



PRESIDIO DI ONCOLOGIA
OSPEDALE DI CATTOLICA

NEOPLASIE DEL PANCREAS: LA TERAPIA MEDICA

Teatro Snaporaz
Cattolica 21.05.2011
Dr. Paolo Fabbri

CANCRO DEL PANCREAS: GLI STADI CLINICI

- ❑ Malattia locale-resecabile (stadio I-II)
- ❑ Malattia localmente avanzata;
considerata non resecabile, ma senza
metastasi a distanza (stadio III)
- ❑ Malattia metastatica

CORRELAZIONE FRA STADIO ALLA DIAGNOSI E SOPRAVVIVENZA

stadio di malattia	% di pazienti alla diagnosi	sopravvivenza mediana (mesi)
resecabile	15	15
localmente avanzato	25	9
metastatico	60	6

Sopravvivenza globale a 5 anni < 5%

Sopravvivenza a 5 anni nei resecati 15-20%

LA CHEMIOTERAPIA: CAMPI DI APPLICAZIONE

- Adiuvante
- Neoadiuvante
- Malattia metastatica
- Seconda linea
- Terapie a bersaglio molecolare

LA CHEMIOTERAPIA ADIUVANTE

STUDI DI RADIO-CHEMIOTERAPIA ADIUVANTE DOPO RESEZIONE RADICALE

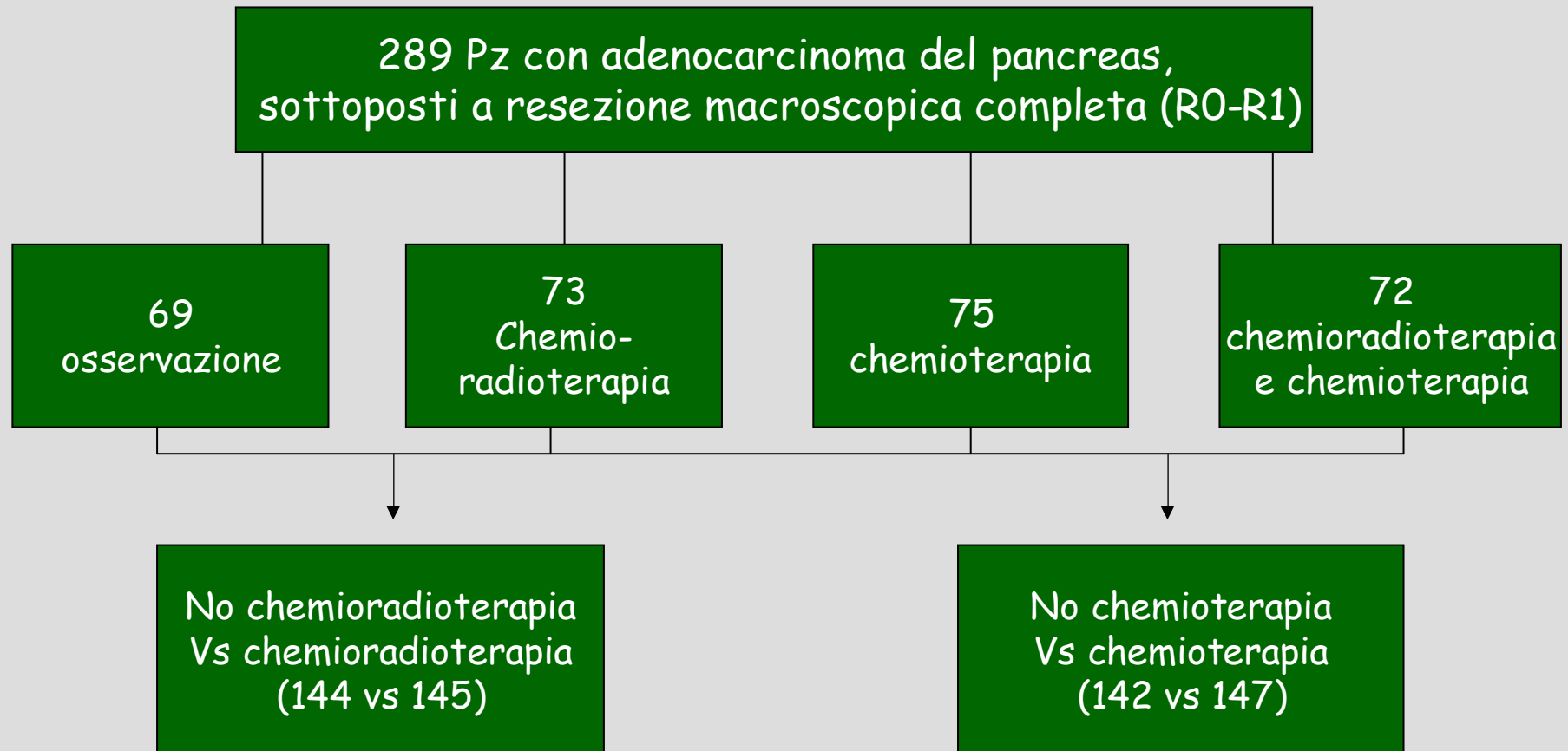
STUDIO	N. PZ	RT-CHT (FU) mOS (mesi)	OSSERVAZIONE mOS (mesi)	P
GITSG 1985	49	21	10.9	0.0005
YEO 1997	173	19.5	13.5	0.03
EORTC 1999	114	17.1	12.6	0.099

ORIGINAL ARTICLE

A Randomized Trial of Chemoradiotherapy and Chemotherapy after Resection of Pancreatic Cancer

John P. Neoptolemos, M.D., Deborah D. Stocken, M.Sc., Helmut Friess, M.D.,
Claudio Bassi, M.D., Janet A. Dunn, M.Sc., Helen Hickey, B.Sc., Hans Beger, M.D.,
Laureano Fernandez-Cruz, M.D., Christos Dervenis, M.D., François Lacaine, M.D.,
Massimo Falconi, M.D., Paolo Pederzoli, M.D., Akos Pap, M.D.,
David Spooner, M.D., David J. Kerr, M.D., and Markus W. Büchler, M.D.,
for the European Study Group for Pancreatic Cancer

ESPAC-1:

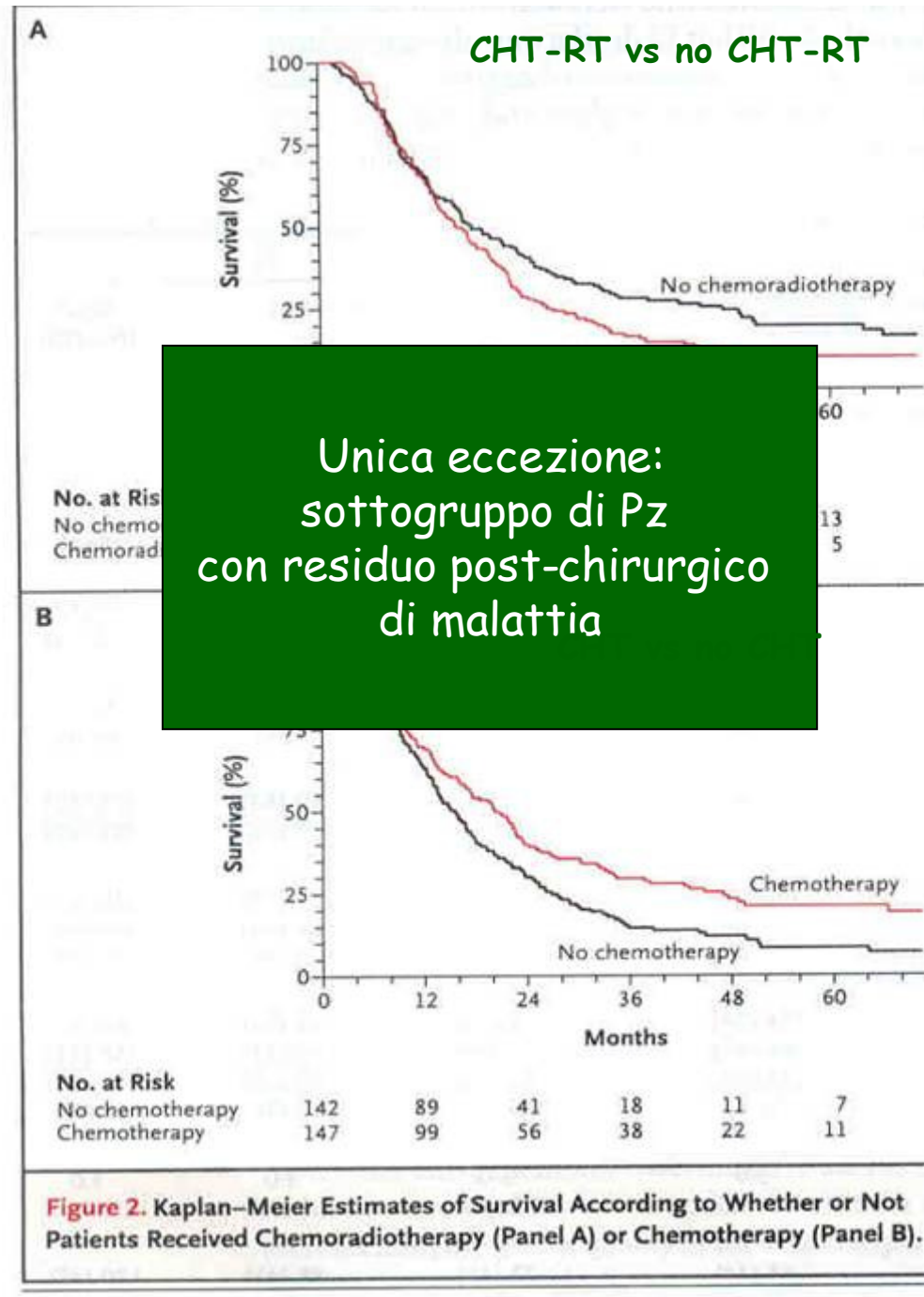


ESPAC - 1

	CH-RT (145pts)	NO CH-RT (144pts)	p
mOS mesi	15.9	17.9	0.05
2y-OS(%)	29	41	
5y-OS(%)	10	20	0.05

	CHT (147pts)	NO CHT (142pts)	p
mOS mesi	20.1	15.5	0.009
2y-OS(%)	40	30	
5y-OS(%)	21	8	0.009

Neoptolemos J.P.: NEJM 2004

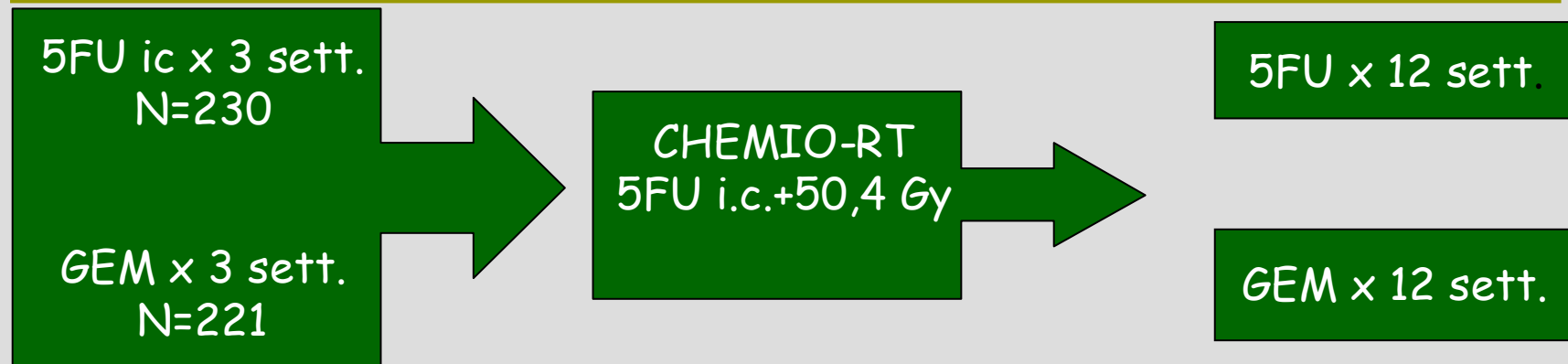


CONKO-001: CHT ADIUVANTE NEL CANCRO DEL PANCREAS RESECATO R0-R1

(N=368) End Point primario: DFS

	GEMCITABINA 1g/m ² 1-8-15 (6 mesi)	OSSERVAZIONE	p
mDFS	13.4	6.9	<0.001
3y-DFS (%)	23.5	8.5	
5y-DFS (%)	16.0	6.5	
mOS (mesi)	22.8	20.2	=0.005
3y-OS (%)	36.5	19.5	
5y-OS (%)	21.0	9.0	

STUDIO RTOG 9704



388 Pz con CA cefalopancreatico	5FU	GEM	p
mOS (mesi)	16.9	20.5	0.09
3y-OS %	22	31	
Tossicità ematologica %	1	14	<0.001

ESPAC-3:

studio di confronto fra FUFA (Mayo Clinic)
vs GEMCITABINA pz. R0-R1

	FUFA (Mayo Clinic)	GEMCITABINA 1000mg/m ² 1-8-15
Pazienti	551	537
Sopravvivenza mediana dalla resezione	23 mesi	23.6 mesi

- Nessuna differenza in sopravvivenza
- Minore tossicità nel braccio GEM
- Importanti fattori prognostici sono il grado, stadio, stato linfonodale e margini di resezione

CHEMIOTERAPIA ADIUVANTE: CONCLUSIONI

- Molti Pazienti hanno un recupero post-operatorio lento e scadute condizioni generali.....CHT?
- Il trattamento adiuvante standard nei resecati è la chemioterapia sistemica
- La durata ottimale è di 6 mesi
- I farmaci da impiegare sono la Gemcitabina ed il 5-FU
- La combinazione di chemio-radioterapia può essere proposta nei casi di chirurgia non radicale (R1);

LA CHEMIOTERAPIA NEOADIUVANTE

CHEMIOTERAPIA NEOADIUVANTE

MALATTIA RESECABILE - MALATTIA NON RESECABILE

- OBIETTIVI:**
- ✓ Aumentare la % di resecabilità
 - ✓ Ridurre la % di recidiva
 - ✓ Aumentare l' OS

Non esistono studi di fase III

CHEMIOTERAPIA NEOADIUVANTE NELLA MALATTIA POTENZIALMENTE RESECABILE

	GEMCITABINA (N=24)	GEM + CISPLATINO (N=26)
Percentuale di resezioni	38% (9 Pz)	70% (18 Pz)
Resezioni R0	75%	75%
Resezioni N0	25%	44%
mOS (mesi)	9.9	15.6
1y-OS	42%	62%

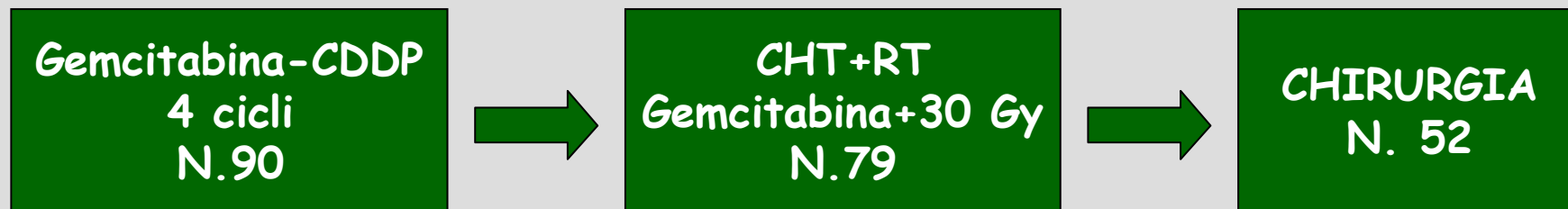
ADENOCARCINOMA RESECABILE DELLA TESTA DEL PANCREAS: CHEMIO-RADIOTERAPIA PREOPERATORIA (gemcitabina) - fase II

N=86
Gemcitabina settimanale
400mg/m²
RT 30 Gy

	Pazienti	mOS (mesi)	OS 5 anni
Totale	86	22,7	27%
CHT+RT CHIRURGIA	64	34	36%
Non resecati	22	7	0%

GEMCITABINA-CDDP PREOPERATORIO SEGUITO DA CHEMIO-RADIOTERAPIA (GEMCITABINA)

ADK resecabile della testa del pancreas - fase II



	Pazienti	mOS (mesi)
Globale	90	17,4
CHT	79	18,7
CHT+RT		
CHT	52	31
CHT+RT		
Chirurgia		
Non resecati	27	10,5

CHEMIOTERAPIA NEOADIUVANTE NEL CANCRO DEL PANCREAS RESECABILE:

revisione sistematica e meta-analisi

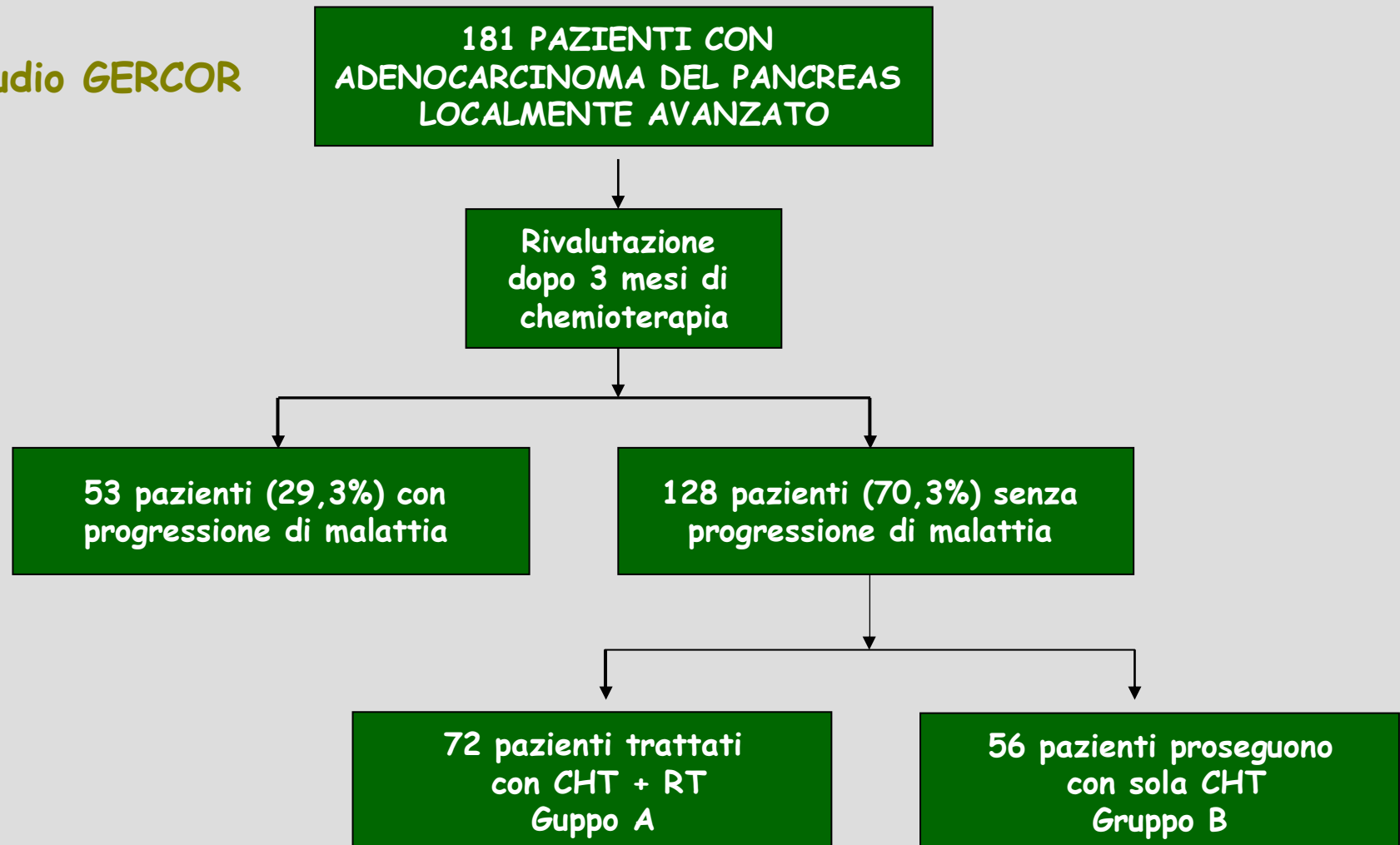
...Non esiste evidenza
che un trattamento chemio e/o
chemio-radioterapico preoperatorio,
possa essere raccomandato al di fuori di
studi clinici controllati

STUDI DI RADIO-CHEMIOTERAPIA NEL CANCRO DEL PANCREAS LOCALMENTE AVANZATO

Studio (anno)	Pazienti	Trattamento	mOS (mesi)	p
Moertel (1969) MAYO CLINIC	69	5FU+RT	6.3	S
Moertel (1981) GITSG	194	5FU+RT	9.6	S
Klaassen (1985) ECOG	91	5FU+RT	8.8	NS
Douglas (1988)	43	5FU+RT	10.5	S
Chauffert (2006)	119	CDDP-FU +RT → GEM vs GEM	interrotto nell'analisi ad interim	

CANCRO DEL PANCREAS LOCALMENTE AVANZATO: CHEMIO-RADIOTERAPIA DOPO CONTROLLO DI MALATTIA CON CHEMIOTERAPIA

Studio **GERCOR**



STUDIO GERCOR

	CHT CHT+RT N=72	CHT N=56	p
pFS (mesi)	10.8	7.4	P=0.005
mOS (mesi)	15.0	11.7	P=0.009
OS % 1 anno	65.3	47.5	

Huguet F. : J Clin Oncol 2007

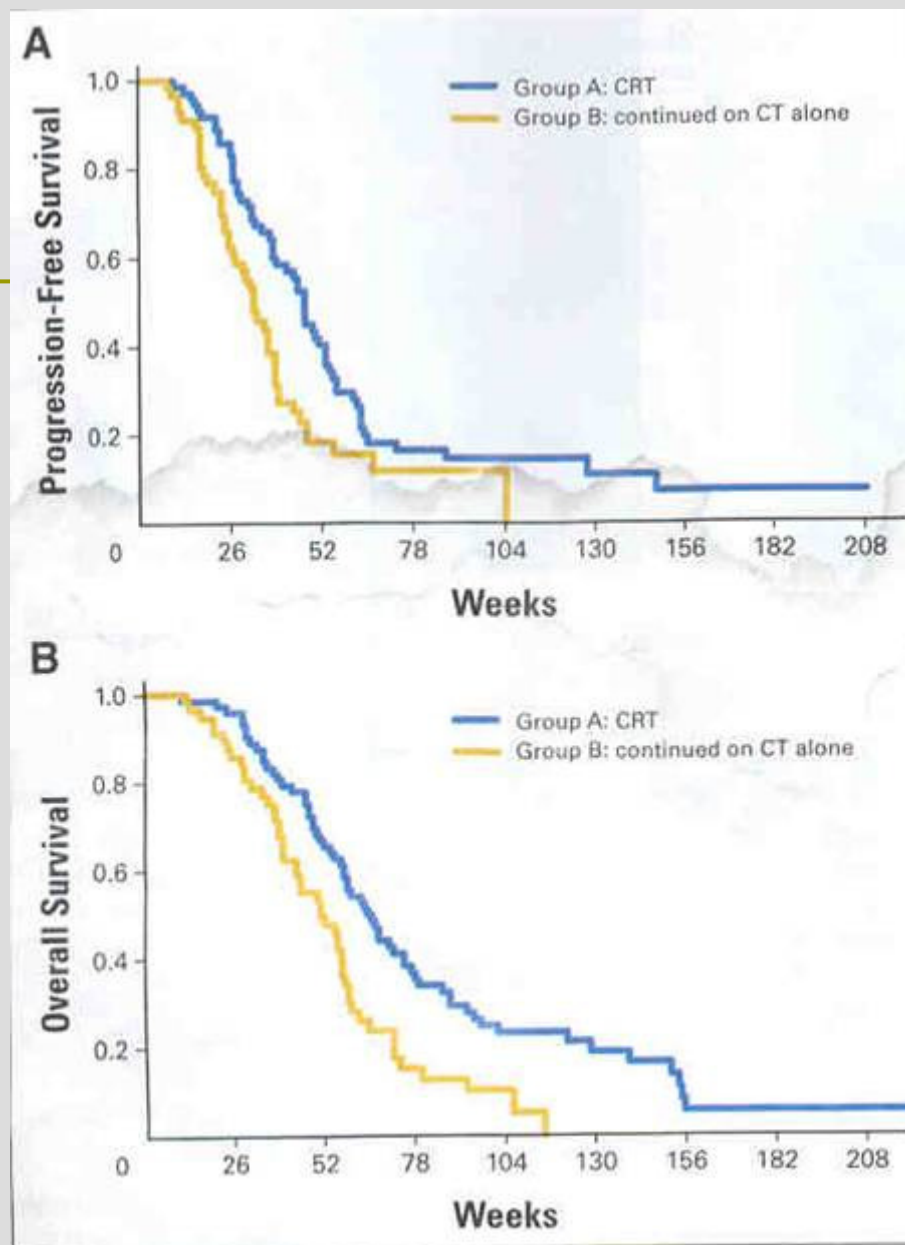


Fig 3. Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival in the 128 patients without disease progression after 3 months of initial chemotherapy (CT). CRT, chemoradiotherapy.

TERAPIA NEOADIUVANTE NEL CANCRO DEL PANCREAS NON RESECABILE:

revisione sistematica e meta-analisi

...I Pazienti con tumori non resecabili dovrebbero essere inclusi in protocolli neoadiuvanti e successivamente rivalutati per l'intervento

LA CHEMIOTERAPIA
NELLA MALATTIA
METASTATICA

Improvements in Survival and Clinical Benefit With Gemcitabine as First-Line Therapy for Patients With Advanced Pancreas Cancer: A Randomized Trial

By Howard A. Burris III, Malcolm J. Moore, John Andersen, Mark R. Green, Mace L. Rothenberg, Manuel R. Modiano, M. Christine Cripps, Russell K. Portenoy, Anna Maria Storniolo, Peter Tarassoff, Robert Nelson, F. Andrew Dorr, C.D. Stephens, and Daniel D. Von Hoff

Purpose: Most patients with advanced pancreas cancer experience pain and must limit their daily activities because of tumor-related symptoms. To date, no treatment has had a significant impact on the disease. In early studies with gemcitabine, patients with pancreas cancer experienced an improvement in disease-related symptoms. Based on those findings, a definitive trial was performed to assess the effectiveness of gemcitabine in patients with newly diagnosed advanced pancreas cancer.

Patients and Methods: One hundred twenty-six patients with advanced symptomatic pancreas cancer completed a lead-in period to characterize and stabilize pain and were randomized to receive either gemcitabine 1,000 mg/m² weekly × 7 followed by 1 week of rest, then weekly × 3 every 4 weeks thereafter (63 patients), or to fluorouracil (5-FU) 600 mg/m² once weekly (63 patients). The primary efficacy measure was clinical benefit response, which was a composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight. Clinical benefit

required a sustained (≥ 4 weeks) improvement in at least one parameter without worsening in any others. Other measures of efficacy included response rate, time to progressive disease, and survival.

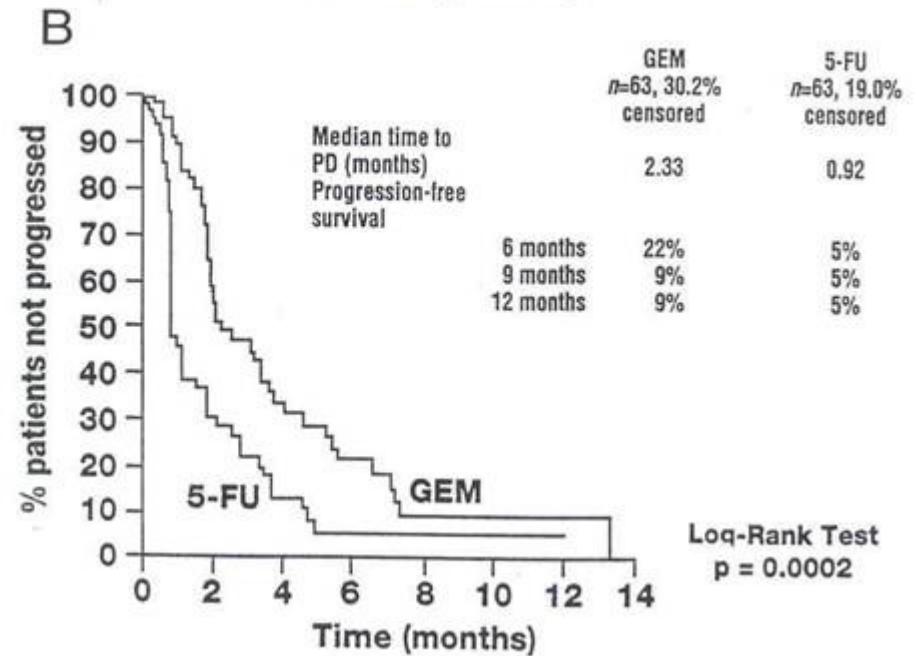
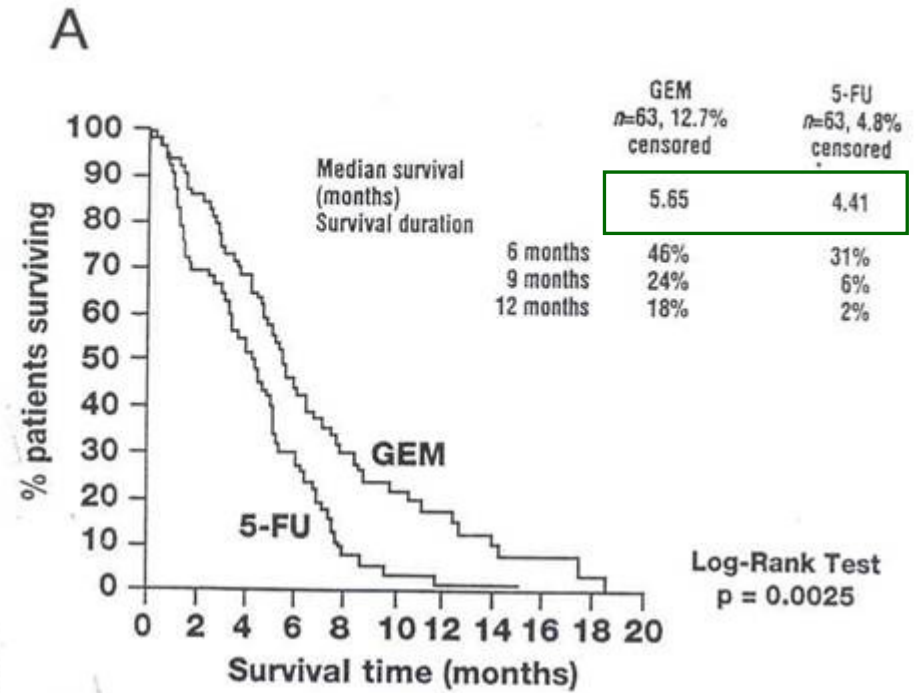
Results: Clinical benefit response was experienced by 23.8% of gemcitabine-treated patients compared with 4.8% of 5-FU-treated patients ($P = .0022$). The median survival durations were 5.65 and 4.41 months for gemcitabine-treated and 5-FU-treated patients, respectively ($P = .0025$). The survival rate at 12 months was 18% for gemcitabine patients and 2% for 5-FU patients. Treatment was well tolerated.

Conclusion: This study demonstrates that gemcitabine is more effective than 5-FU in alleviation of some disease-related symptoms in patients with advanced, symptomatic pancreas cancer. Gemcitabine also confers a modest survival advantage over treatment with 5-FU.

J Clin Oncol 15:2403-2413. © 1997 by American Society of Clinical Oncology.

GEMCITABINA VS 5-FLUOROURACILE

Fig 3. (A) Survival with treatment with gemcitabine and 5-FU. b) Time to tumor progression during treatment with gemcitabine and 5-FU.



Burris H.A.: J Clin Oncol 1997

STUDIO GERCOR/GISCAD

	GEMOX N. 157	GEM N. 156
ORR%	26.8	17.3
PFS (mesi)	5.8	3.7
OS (mesi)	9.0	7.1 (p=0.13)
Clinical benefit %	38.2	26.9

**GEMCITABINA+CAPECITABINA vs GEMCITABINA
NEL CANCRO DEL PANCREAS AVANZATO:
Swiss Group for Clinical Cancer Research and the
Central European Cooperative Oncology Group**

	GEM-CAP 160 Pz	GEM 159 Pz
mPFS (mesi)	4.3	3.9
mOS (mesi)	8.4	7.2
mOS (mesi) PS = 0/1	10.1	7.4 (p=0.04)
ORR %	10.0	7.8

Herrmann R.: J Clin Oncol 2007

CAPECITABINA+OXALIPLATINO vs CAPECITABINA +GEMCITABINA vs GEMCITABINA+OXALIPLATINO: studio randomizzato di fase II nel cancro del pancreas avanzato

	CAPOX N=61	CAP-GEM N=64	GEMOX N=63
PFS 3 mesi	51 %	64 %	60 %
mPFS mesi	4.2	5.7	3.9
mOS mesi	8.1	9.0	6.9

GEMCITABINA + CISPLATINO vs GEMCITABINA NEL CANCRO DEL PANCREAS AVANZATO: studio di fase III

	GEM/CDDP N=98	GEMCITABINA N=97
PFS (mesi)	5.3	3.1
OS (mesi)	7.5	6.0
RR %	10.2	8.2
SD %	60.2	40.2 p<0.001

GEMCITABINA+CDDP vs GEMCITABINA: I LINEA DI CHT NEL CANCRO DEL PANCREAS AVANZATO: studio GIP-1 (fase III)

	GEMCITABINA N=199	GEM+CDDP N=201
mOS (mesi)	8.3	7.2
mPFS (mesi)	3.9	3.8
ORR %	10.1	12.9
CB %	23	15.1

GEMCITABINA vs CDDP-EPIRUBICINA- FLUOROURACILE-GEMCITABINA NEL CANCRO DEL PANCREAS AVANZATO: fase III

	PEFG N=52	GEM N=47
PFS (4 mesi)	60%	28%
ORR%	38.5	8.5
PFS mediano	5.4	3.3
OS (%) 1 anno	38.5	21.3
OS (%) 2 anni	11.5	2.1

Reni M.: Lancet Oncology 2005

FOLFIRINOX vs GEMCITABINA: CHT DI PRIMA LINEA NEL CANCRO METASTATICO DEL PANCREAS TRIAL PRODIGE 4-ACCORD 11

	FOLFIRINOX N=167	GEMCITABINA N=169	p
mOS (mesi)	11.1	6.8	< 0.001
mPFS (mesi)	6.4	3.3	< 0.001
ORR %	31.6	9.4	< 0.001
Somministrazione di Filgrastim	42.5%	5.3%	< 0.001
Scadimento di QL a 6 mesi	31%	66%	< 0.001

Conroy T.: NEJM-May 2011

Meta-Analyses of Chemotherapy for Locally Advanced and Metastatic Pancreatic Cancer

Asma Sultana, Catrin Tudur Smith, David Cunningham, Naureen Starling, John P. Neoptolemos, and Paula Ghaneh

A B S T R A C T

Purpose

There are a large number of randomized controlled trials involving chemotherapy in the management of advanced pancreatic cancer. Several chemotherapeutic agents, either alone or in combination with other chemotherapy or novel agents, have been used. The aim of these meta-analyses was to examine the different therapeutic approaches, and the comparisons examined were as follows: chemotherapy versus best supportive care; fluorouracil (FU) versus FU combination chemotherapy; gemcitabine versus FU; and gemcitabine versus gemcitabine combination chemotherapy.

Methods

Relevant trials were identified by searching databases, trial registers, and conference proceedings. The primary end point was overall survival.

Results

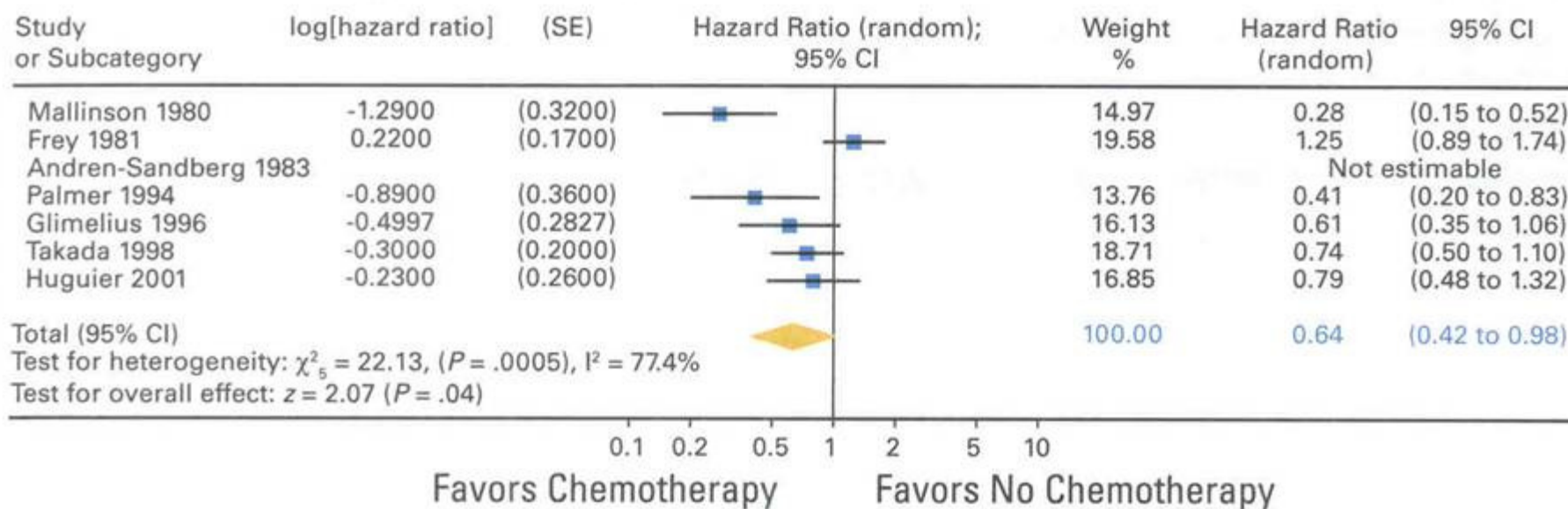
One hundred thirteen randomized controlled trials were identified, of which 51 trials involving 9,970 patients met the inclusion criteria. Chemotherapy improved survival compared with best supportive care (hazard ratio [HR] = 0.64; 95% CI, 0.42 to 0.98). FU-based combination chemotherapy did not result in better overall survival compared with FU alone (HR = 0.94; 95% CI, 0.82 to 1.08). There was insufficient evidence of a survival difference between gemcitabine and FU, but the wide CI includes clinically important differences in both directions, making a clear conclusion difficult (HR = 0.75; 95% CI, 0.42 to 1.31). Survival was improved after gemcitabine combination chemotherapy compared with gemcitabine alone (HR = 0.91; 95% CI, 0.85 to 0.97).

Conclusion

There was a significant survival benefit for chemotherapy over best supportive care and gemcitabine combinations over gemcitabine alone. This supports the use of gemcitabine-based combination chemotherapy in the treatment of advanced pancreatic cancer.

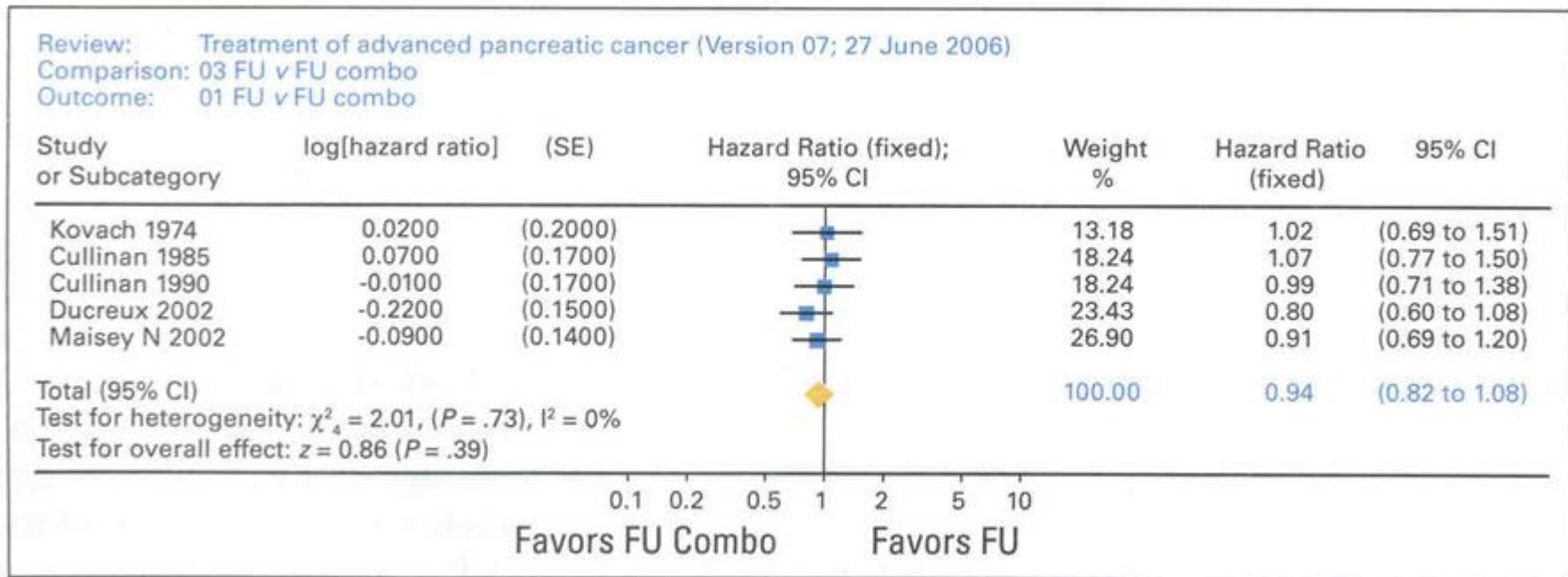
SOPRAVVIVENZA GLOBALE: CHT vs NO CHT

Review: Treatment of advanced pancreatic cancer (Version 07; 27 June 2006)
 Comparison: 01 chemotherapy v no chemotherapy
 Outcome: 01 chemotherapy v no chemotherapy



Sultana A.: J Clin Oncol 2007

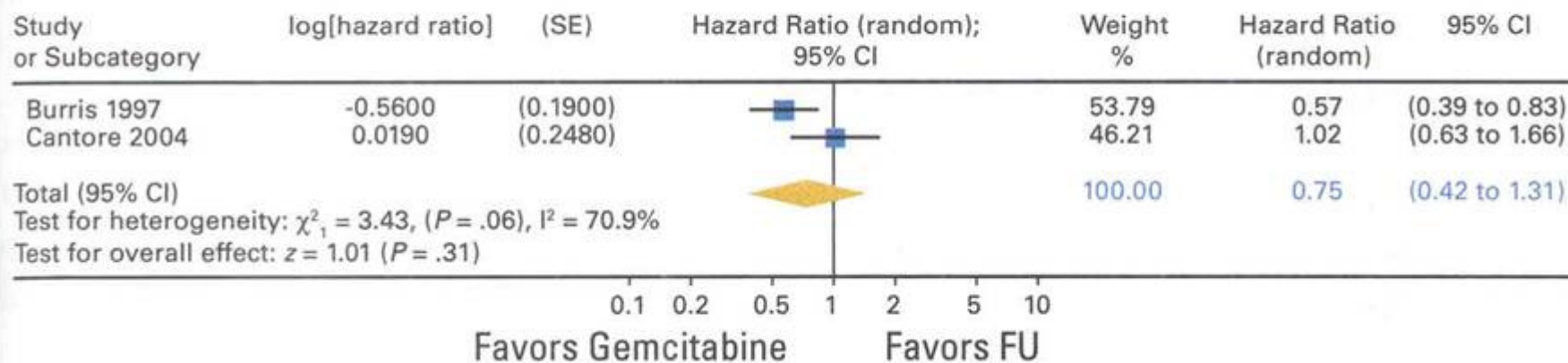
SOPRAVVIVENZA GLOBALE: FLUOROURACILE vs CHEMIOTERAPIA CON FLUOROURACILE IN COMBINAZIONE



Sultana A.: J Clin Oncol 2007

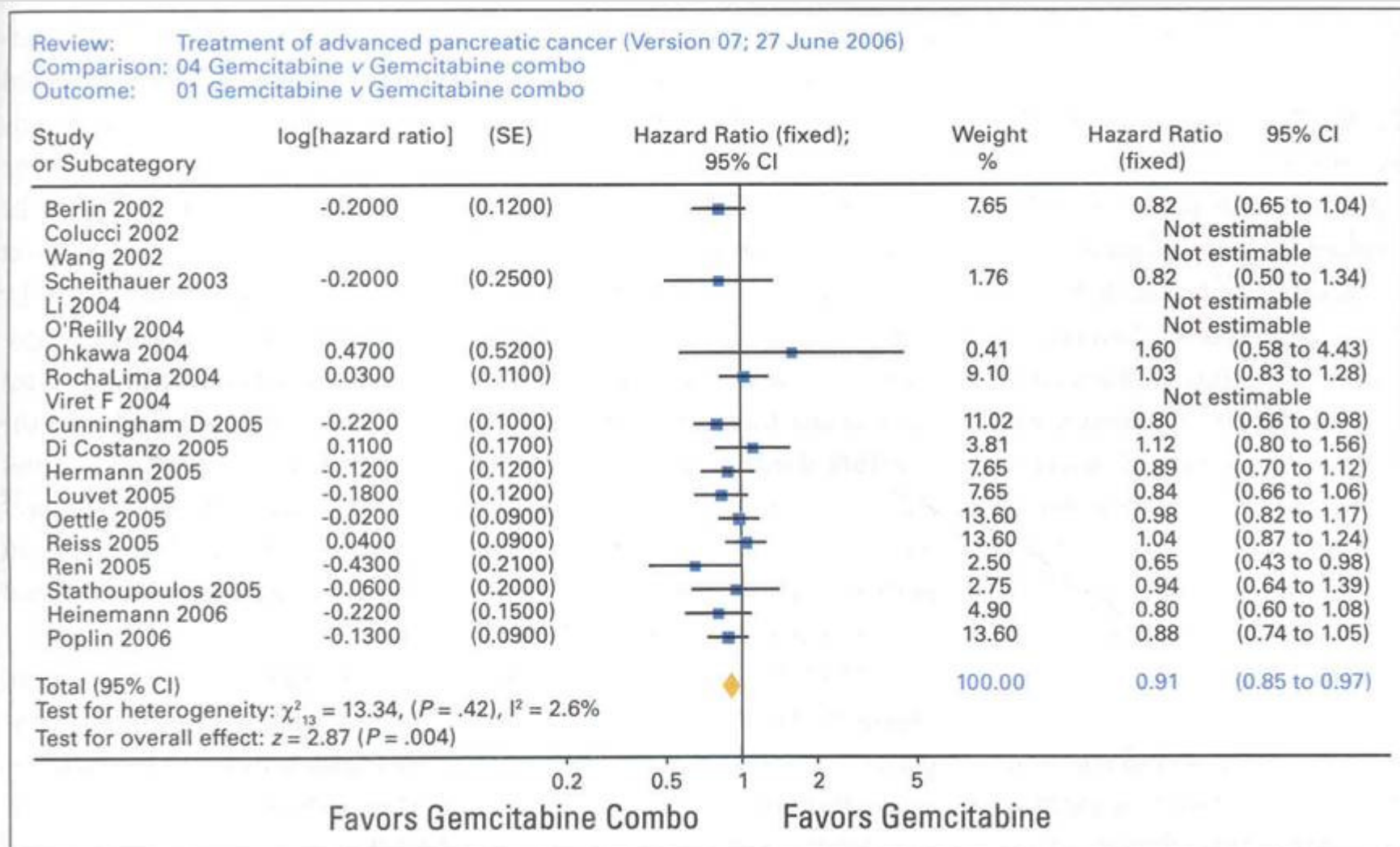
SOPRAVVIVENZA GLOBALE: GEMCITABINA vs FLUOROURACILE

Review: Treatment of advanced pancreatic cancer (Version 07; 27 June 2006)
 Comparison: 07 Gemcitabine v FU
 Outcome: 01 Overall Survival : Gemcitabine v FU



Sultana A.: J Clin Oncol 2007

SOPRAVVIVENZA GLOBALE: GEMCITABINA vs GEMCITABINA IN COMBINAZIONE



LA CHEMIOTERAPIA DI SECONDA LINEA

	PR %	SD %	mOS (mesi)	
PEMETREXED (52 Pz)	3,8	19,2	4,7	Boeck S. Ann Oncol - 2007
FOLFOX-4 (42 Pz)	14	38	6,7	Gebbia V. Ann Oncol - 2007
IRINO-OXA (30 Pz)	10	23	5,9	Cantore M. Oncology - 2004

CHT NELLA MALATTIA METASTATICA: CONCLUSIONI - I

- Non vi sono al momento farmaci che da soli o in combinazione sono in grado di aumentare significativamente la sopravvivenza
- L'associazione di 2 farmaci (Gem/Ox oppure Gem/Cisplatino) sembra la terapia consigliabile in pazienti con un buon PS (0-1)

CHT NELLA MALATTIA METASTATICA: CONCLUSIONI - II

- Nei pazienti con PS=2 la Gemcitabina da sola è il farmaco di scelta
- Una chemioterapia di 2° linea può essere proposta ai pazienti con buon PS che abbiano risposto ad una prima linea

**LE TERAPIE
A
BERSAGLIO MOLECOLARE**

ERLOTINIB

- La sovraespressione di EGFR si riscontra frequentemente nel cancro del pancreas; si associa a malattia più aggressiva ed a prognosi peggiore
- ERLOTINIB (TARCEVA): inibitore tirosin-kinasico dell'Epidermal Growth Factor Receptor (EGFR)

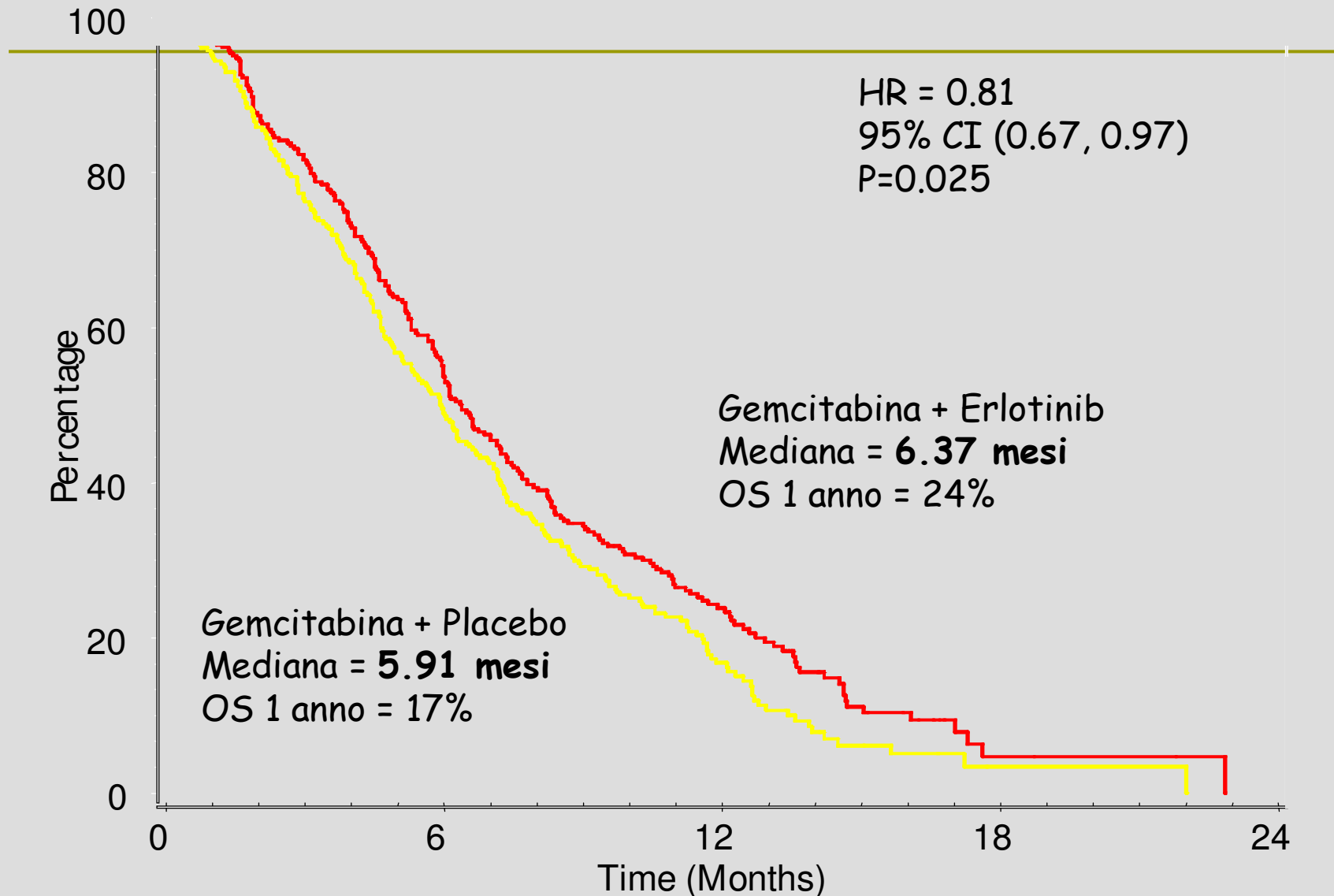
National Cancer Institute of Canada Clinical Trials Group
Studio di fase III - malattia metastatica-localmente avanzata

Gemcitabina settimanale
1000 mg/m²
+
Placebo n=284

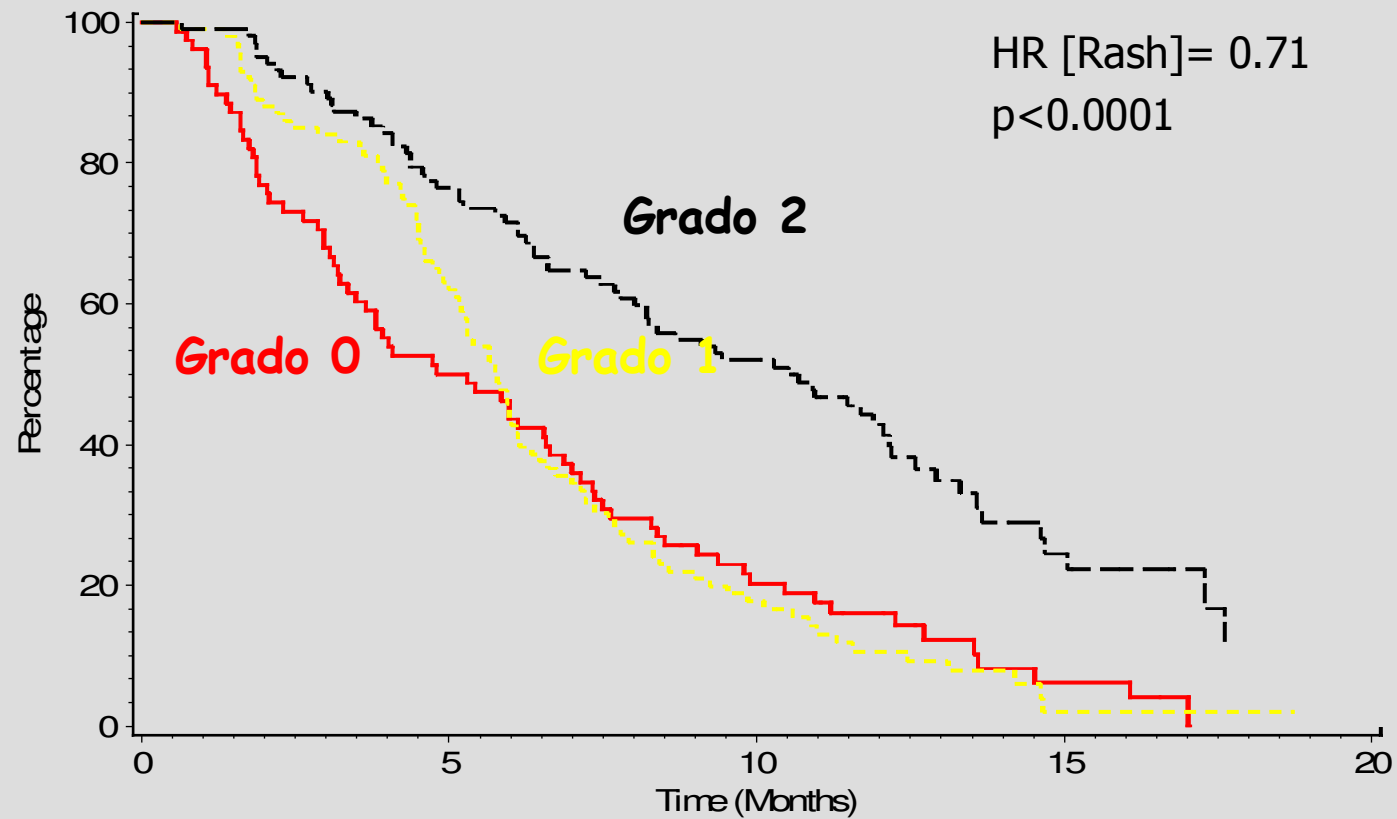
VS

Gemcitabina settimanale
1000 mg/m²
+
TARCEVA n=285

ERLOTINIB NEL CANCRO DEL PANCREAS METASTATICO/ LOCALMENTE AVANZATO



ERLOTINIB NEL CANCRO DEL PANCREAS METASTATICO/LA: Rush e Sopravvivenza



Moore J Clin Oncol - 2007

GEMCITABINA-CETUXIMAB vs GEMCITABINA NEL CANCRO DEL PANCREAS AVANZATO

SWOG Intergroup Trial S0205

	GEMCITABINA (N=331)	GEM+CETUXIMAB (N=329)
mOS (mesi)	5.9	6.3
RR %	14	12
SD %	30	37
mPFS (mesi)	3.0	3.4

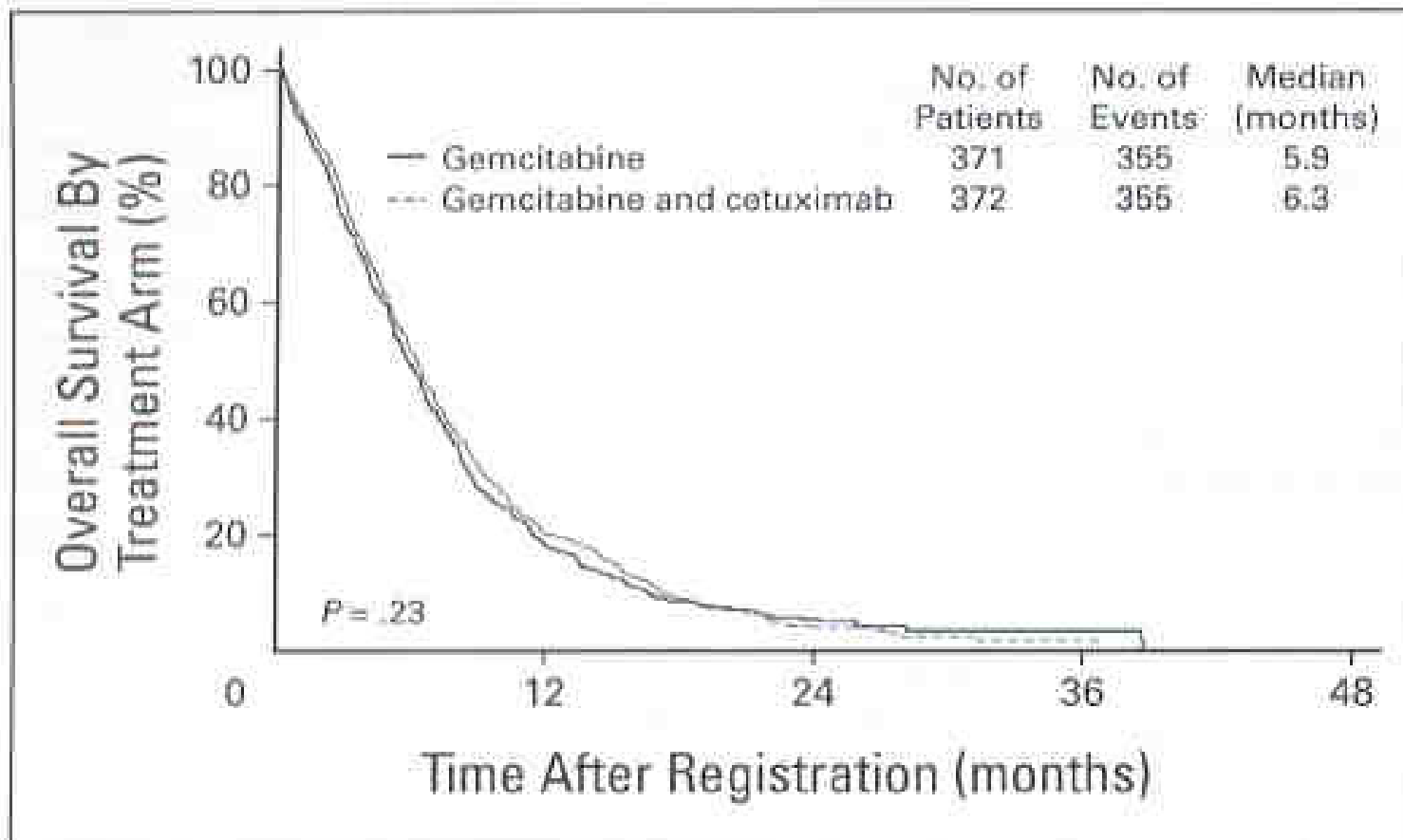


Fig 2. Kaplan-Meier curves for overall survival in patients with advanced pancreas cancer treated with either gemcitabine alone or gemcitabine plus cetuximab.

GEMCITABINA-BEVACIZUMAB vs GEMCITABINA-PLACEBO NEL CANCRO AVANZATO DEL PANCREAS

Cancer and Leukemia Group B (CALGB 80303)

	GEM + PLACEBO (N=300)	GEM + BEV (N=302)
mOS (mesi)	5.9	5.8 (P=0.95)
mPFS (mesi)	2.9	3.8
ORR(%)	10	13

GEMCITABINA-ERLOTINIB-BEVACIZUMAB vs GEMCITABINA-ERLOTINIB-PLACEBO NEL CANCRO AVANZATO DEL PANCREAS:

	GEM+ERLOTINIB +PLACEBO (N=301)	GEM+ERLOTINIB+ BEVACIZUMAB (N=306)
mOS (mesi)	6.0	7.1

I farmaci a "bersaglio molecolare"
non hanno al momento
impatto significativo
né sulle risposte obiettive
né sulla sopravvivenza

...NEGLI ULTIMI 3 ANNI
NON CI SONO STATI
REALI PROGRESSI
NEL MIGLIORAMENTO DELLA PROGNOSE
DEL CANCRO DEL PANCREAS

Mossner J.: Dig Dis. - 2010