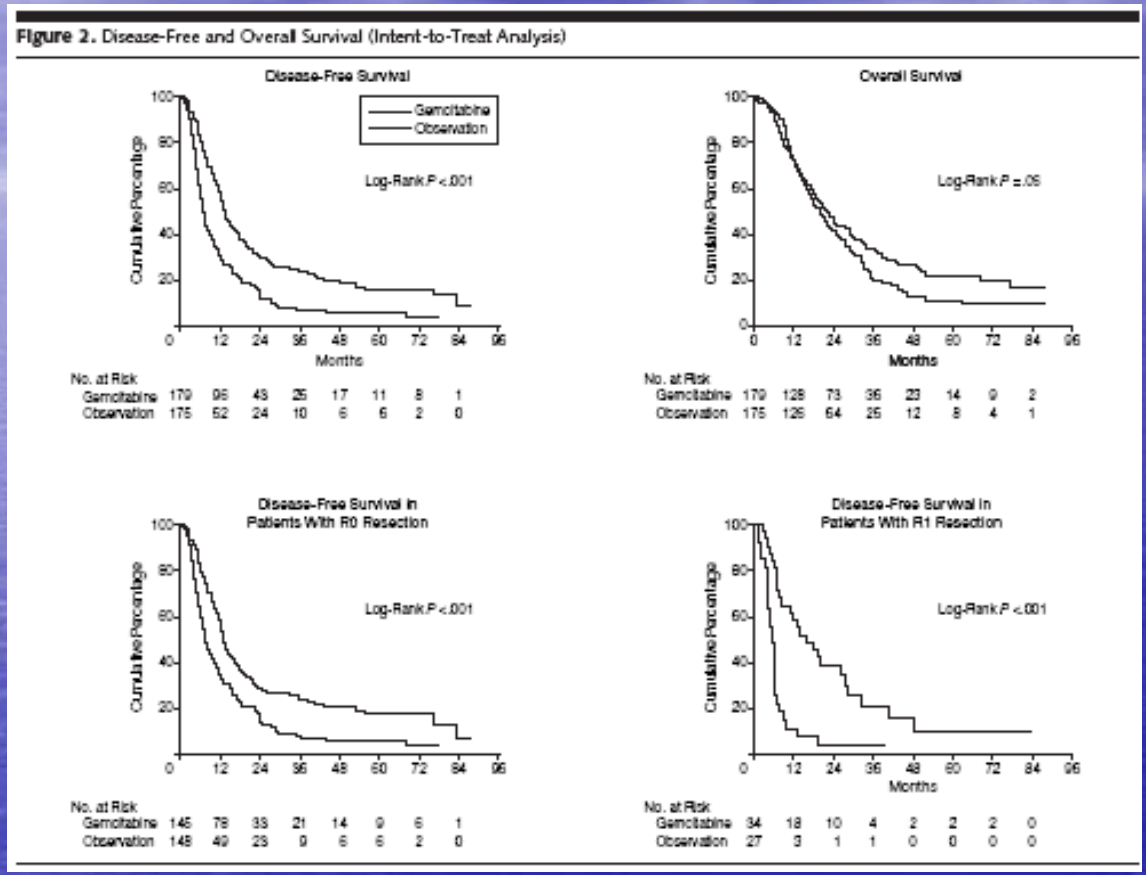
RESECTABLE DISEASE

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

SEER Cancer Statistics Review 1975-2001

RESECTABLE DISEASE

CONKO-001, Gem vs observation

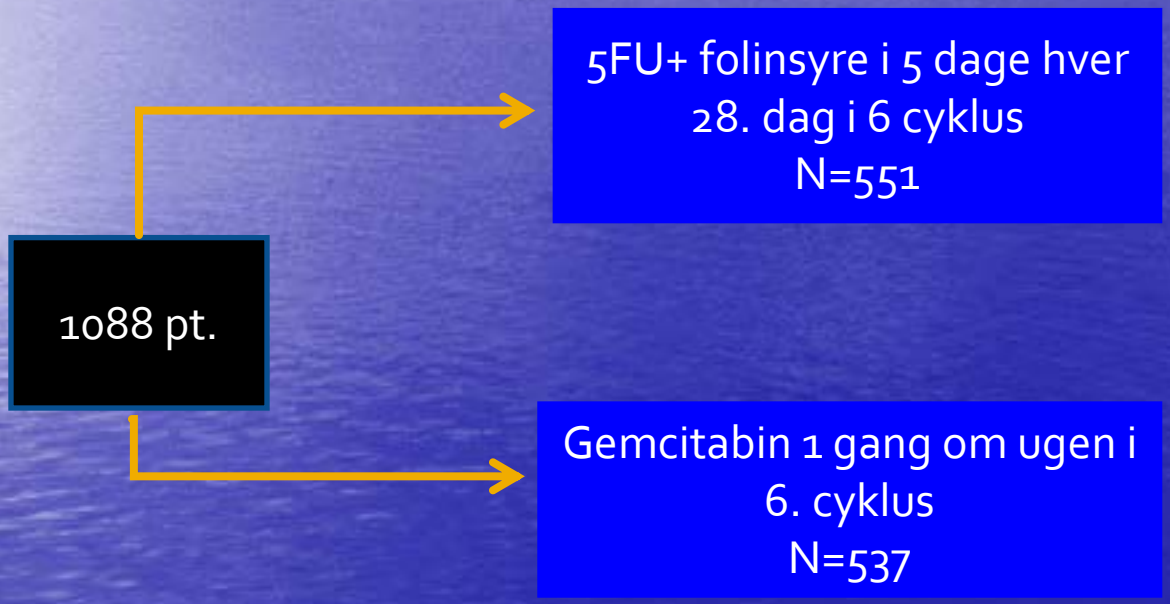


Significant increase in median survival from 20 to 23 months
Increase in est. 5-year survival rate from 9% to 21%
Beneficial effect in all subgroups

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

ESPAC-3

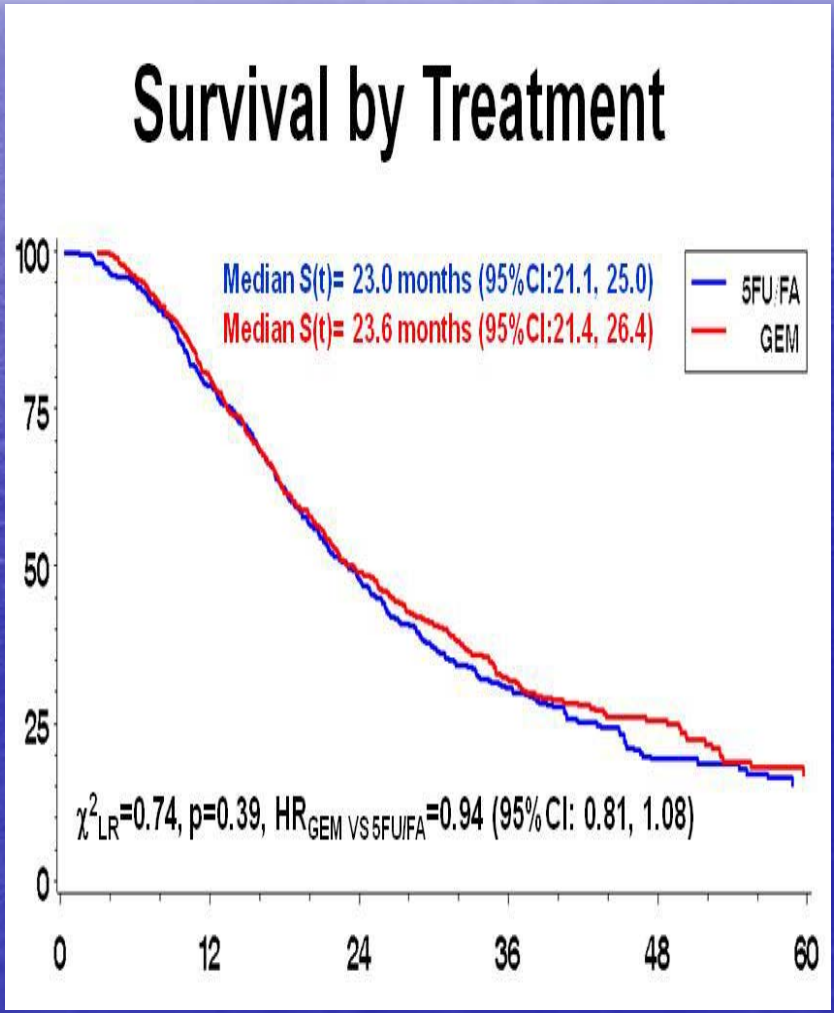
ESPAC-3: A multicenter, international, open-label, randomized, controlled phase III trial of adjuvant 5-fluorouracil/folinic acid (5-FU/FA) versus gemcitabine (GEM) in patients with resected pancreatic ductal adenocarcinoma. Neoptolemos et al., ASCO 2009



3. arm BSC lukket præmaturt grundet signifikant effekt af Gem vs BSC.
R0/R1 resektion < 8 uger efter operation

ESPAC-3

ESPAC-3: A multicenter, international, open-label, randomized, controlled phase III trial of adjuvant 5-fluorouracil/folinic acid (5-FU/FA) versus gemcitabine (GEM) in patients with resected pancreatic ductal adenocarcinoma. Neoptolemos et al



News 2009, adjuvant treatment

- Gem og 5FU er lige effektive, men Gem er mindst toksisk
- GemCap vs. Gem er i fase III (ESPAC-4)

LOCALLY ADVANCED DISEASE

Options

- Chemotherapy
  - Gem
  - Gem in combinations
- Chemoradiotherapy

Overall survival on Gem

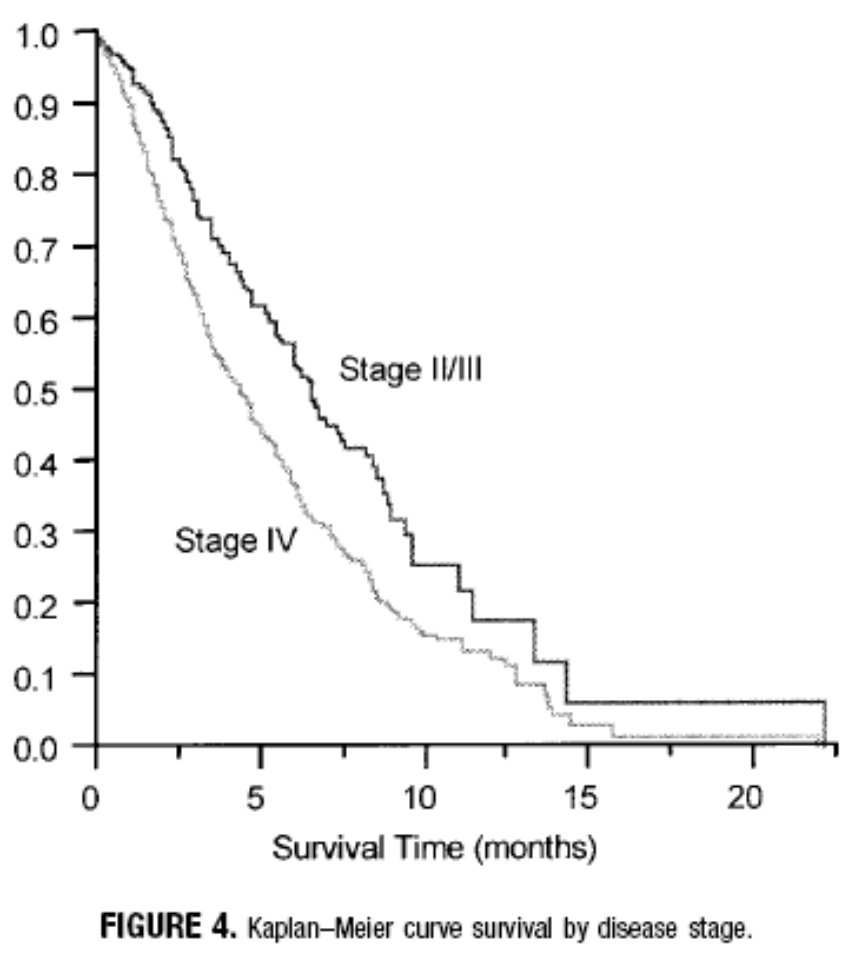


FIGURE 4. Kaplan–Meier curve survival by disease stage.

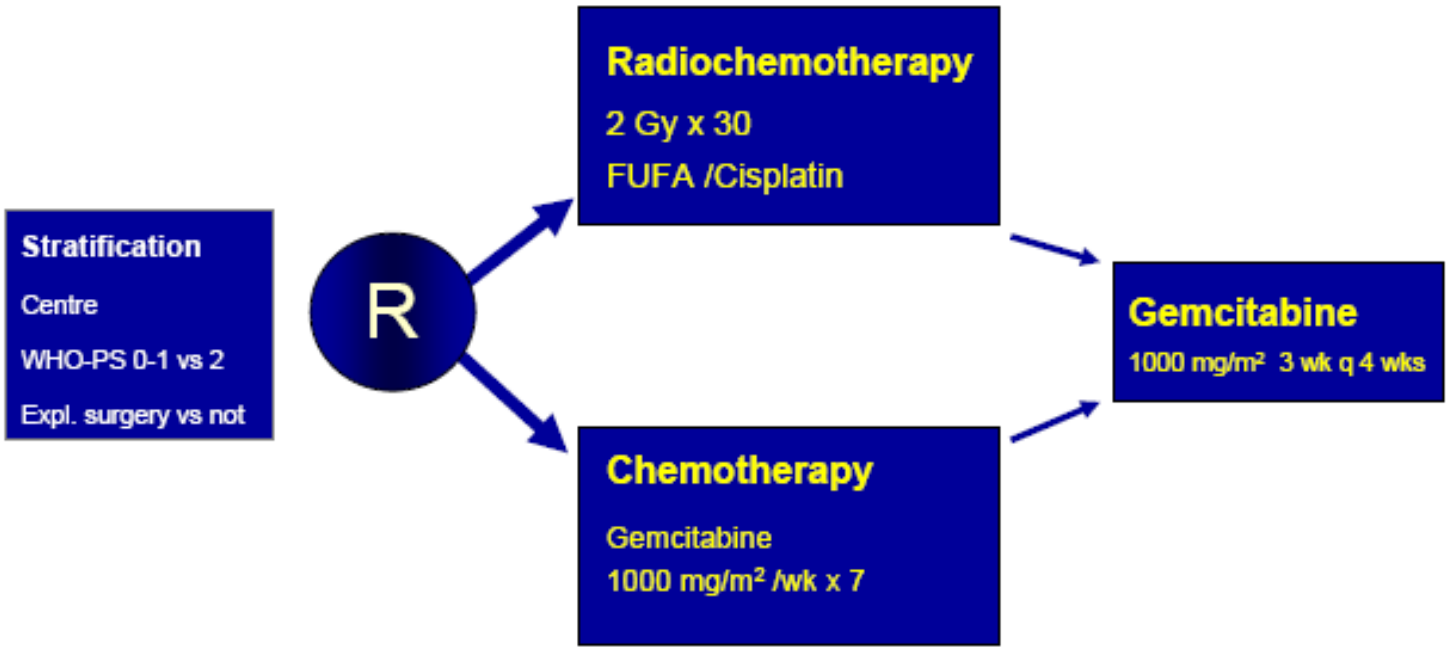
Storinolo et al., Cancer 1998

Chauffert et al.,

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

Chemoradiotherapy vs Chemotherapy

in locally advanced pancreatic cancer

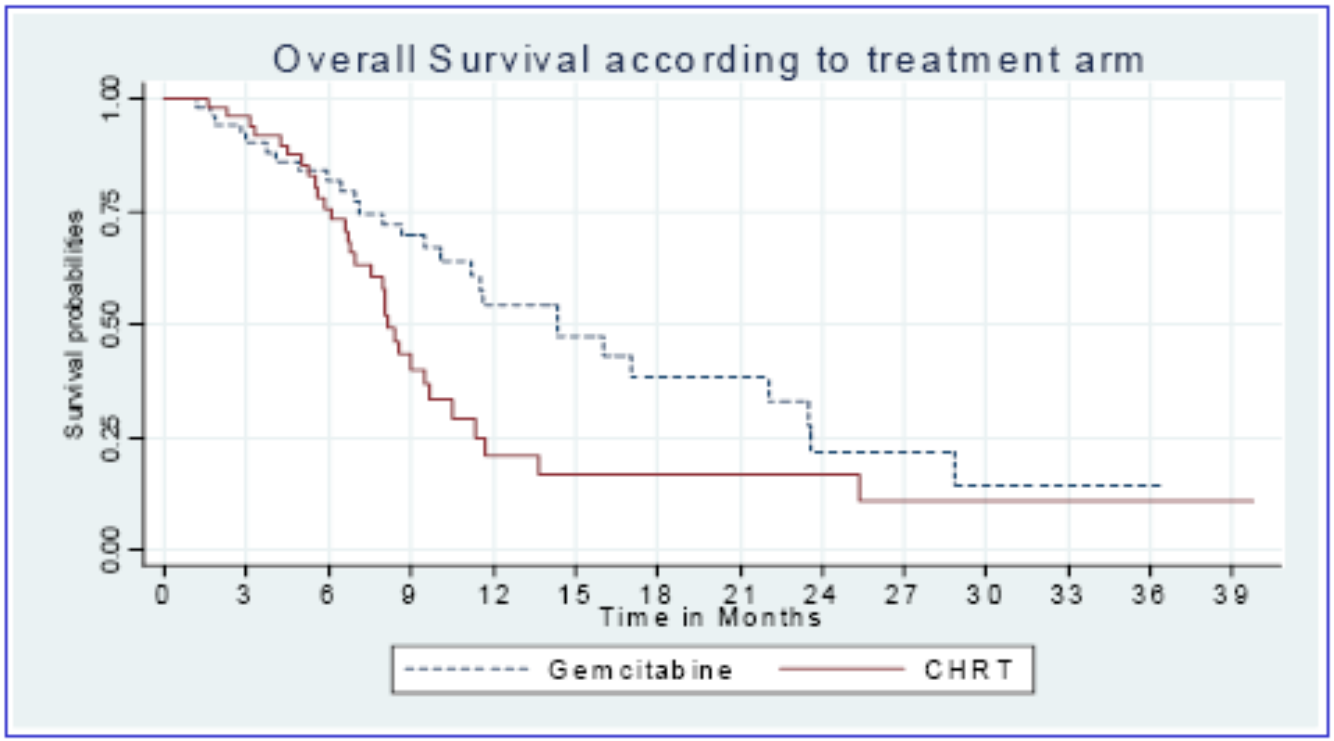


recruitment
planned: 176 pts
stop after: 119 pts

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 vs. 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

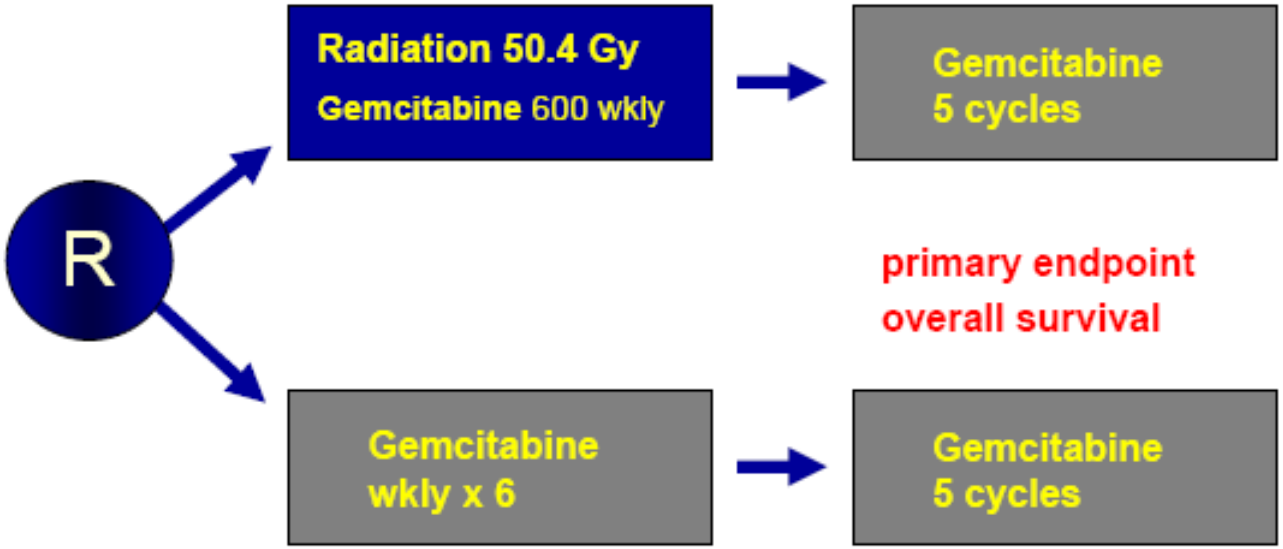
Cumulative dose of gemcitabine

	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

Loehrer et al.,
Phase III-study of Gem vs. Gem-based CRT

E4201 Study: Phase III in LAPC

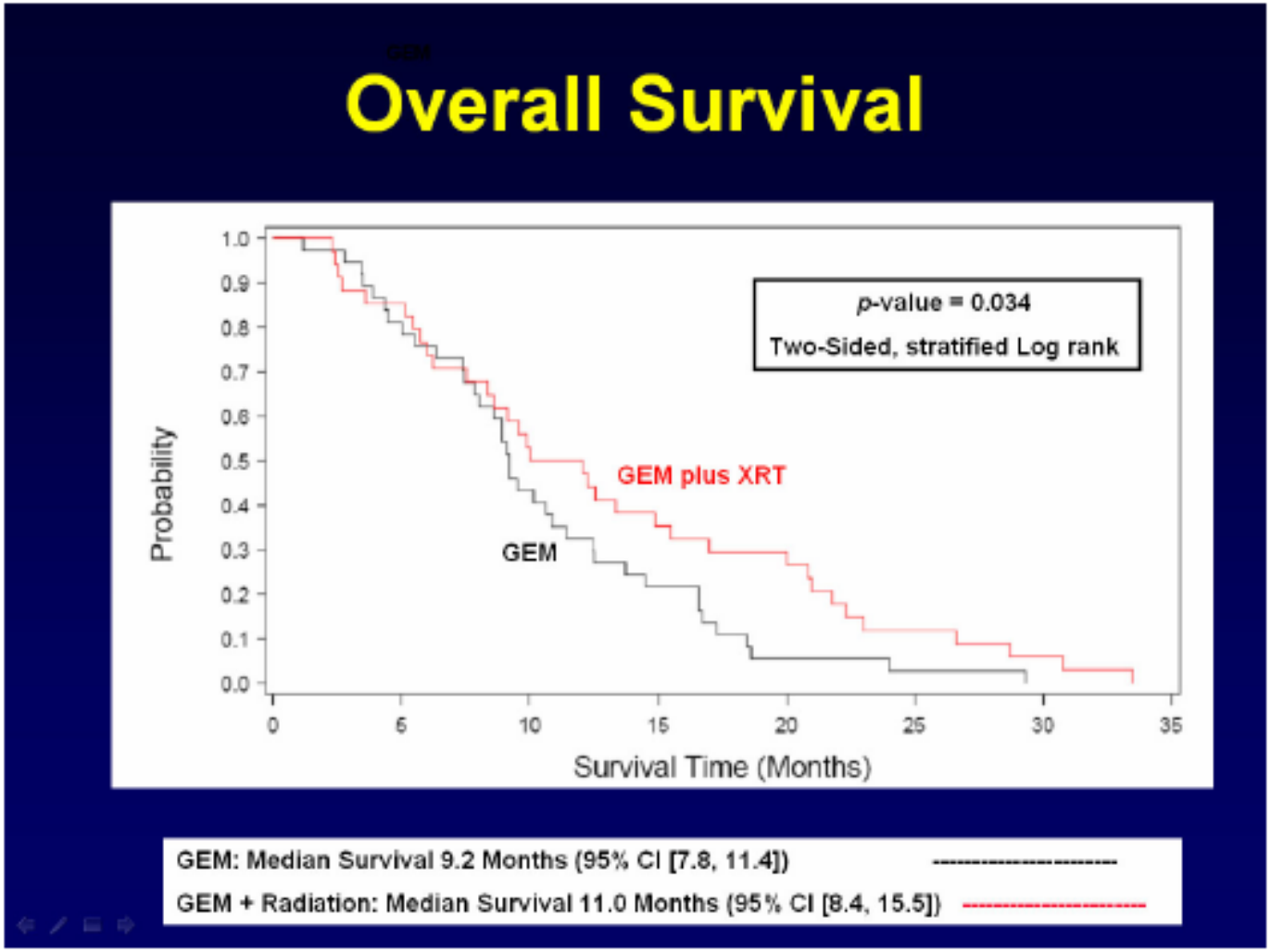


3D conformal radiation
central review of treatment dose volume

recruitment
planned: 316 pts
stop after: 74 pts

Loehrer et al. ASCO 2008, #4506,.

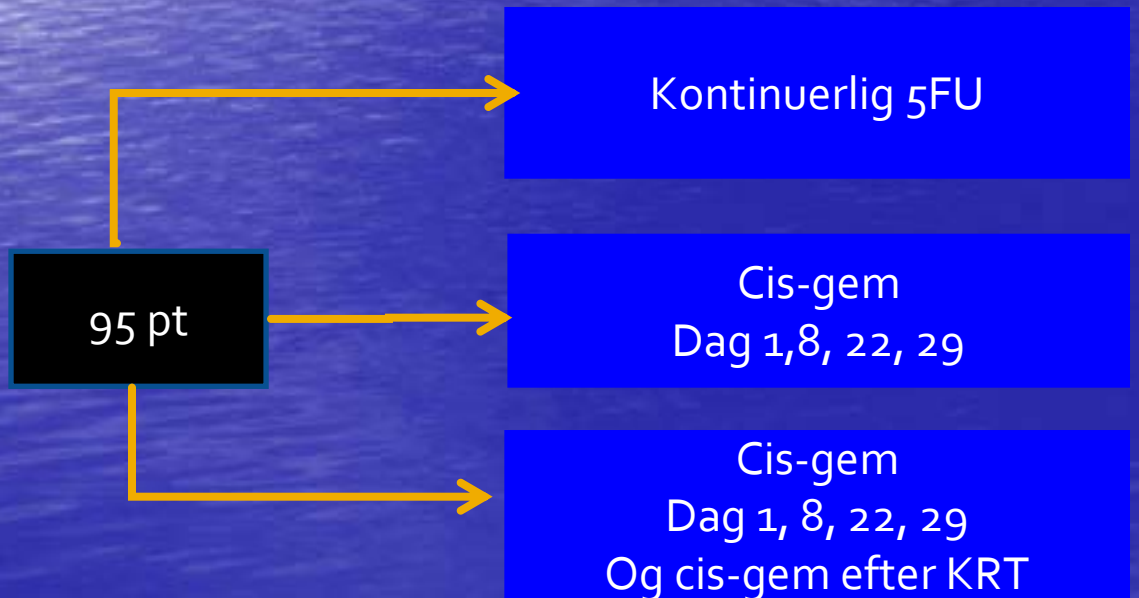
Loehrer et al.,
Phase III-study of Gem vs. Gem-based CRT



Loehrer et al. ASCO 2008, #4506,.

Wilkowski et al. Final analysis of a multicenter, randomized phase II trial comparing three different chemoradiotherapy regimens in the treatment of patients with locally advanced, nonmetastatic pancreatic cancer. ASCO 2009

- 3 forskellige kemo-regimer med konkomittant strålebehandling á 50GY/25fr.



Final analysis of a multicenter, randomized phase II trial comparing three different chemoradiotherapy regimens in the treatment of patients with locally advanced, nonmetastatic pancreatic cancer. Ralf Wilkowski

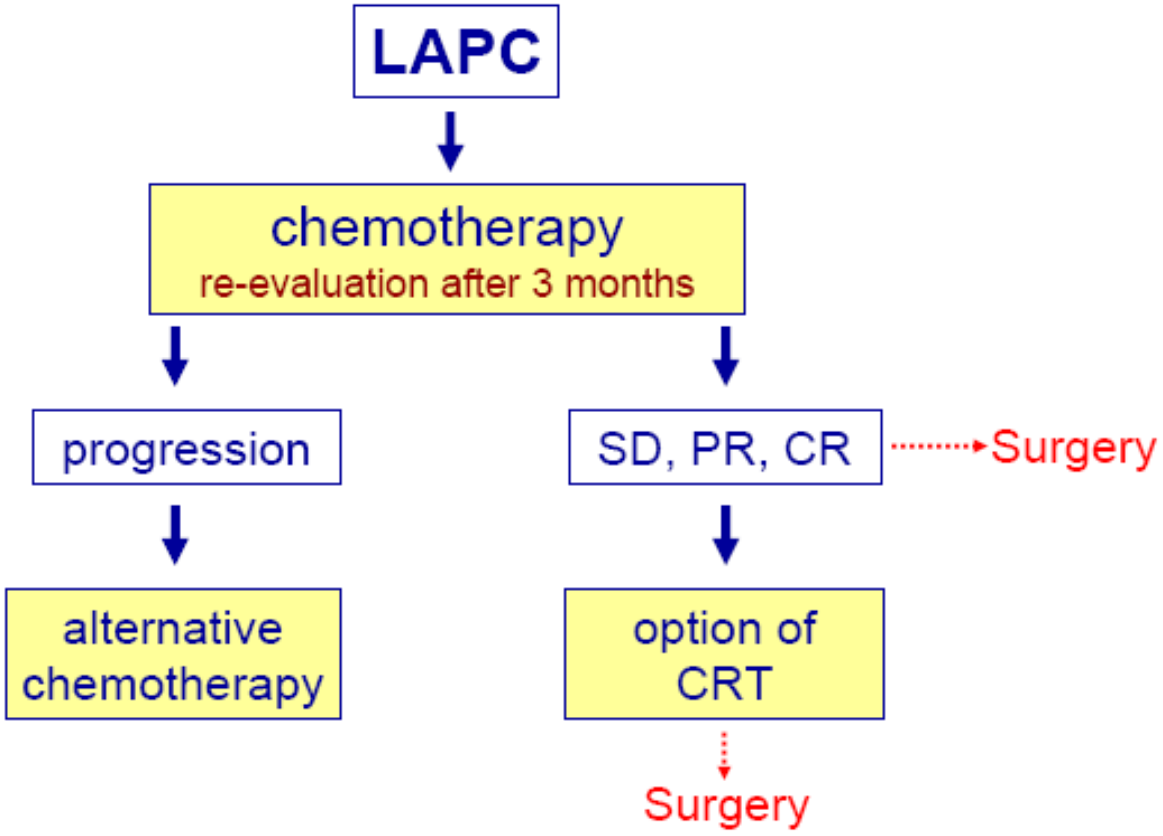
	PFS (mdr)	OS (mdr)	Hæm.tox	Diarre
RKT-5FU	4	9,6		+
RKT-GC	5,6	9,3	+	
RKT-GC + GC	6	7,3	+	

- 18 patienter blev opereret. Fordeling ukendt!
- Højere frekvens af grad 3/4 hæmotologiske bivirkninger i GC armene
- Ingen forskel mellem 5FU og Gem/Cis.

Konklusioner

- Stadig ikke afklaret om kemo-radioterapi forlænger overlevelsen i forhold til kemoterapi alene
- Ikke afklaret, hvilken kemoterapi der er bedst sammen med radioterapi
- Kemo-radioterapi kan i udvalgte tilfælde medføre konvertering af sygdom fra ikke-resektabel til resektabel, men det kan kemoterapi alene også

Treatment Algorithm in LAPC

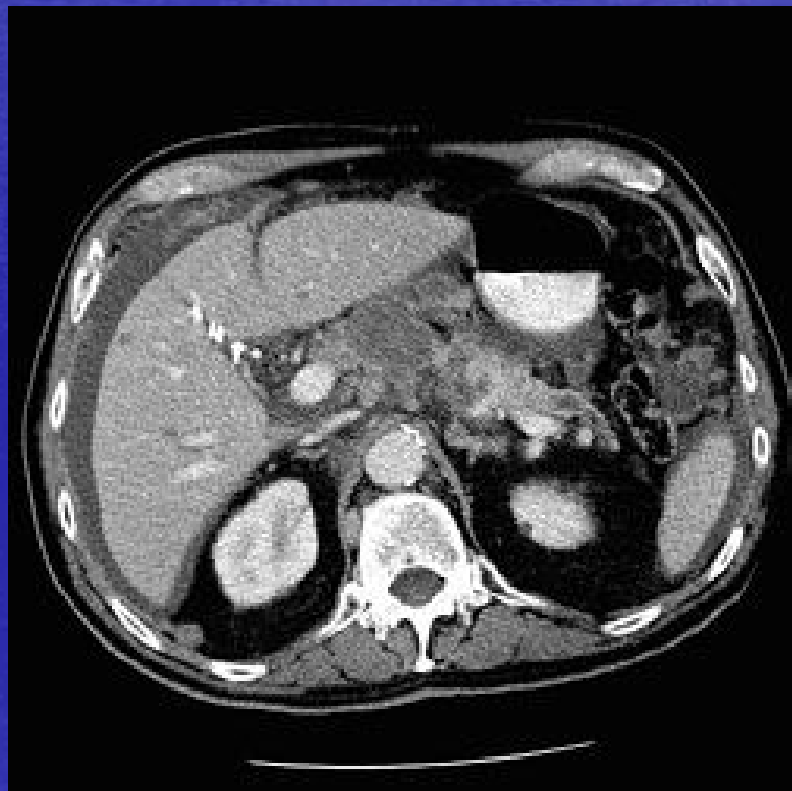


Herrmann 2008

ADVANCED DISEASE

Advanced disease

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



Gemcitabine 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. *J Clin Oncol.* 1997;15:2403-2413

Survival of Gem-treated patients according to performance status

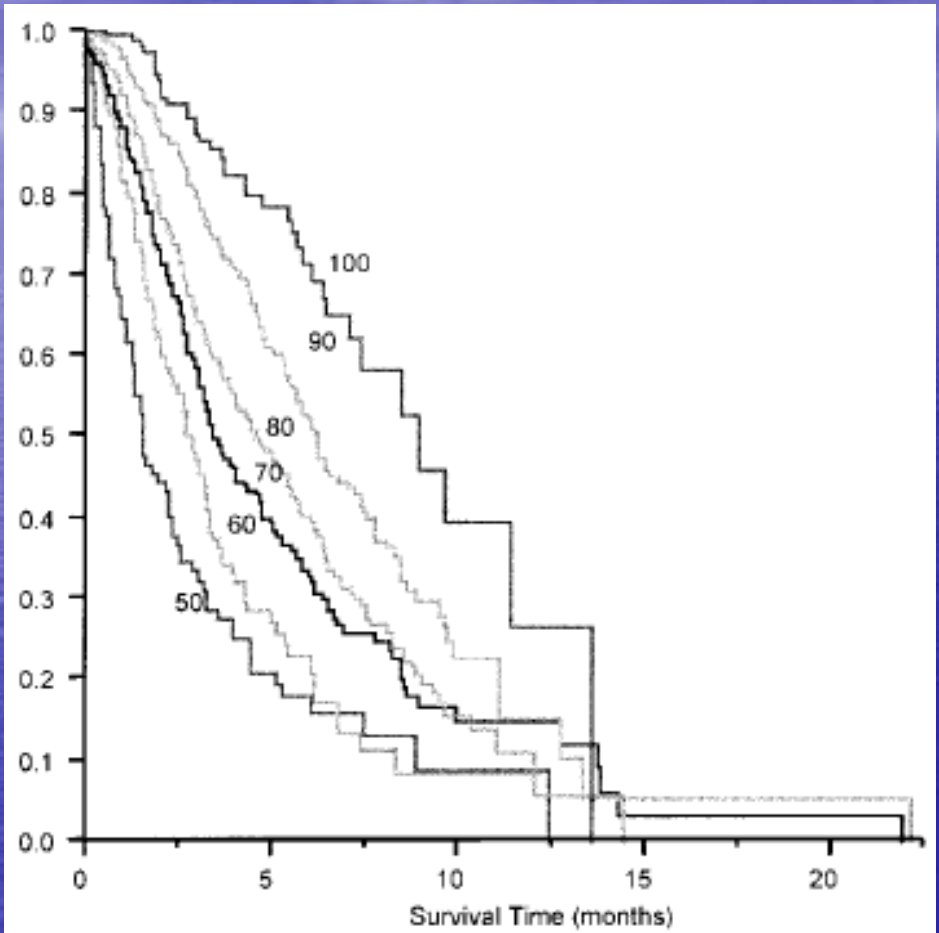


FIGURE 3. Kaplan–Meier curve survival by baseline Karnofsky performance status.

Storinolo et al., Cancer 1998

Combination chemotherapy Gem-Cap

Phase III Randomized Comparison of Gemcitabine Versus Gemcitabine Plus Capecitabine in Patients With Advanced Pancreatic Cancer

David Cunningham, Ian Chau, Deborah D. Stocken, Juan W. Valle, David Smith, William Steward, Peter G. Harper, Janet Dunn, Catrin Tudur-Smith, Julia West, Stephen Falk, Adrian Crellin, Fawzi Adab, Joyce Thompson, Pauline Leonard, Joe Ostrowski, Martin Eatock, Werner Scheithauer, Richard Herrmann, and John P. Neoptolemos

JCO, october 2009

Cunningham et al.: GEM-CAP

Final analysis 2009

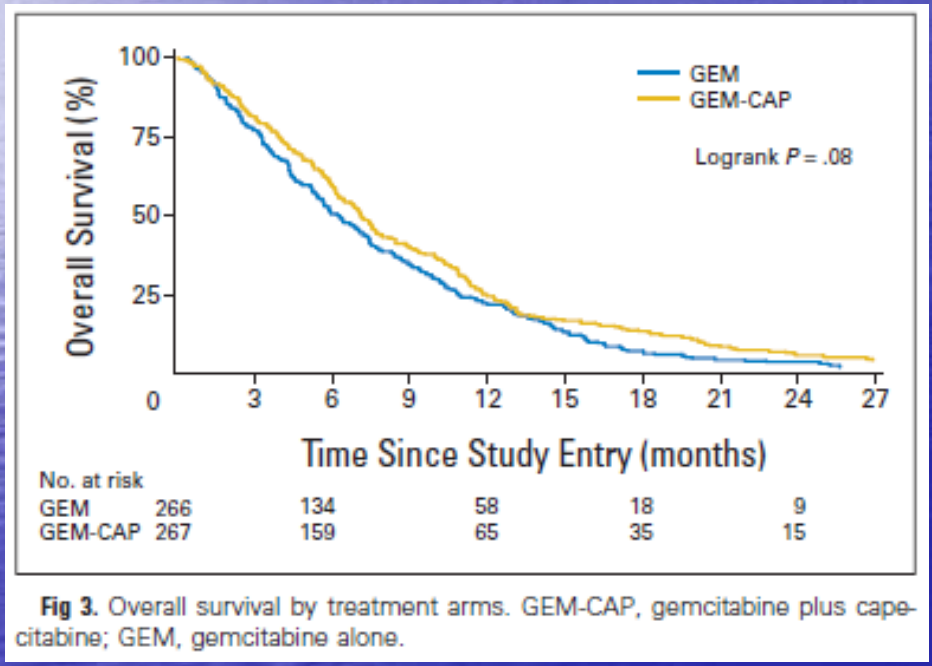
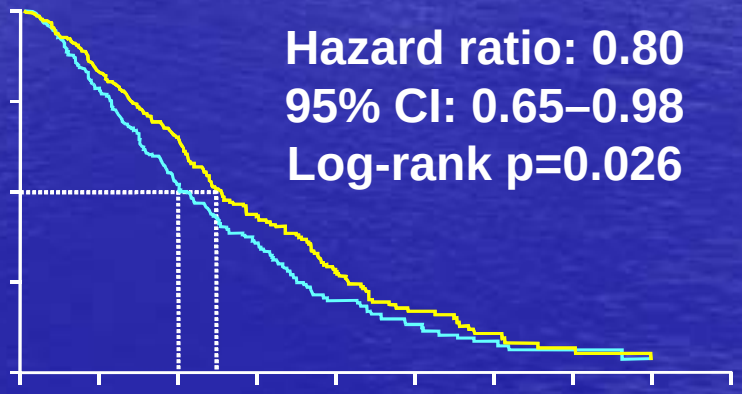


Fig 3. Overall survival by treatment arms. GEM-CAP, gemcitabine plus capecitabine; GEM, gemcitabine alone.

Interim analysis 2005



Hazard ratio: 0.80
95% CI: 0.65–0.98
Log-rank p=0.026

Eur J Cancer Suppl 2005

Meta-analysis of GEM-CAP

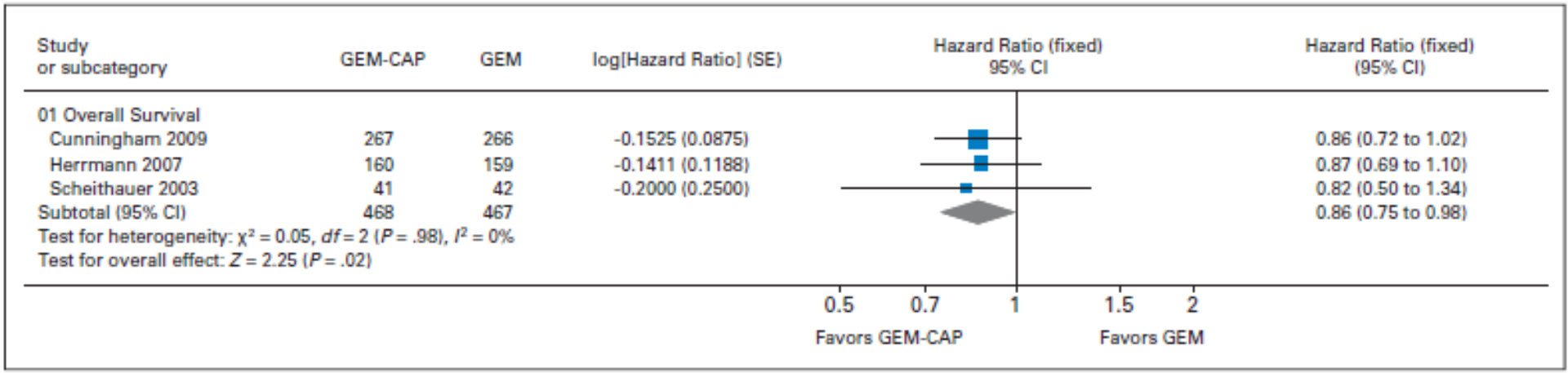
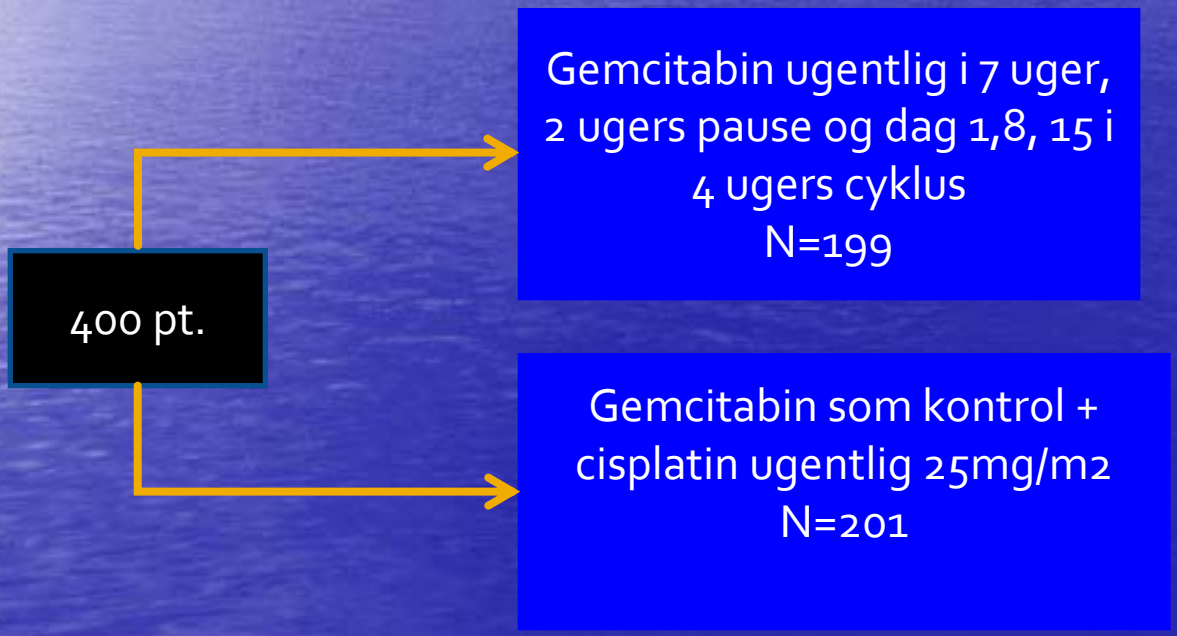


Fig 4. Forest plot of meta-analysis of published randomized controlled trials (including current trial). GEM-CAP, gemcitabine plus capecitabine; GEM, gemcitabine alone; SE, standard error.

Cunningham et al., JCO 2009

Gem vs. Gem-platinum

Di Miao. A randomized trial of gemcitabine (G) versus G plus cisplatin in chemotherapy-naive advanced pancreatic adenocarcinoma: The GIP-1 *(Gruppo Italiano Pancreas— GOIM/GISCAD/GOIRC)* study. ASCO 2009



A randomized trial of gemcitabine (G) versus G plus cisplatin in chemotherapy-naive advanced pancreatic adenocarcinoma: The GIP-1 *(Gruppo Italiano Pancreas— GOIM/GISCAD/GOIRC)* study. Di Miao

		Gem	Gem/Cis
OS		8,3 mdr.	7,2 mdr.
1-year survival		34,0 %	30,7 %
PFS		3,9 mdr.	3,8 mdr.
Anæmi		39%	50%
Trombocytopeni		29%	57%

- Alle endepunkter insignifikante
- Subgruppeanalyse af PS 0: Signifikant negativ effekt!
- Tidligere meta-analyse, som viste effekt af Gem-platin-kombinationer, nu insignifikant efter inklusion af dette studium

Combination chemotherapy and effect according to performance status

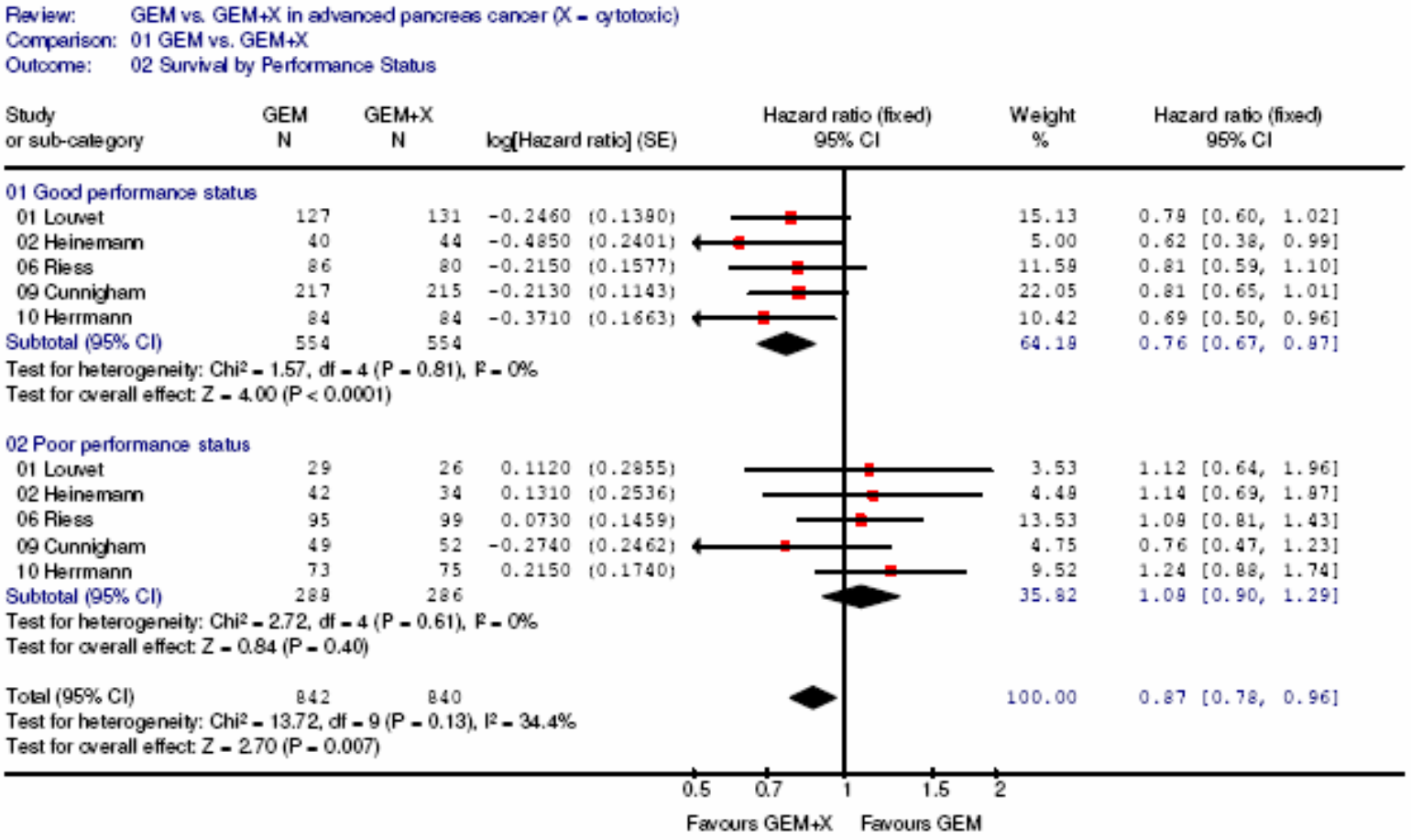
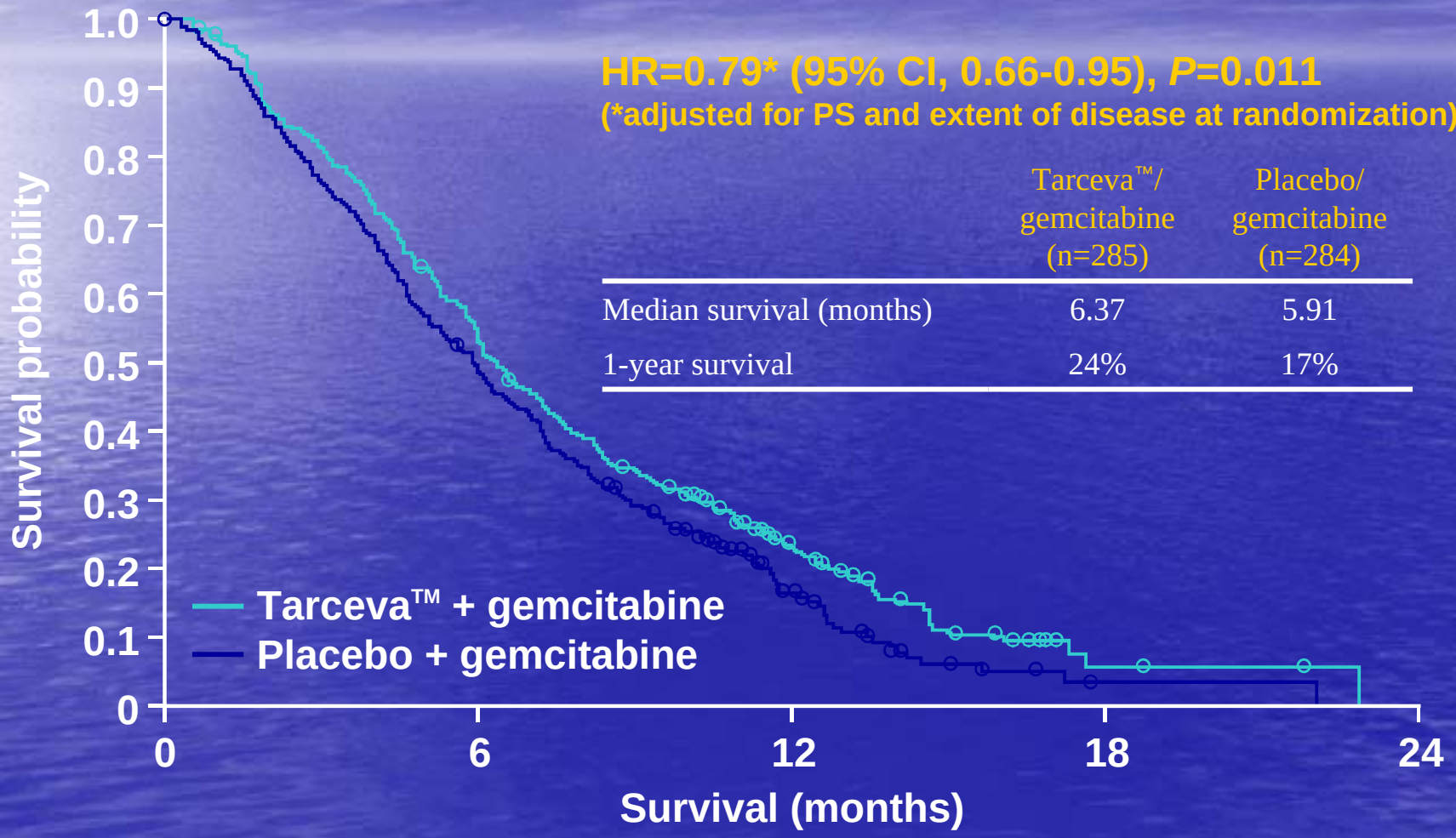


Figure 2
Meta-analysis for combination chemotherapy in advanced pancreatic cancer – overall survival with regard to performance status.

Heinemann et al., BMC Cancer 2008

PA.3 study: Gem-erlotinib

Overall survival



HR=0.79* (95% CI, 0.66-0.95), *P*=0.011

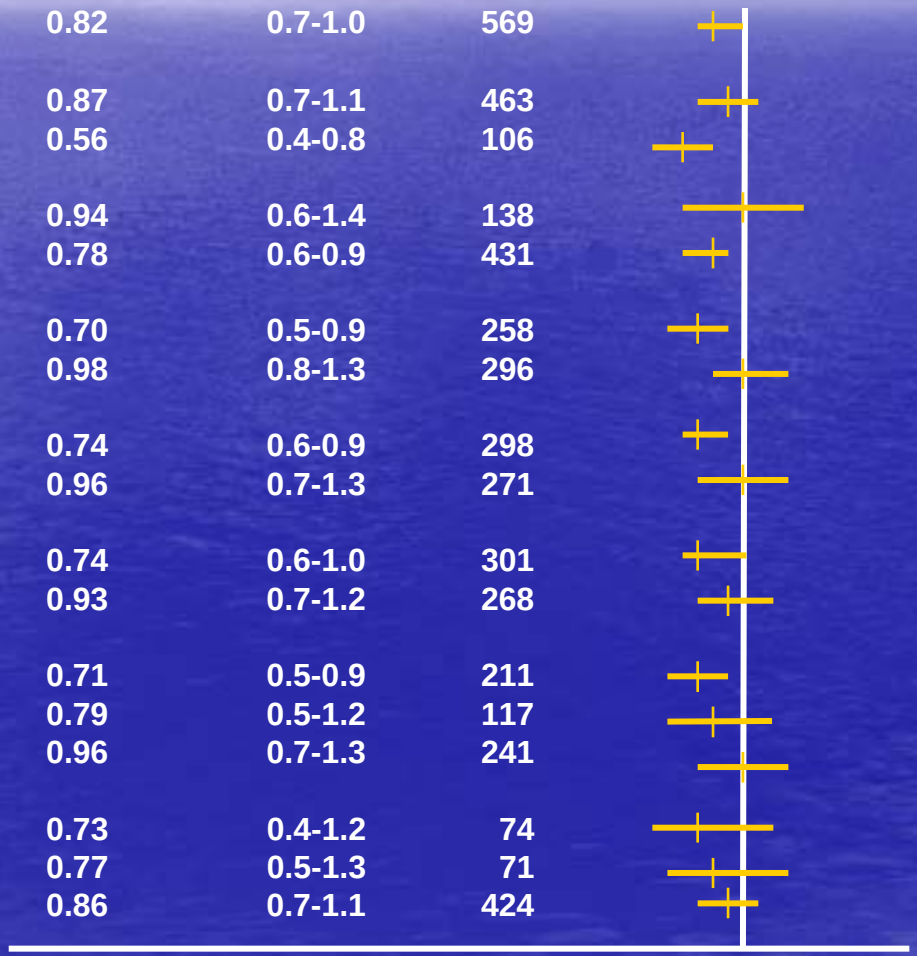
(*adjusted for PS and extent of disease at randomization)

	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

Accetable standard systemic treatment options 2009

- GEM alone
- GEM-erlotinib
  - registred for metastatic PC only, mOS + 12 days, some additional toxicity
- GEM-CAP

  mOS + 1 month, only significant in meta-analysis
- GEM-platinum ?
  - doubtful effect - now not significant in meta-analysis, significant toxicity

SUPPORTIVE CARE

Forebyggelse af venøse tromboemboliske events (VTE) ved pancreascancer

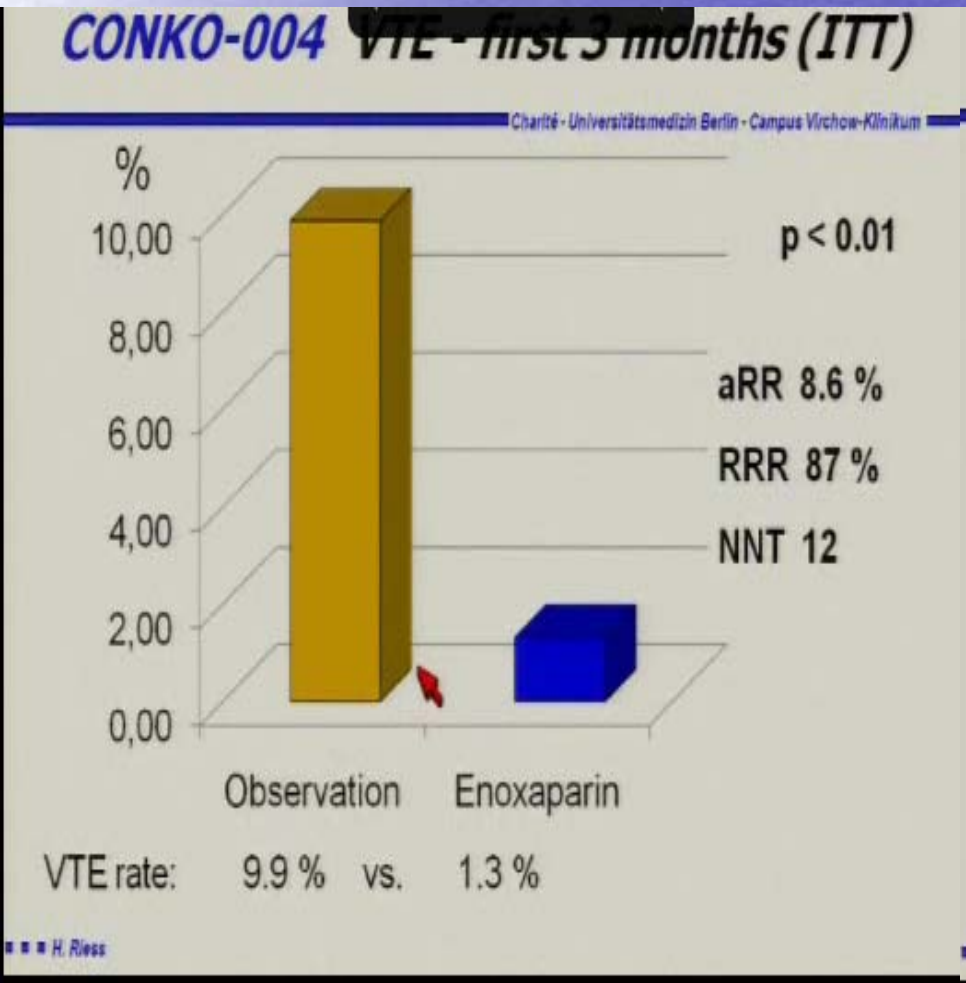
GONKO 004 trial

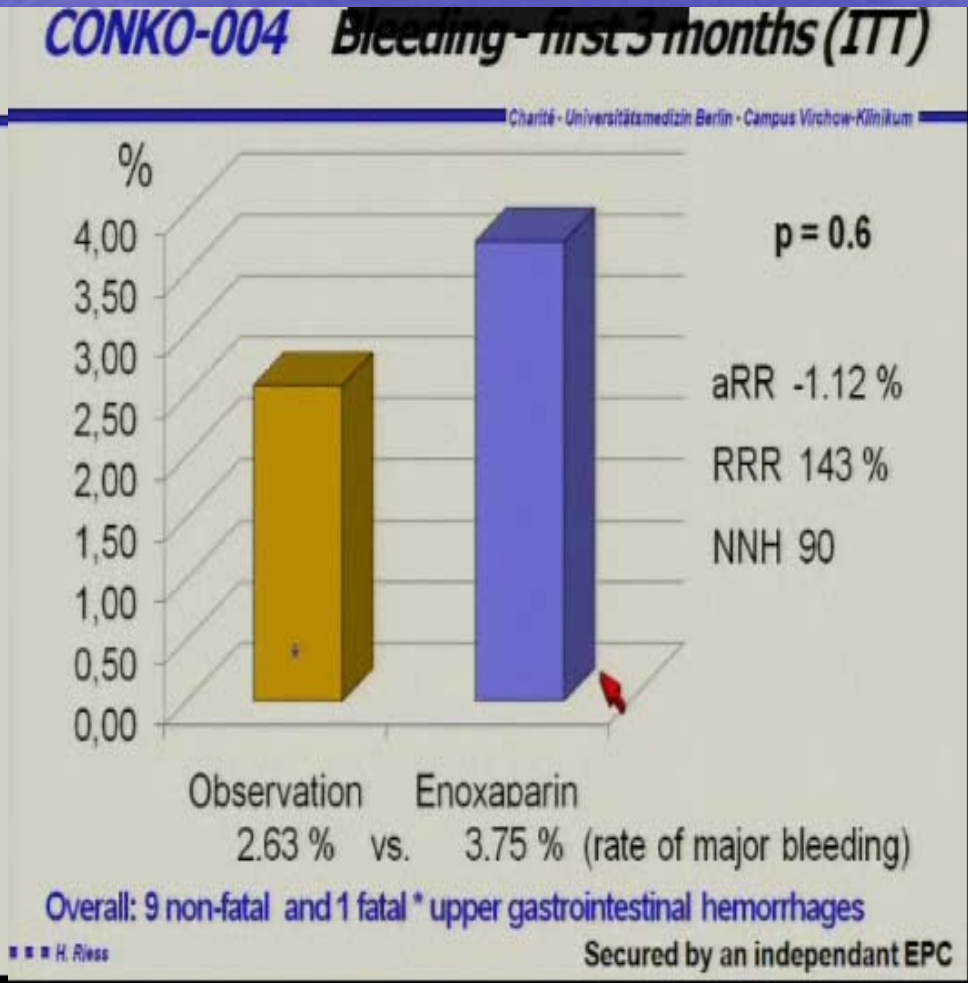
A prospective, randomized trial of chemotherapy with or without the low molecular weight heparin (LMWH) enoxaparin in patients (pts) with advanced pancreatic cancer (APC): Results of the CONKO 004 trial. H.Reiss et al. ASCO 2009

- **Baggrund:**
  - VTE forekommer hos ca. 10% af patienter med PC
- **Formål:**
  - Undersøge effekt af LMWH (Klexane) i kombination med kemoterapi mht. frekvens af VTE og mOS
- **Inklusion:**
  - Avanceret PC, ikke tidligere kemoterapi
  - Karnofsky PS > 60
  - Ingen større blødning indenfor 2 uger, ingen VTE indenfor 2 år

A prospective, randomized trial of chemotherapy with or without the low molecular weight heparin (LMWH) enoxaparin in patients (pts) with advanced pancreatic cancer (APC): Results of the CONKO 004 trial. H.Reiss et al. ASCO 2009

Antal af VTE: 15/152 i observation – 2/160 i LMWH





A prospective, randomized trial of chemotherapy with or without the low molecular weight heparin (LMWH) enoxaparin in patients (pts) with advanced pancreatic cancer (APC): Results of the CONKO 004 trial. H.Reiss et al.

- **Konklusion:**
  - LMWH er effektiv og sikker behandling til forebyggelse af VTE hos patienter med pancreascancer.
  - Endelige resultater på mOS og mTTP afventes

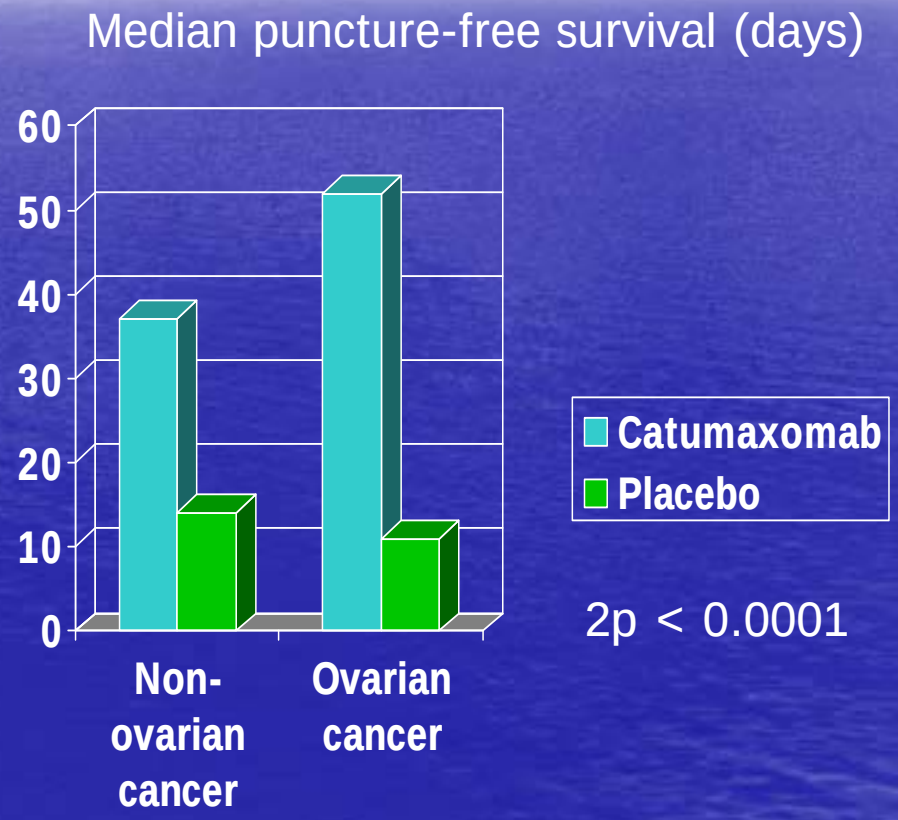
Treatment of malignant ascites

Heiss M, et al. Catumaxomab – a new treatment option for patients with malignant ascites. Ann. Oncol.;20:Suppl. 7, 2009

- Catumaxomab: Trifunctional antibody, 4 infusions i.p. over 6 h in ascending doses
- Multicenter, randomized, open-label phase II/III study
- 258 pts with symptomatic malignant ascites due to epithelial cancer

Heiss M, et al. Catumaxomab – a new treatment option for patients with malignant ascites. Ann. Oncol.;20:Suppl. 7, 2009

- Subgroup analysis of 129 ovarian and 129 non-ovarian (gastric, pancreatic, CRC etc.) cancer patients randomized
- AEs: Cytokine release related symptoms in 80%, mostly short-lasting and of grade 1-2



Pancreatic islet cell tumours

Raymond E, et al. Phase III, randomized, double-blind trial of sunitinib versus placebo in patients with progressive, well-differentiated pancreatic islet cell tumours. Ann. Oncol.;20:Suppl. 7, 2009

- Sunitinib: Oral, multitargeted tyrosine kinase inhibitor used for mRCC and GIST
- Phase II-study of sunitinib in NET[1]: ORR of 16.7% in 66 pts with pNET

1) Kulke MH, et al. JCO; 26:3403-10, 2008

Raymond E, et al. Phase III, randomized, double-blind trial of sunitinib versus placebo in patients with progressive, well-differentiated pancreatic islet cell tumours. Ann. Oncol.;20:Suppl. 7, 2009

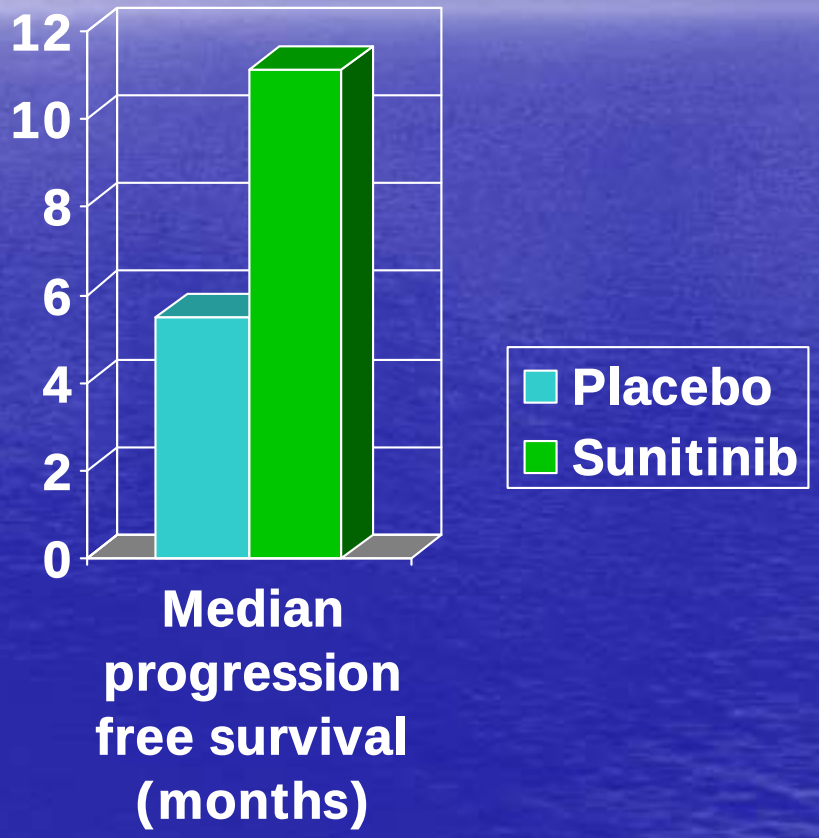
- Local, locally advanced, or metastatic, well-differentiated pNET not amenable to curative therapy and with disease progression in the prior 12 months
- Primary end point PFS
- Sunitinib 37.5 mg/day or placebo

Raymond E, et al. Phase III, randomized, double-blind trial of sunitinib versus placebo in patients with progressive, well-differentiated pancreatic islet cell tumours. Ann. Oncol.;20:Suppl. 7, 2009

- 154 pts randomized
- Toxicity events, sunitinib
  - Diarrhea, nausea, vomiting, asthenia, fatigue
  - Grade 3-4 neutropenia (12%), hypertension (9%), diarrhea (7%), hypoglycemia (7%), palmar-plantar erythrodysesthesia (7%)

Raymond E, et al. Phase III, randomized, double-blind trial of sunitinib versus placebo in patients with progressive, well-differentiated pancreatic islet cell tumours. Ann. Oncol.;20:Suppl. 7, 2009

- Interim analysis with 73 events
  - 5 deaths in sunitinib arm vs 15 in placebo arm
- Study halted early and patients on placebo given the opportunity to cross over to sunitinib



HR 0.397, 2p <0.001