PFS and OS in Oncology Problems…?

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Randomized Controlled Trials

- Gold standard
- Quality of study design and conduction
- Extent of generalization of results
- Clinical relevance

Assessment of clinical impact of the results

RCT in adjuvant Therapy:

Median absolute benefit over time: experimental arm has decreased, control arm outcome has improved

RCT in metastatic Therapy:

No improvement over time

Monthly cost has increased (100X)

Authors' endorsement has increased despite no gain in absolute benefits

Seruga, Ann Oncol. 2009

Experimental cancer treatment results

- 25-50% of new cancer treatments clinical benefits prove successful
- In 15% of trials, it is estimated that results should immediately become standard
- Comparison of pooled results of real effect of new vs standard treatments in terms of patient outcomes: HR 0,95 for OS.

Majority of new treatments are of marginal clinical benefit

Arch Int Med 2008, 168: 632

KRAS mutation status in cetuximab treated CRC

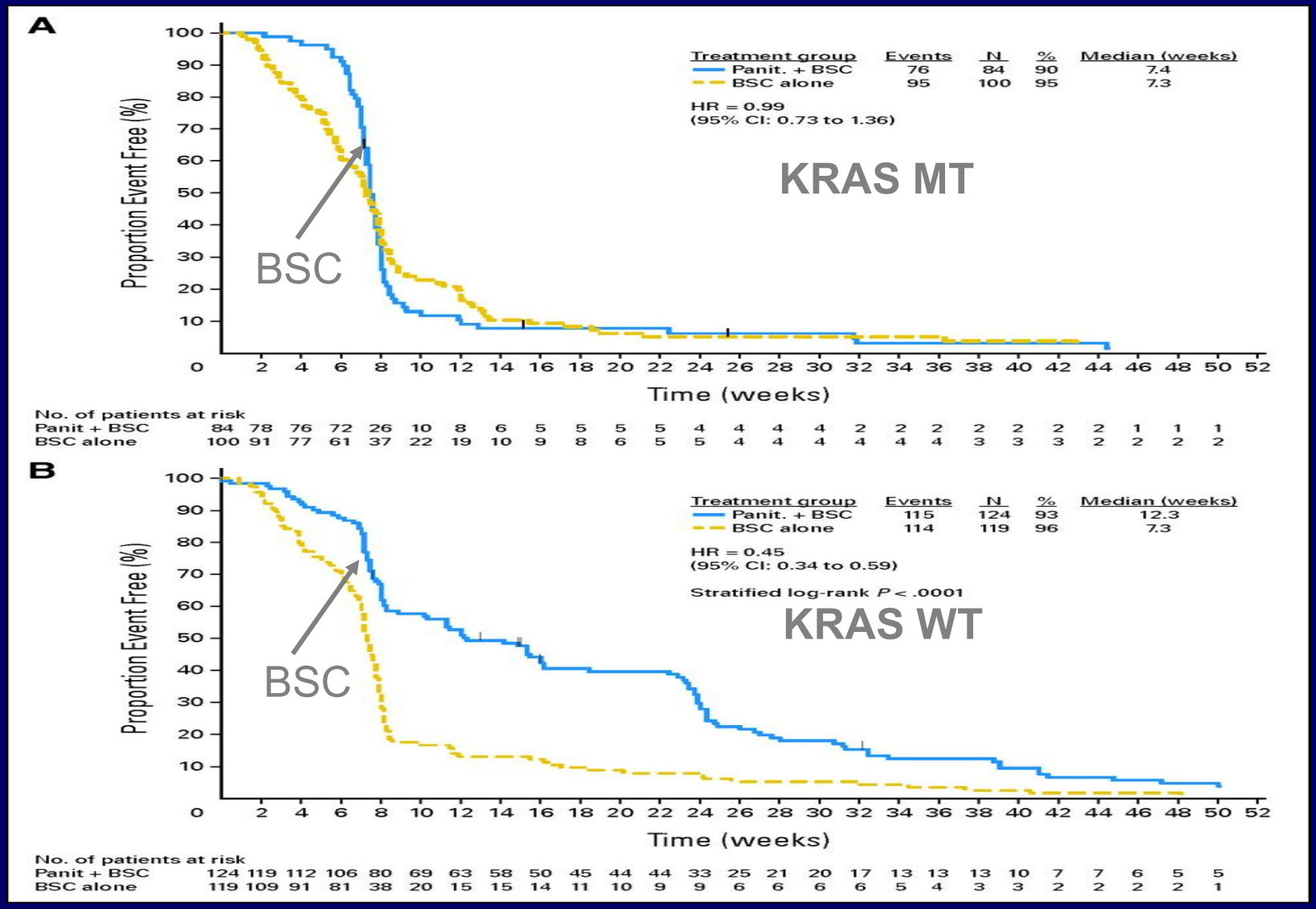
KRASwt cetuximab PFS < 2 mo

OS no difference

Cost/Benefit: negative

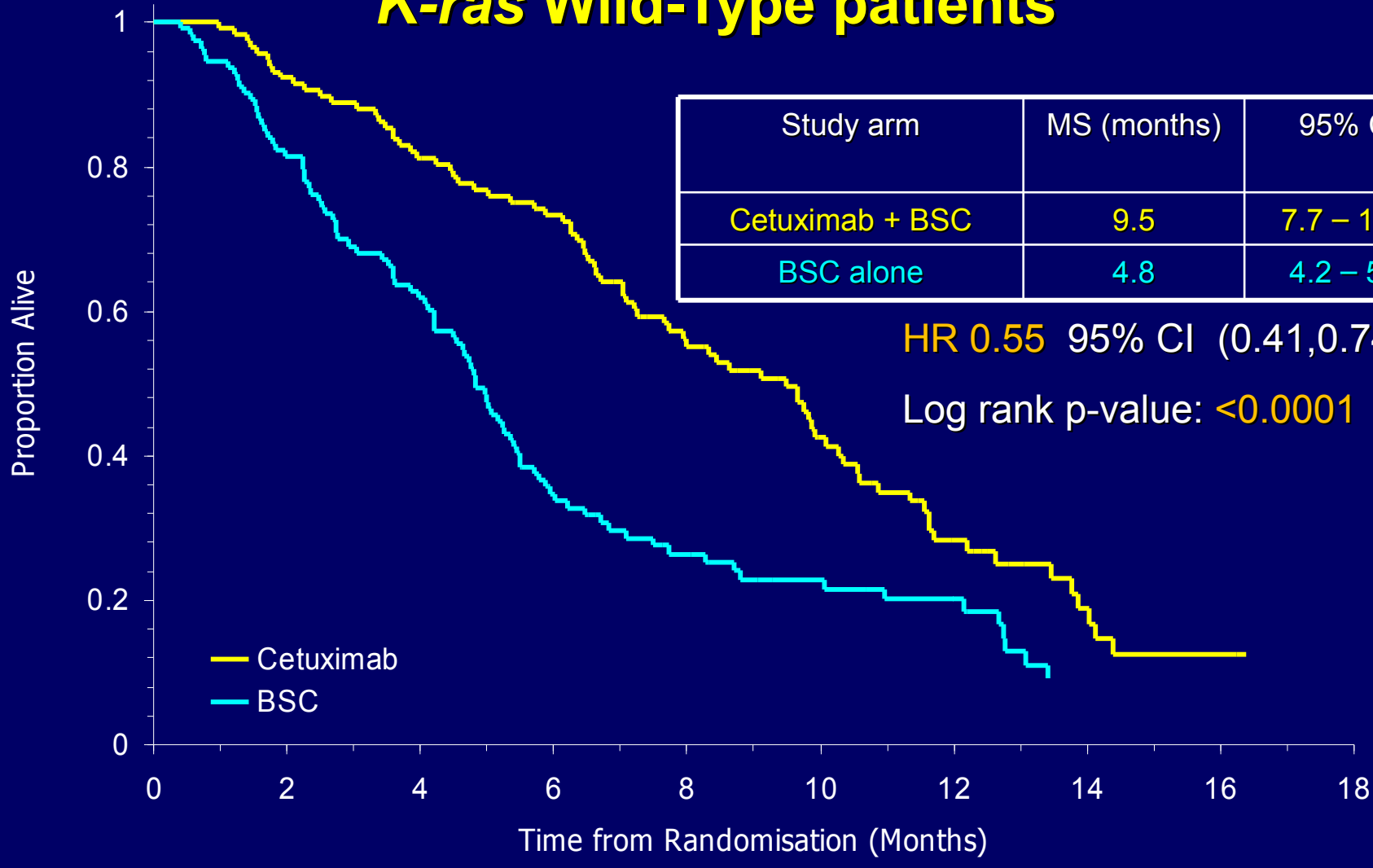
Panitumumab vs BSC in chemorefractory CRC

PFS by treatment within *KRAS* groups



Amado R, Van Cutsem E et al. J Clin Oncol; 2008

NCIC CTG C0.17: Overall survival in *K-ras* Wild-Type patients



Study arm	MS (months)	95% CI
Cetuximab + BSC	9.5	7.7 – 10.3
BSC alone	4.8	4.2 – 5.5

HR 0.55 95% CI (0.41,0.74)

Log rank p-value: <0.0001

Cetuximab	117	108	95	81	52	34	20	9	6	2
BSC	113	92	69	36	24	17	12	5	3	3

Karapetis C et al, New Engl J Med 2008

PFS and survival according to BRAF status in chemorefractory mCRC

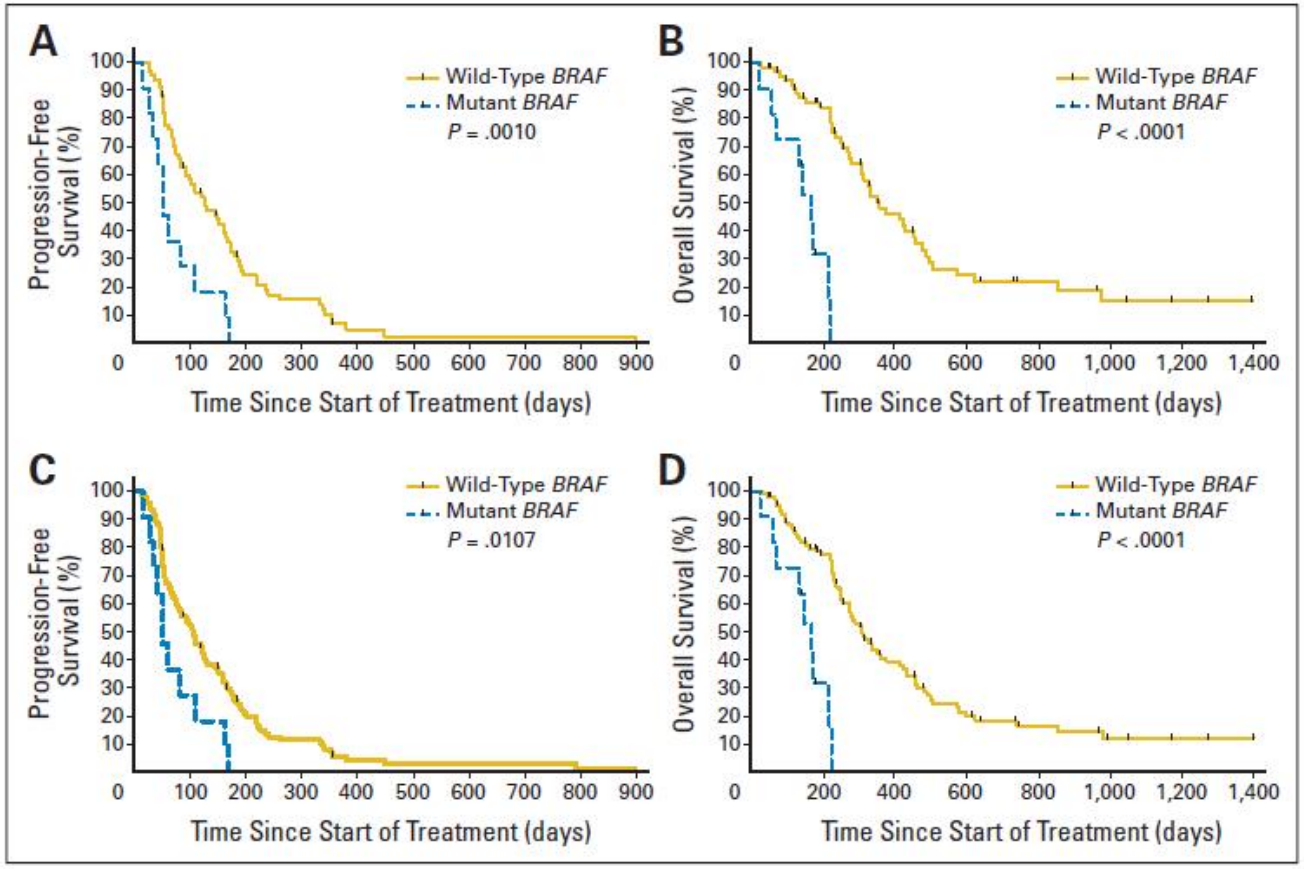
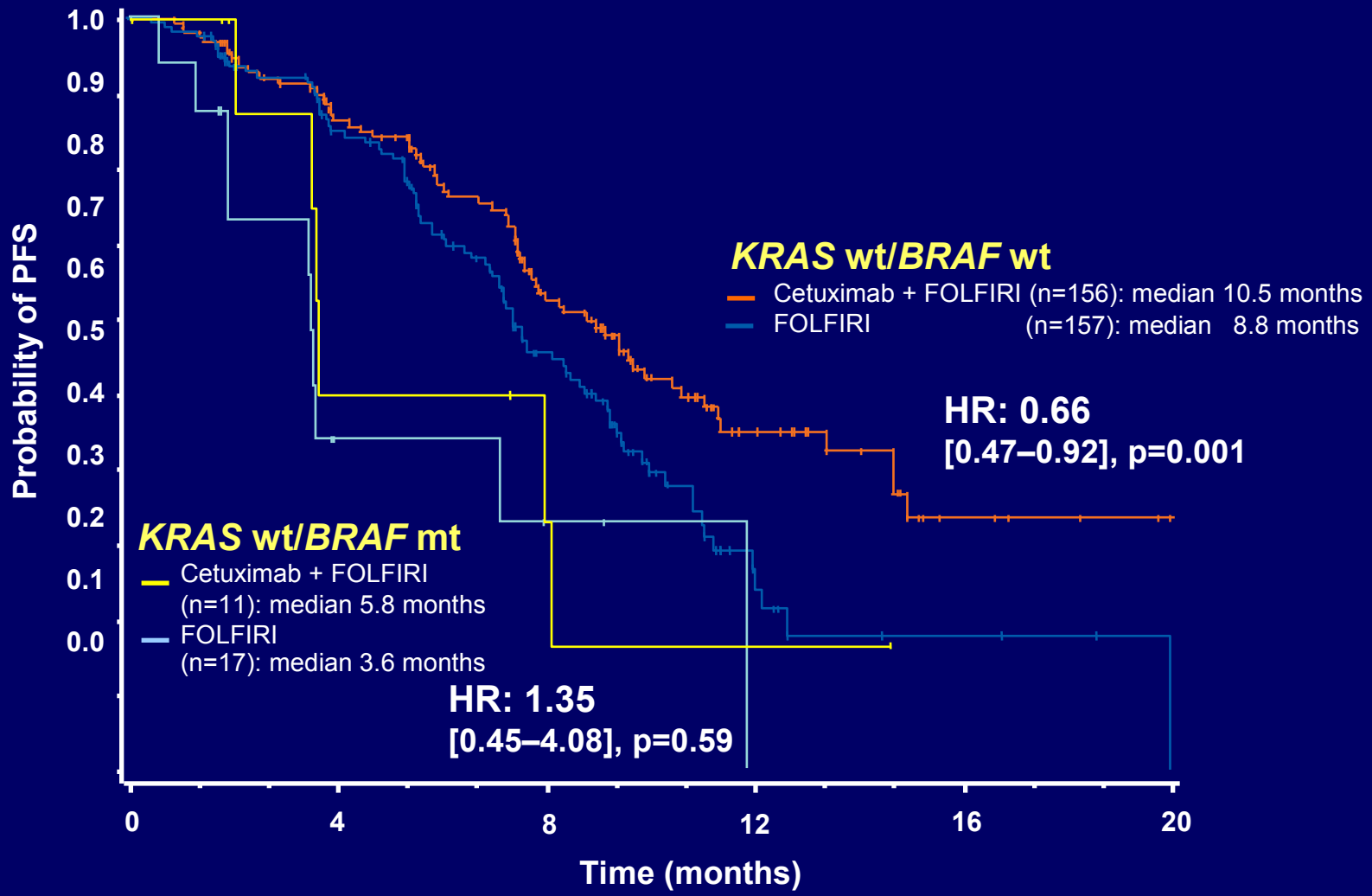


Fig 3. (A and B) In wild-type *KRAS* patients, those carrying a *BRAF*-mutated tumor had a shorter progression-free survival (PFS) and overall survival (OS) than wild-type *BRAF* patients (log-rank test, $P = .0010$ and $P < .0001$, respectively). (C and D) In the entire cohort of patients, individuals with wild-type *BRAF* tumors still displayed longer PFS and OS than patients with *BRAF*-mutated tumors ($P = .0107$ and $P < .0001$, respectively).

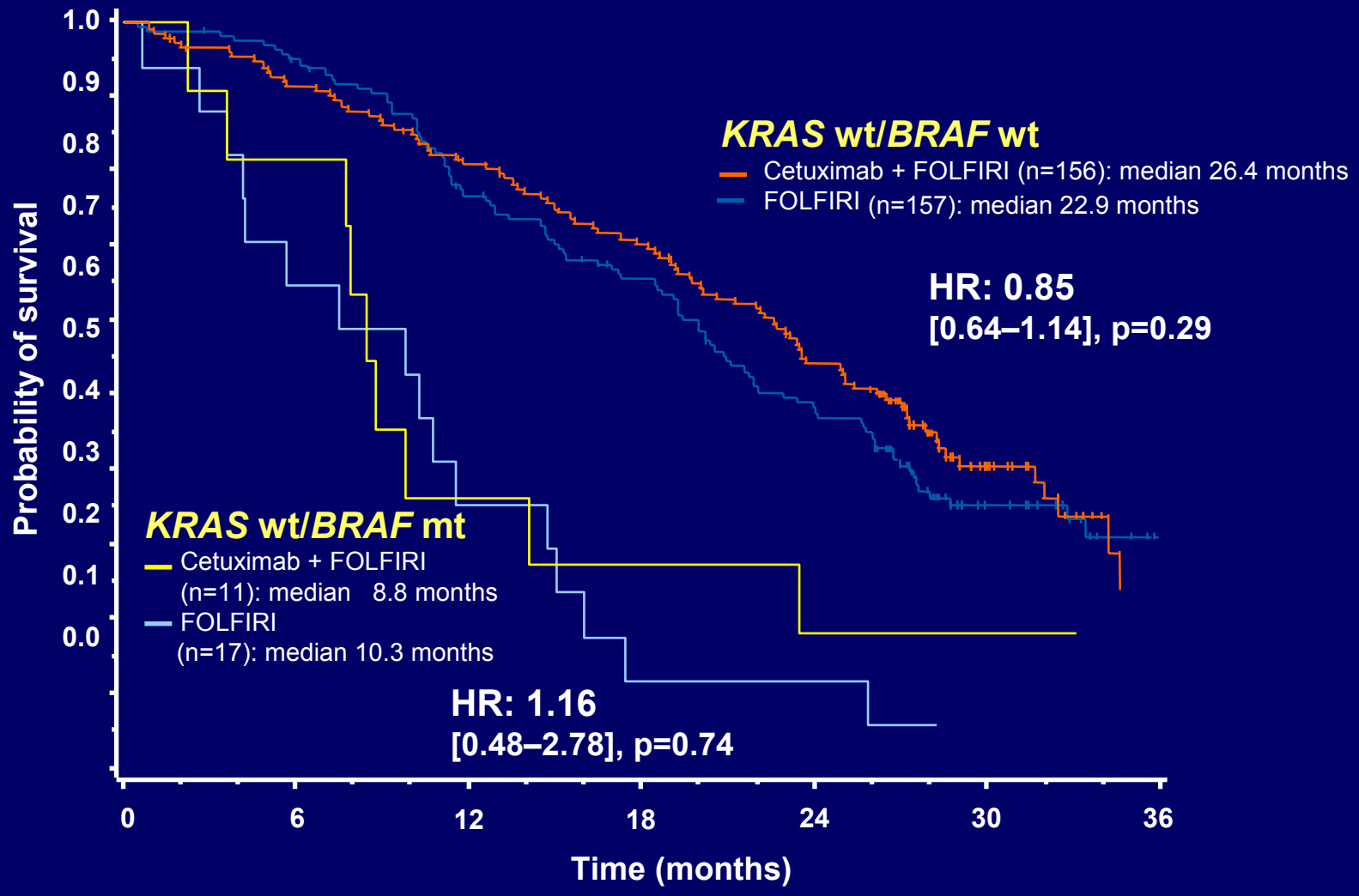
Di Nicolantonio et al, J Clin Oncol 2008

Crystal trial: PFS in the *KRAS* wild-type/*BRAF* population



Rougier P …..Van Cutsem E, et al.Ann Oncol, Suppl 2009, WCGIC Barcelona 2009

Overall survival in the *KRAS* wild-type/BRAF population



Rougier P …..Van Cutsem E, et al.Ann Oncol, Suppl 2009, WCGIC Barcelona 2009

NSCLC

- Carbo- Tax +/- bevacizumab

  survival benefit: HR 0.79, p= 0.003

  significant bleeding: 4.4 vs 0.7 %

Prevention of 1 death/1 y: 12 patients treated

Excess of 1 death/1y: 24 patients treated

NEJM 2006, 355:2542

Breast Cancer

Paclitaxel + bevacizumab vs Pacl +placebo

- PFS prolonged 11.8 vs 5.9 mo, $p<0.001$
- OS = no difference
- QOL ?

NEJM 2007, 357:2666

Renal Cell Carcinoma

- Sorafenib > placebo only in non-cross- over patients

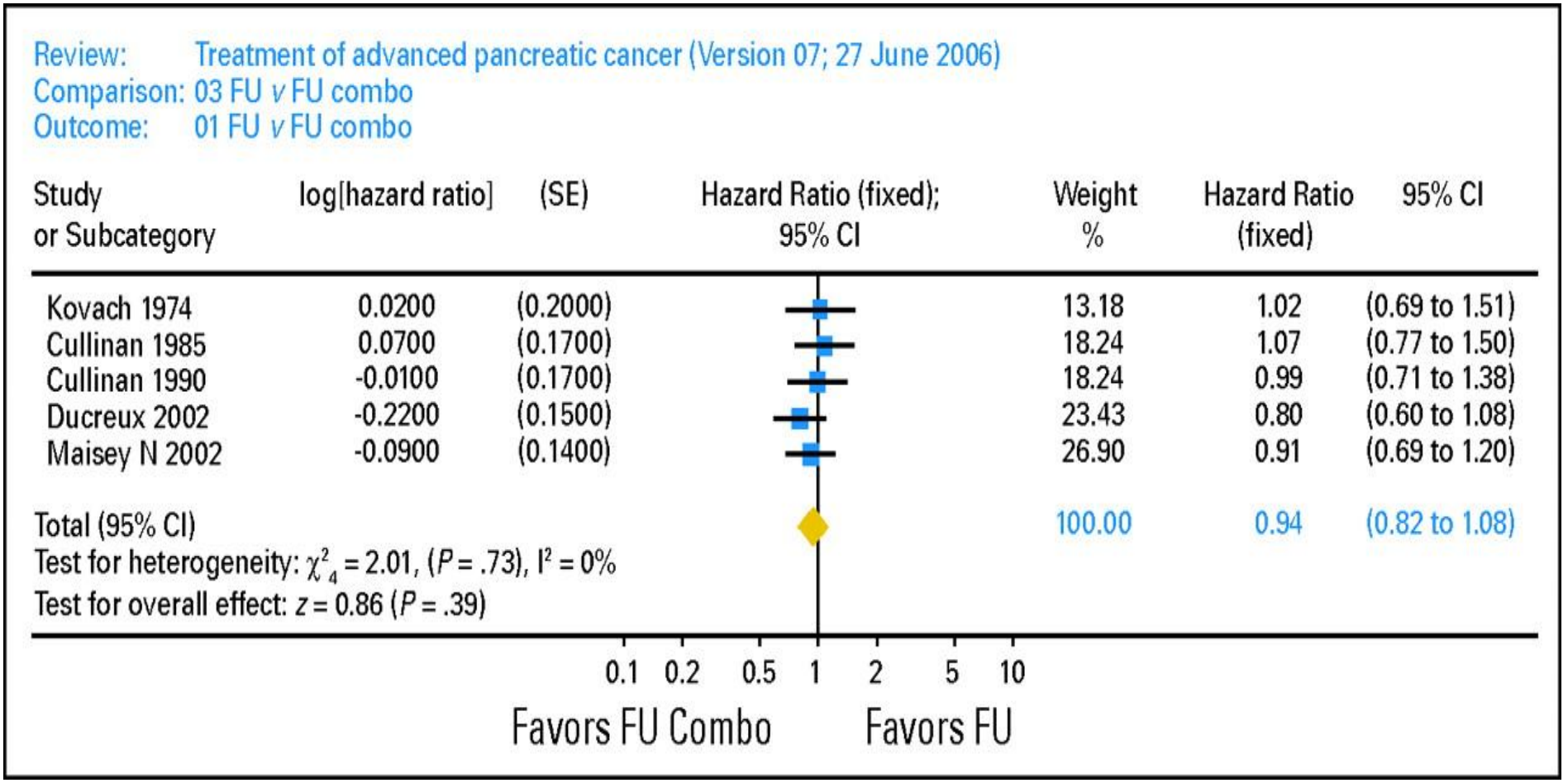
NEJM 2007,356: 125

Pancreatic Cancer

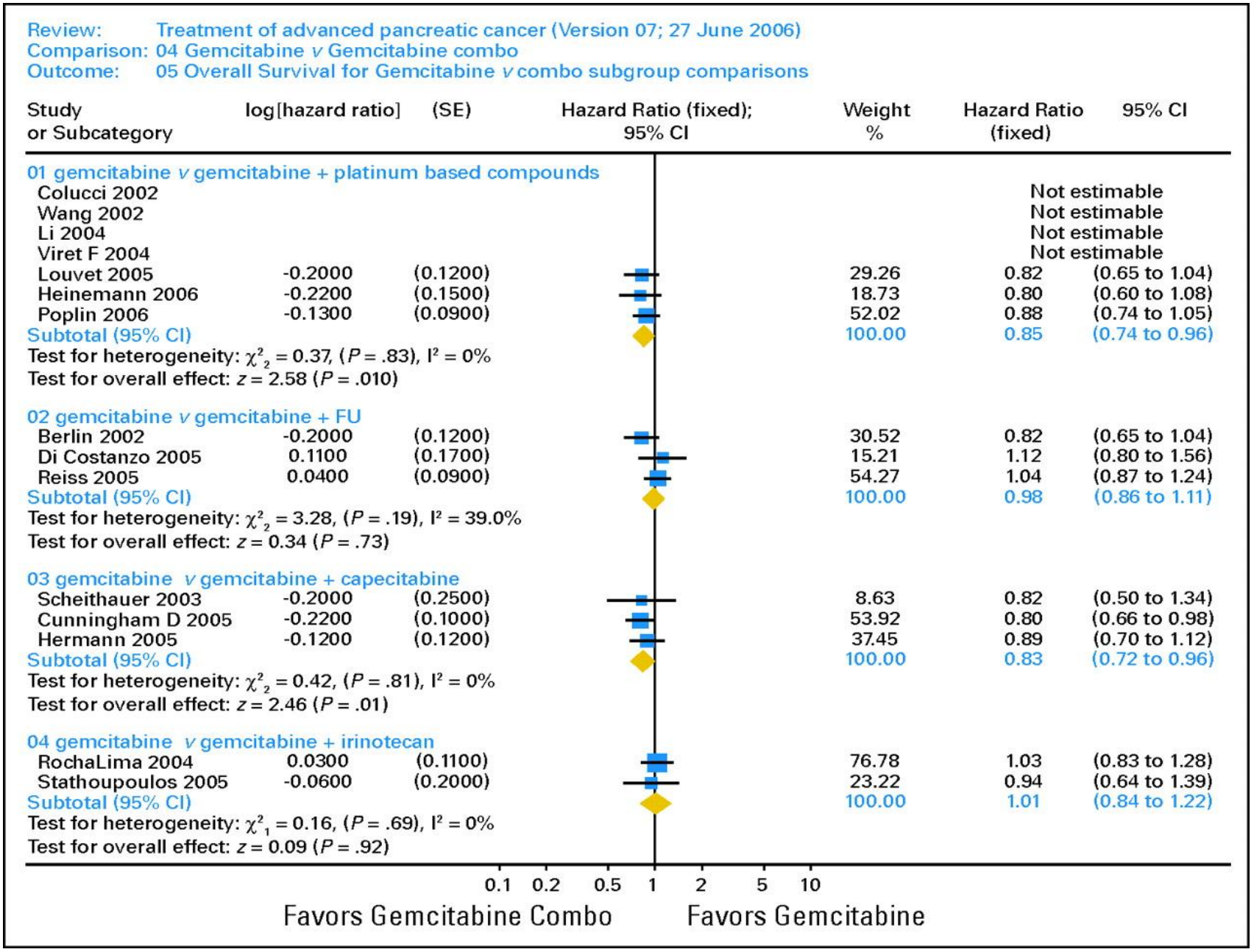
Gemcitabine+/- erlotinib:

OS improved by 10 days (6,24 vs 5,91 mos)

JCO 2007, 25:1960



Sultana A et al. JCO 2007;25:2607-2615



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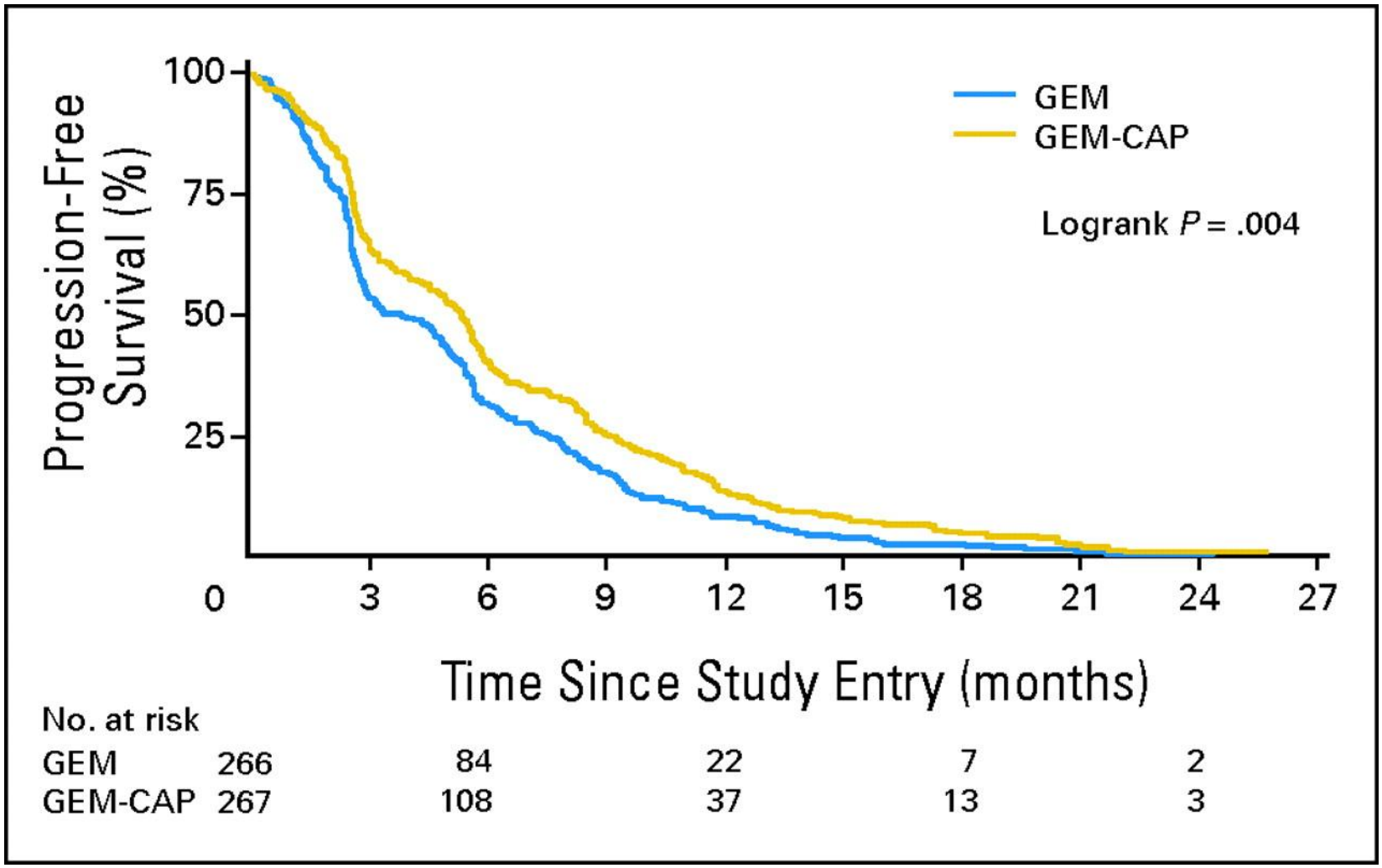
Pancreatic Cancer: Progression-free survival by treatment arms.



Cunningham D et al. JCO 2009;27:5513-5518

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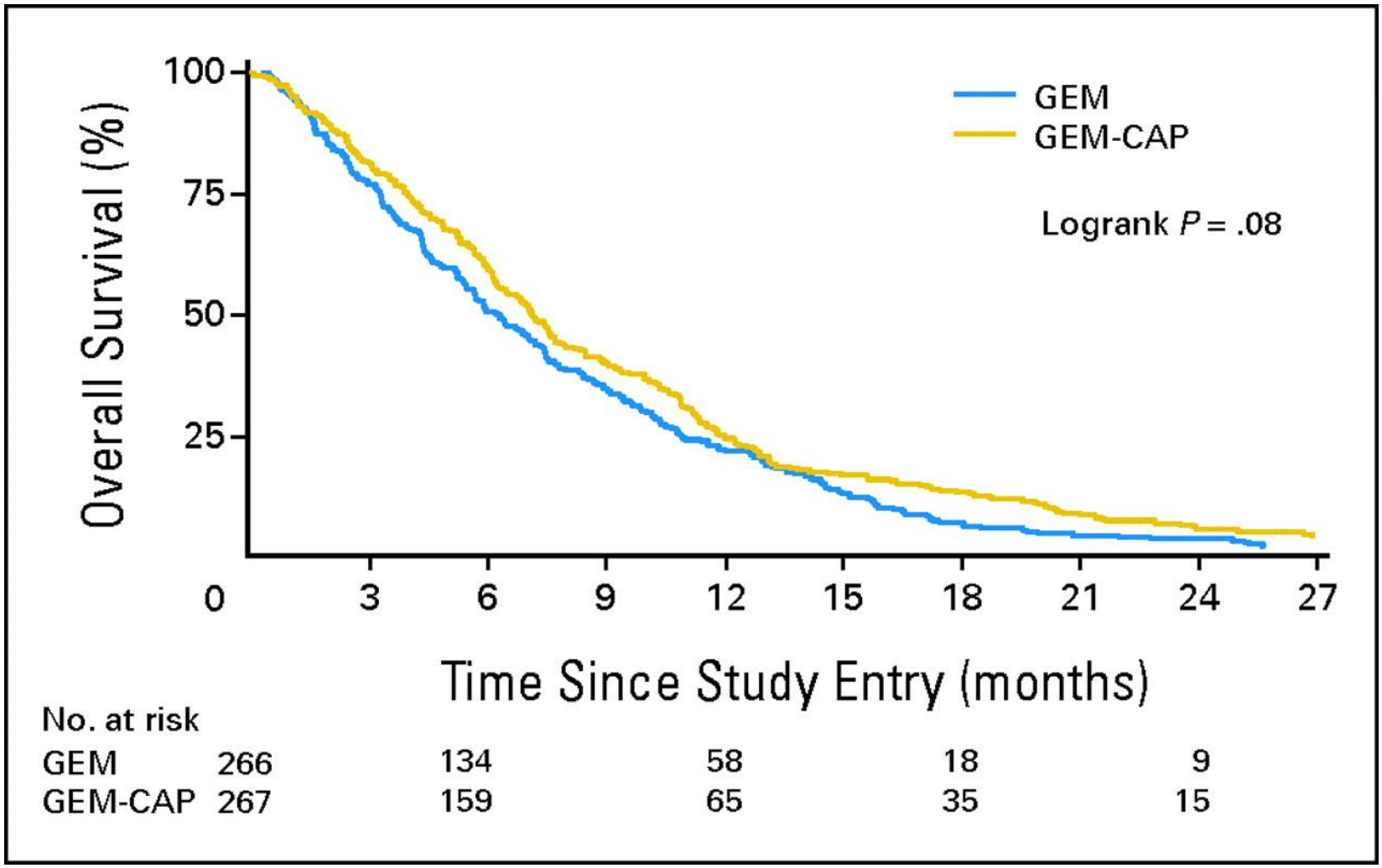
Pancreatic Cancer: Overall survival by treatment arms.



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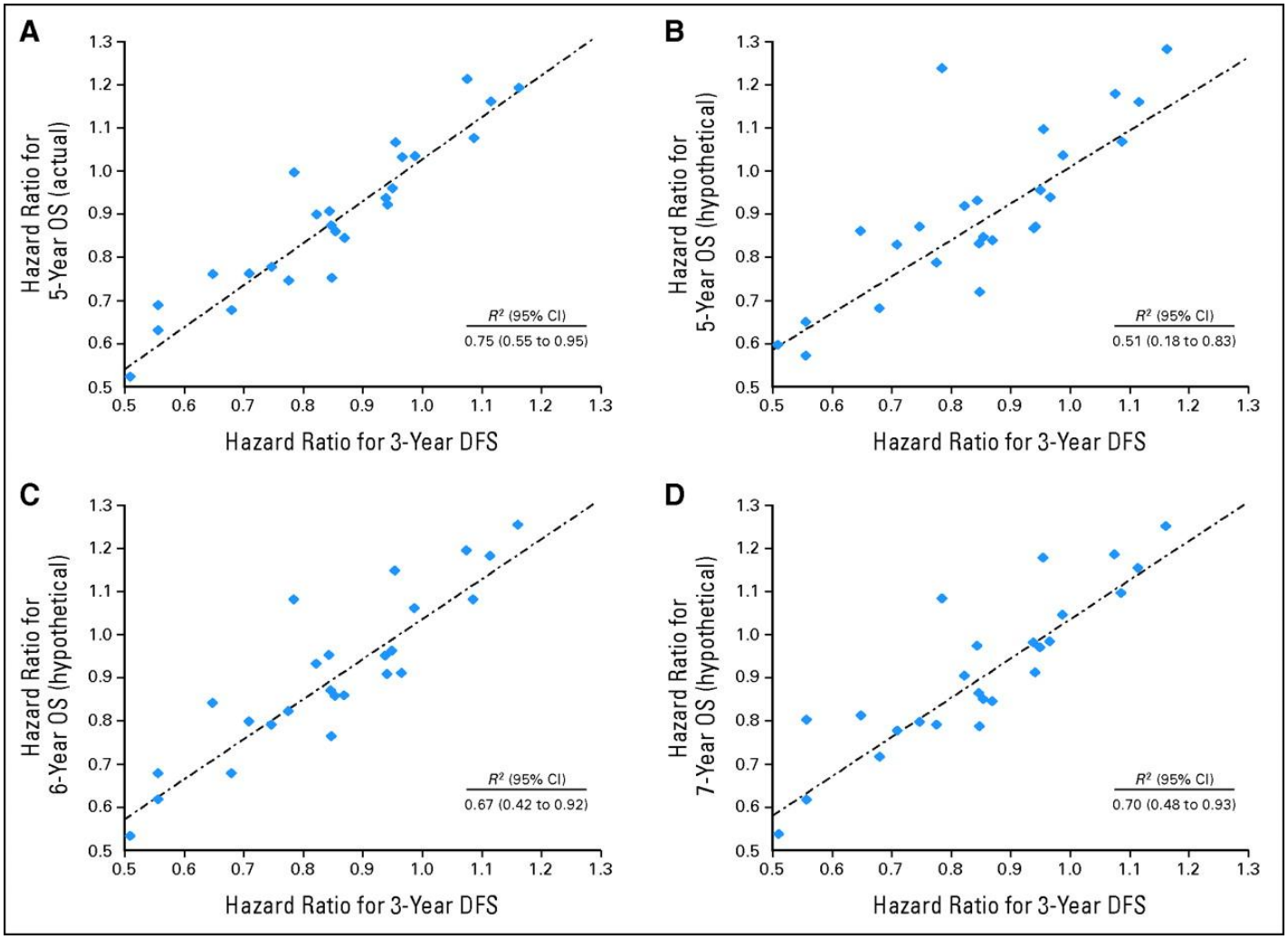
Scatter plots of hazard ratios by trial (disease-free survival [DFS] v overall survival [OS]).



de Gramont A et al. JCO 2010;28:460-465

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Accelerated approval

Surrogate Endpoints

RR, PFS, Lab tests…are considered when disease is incurable and OS confounding (comorbidities, additional treatments…)

Accelerated approval gives earlier access to potentially useful drugs but needs thereafter further confirmatory studies

Bevacizumab in Metastatic Breast Cancer

- Febr. 22. 2008 FDA accelerated approval, single trial: improvement of PFS 5,5 mo (vote 5:4 against)

  AVADO & RIBBON-1: PFS benefit but less

  OS no benefit

- July 2010: ODAC 12:1 withdrawal. FDA decision pending

Bevacizumab in Glioblastoma

- Accelerated approval based on response, difficulties in measuring imaging response
- EMA no approval for GB

Gemtuzumab ozogamicin in AML

- Marketed in 2000
- 2006 Toxicity concerns: veno-occlusive disease
- Latest trial S0106: efficacy benefit not confirmed
- Withdrawal Oct. 15, 2010

Carfilzomib

- Approval asked for shrinking tumor by 24% in myeloma (phase 2 single arm trial)

- 5% of authors express their results in absolute benefit, the others in relative

JAMA 2002,287, 2813

Late Stage Cancers Remain Incurable: Response Rates to First-Line Therapy

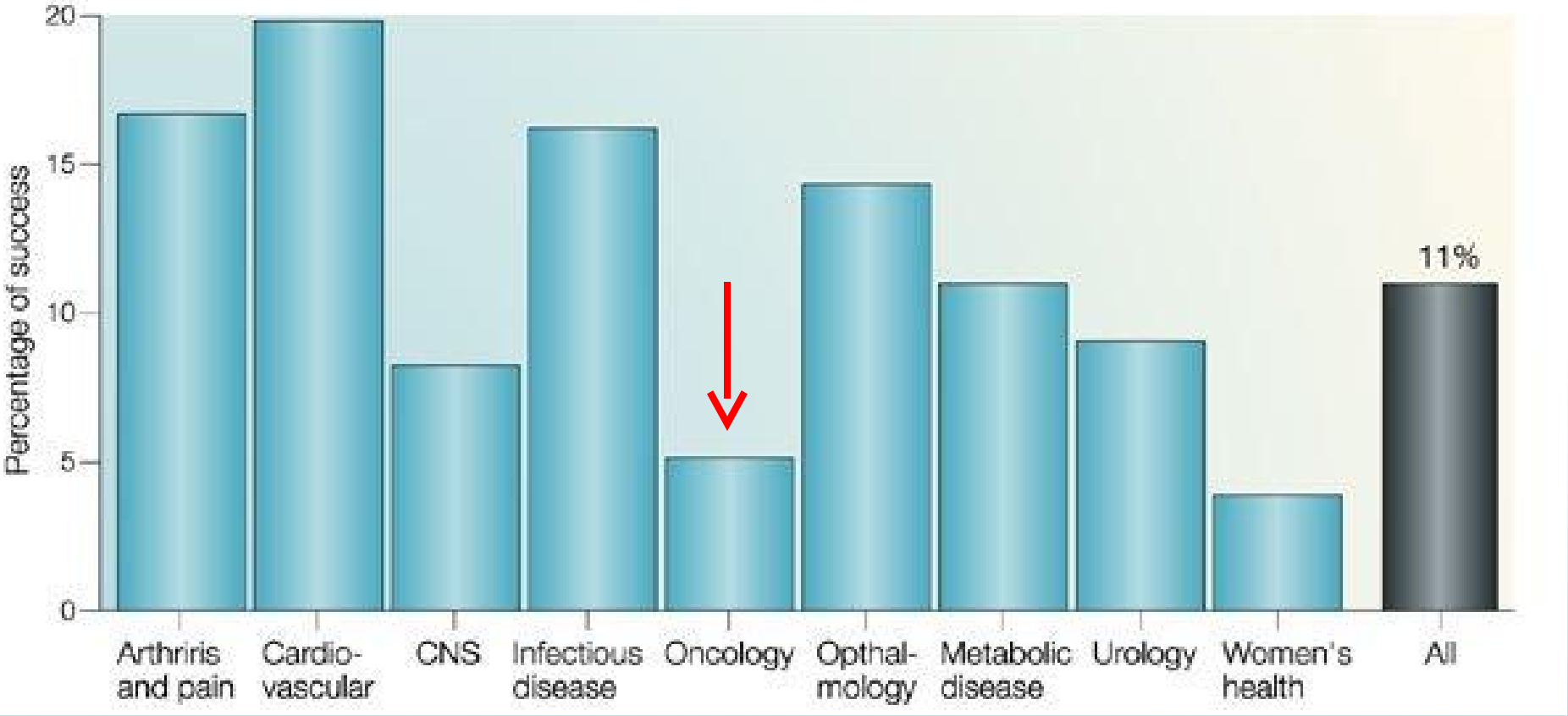
Tumors (Stage IV)	Overall Response Rate (%)	Time to Disease Progression (months)
Breast	59.6%	13.8
	61.9%	15.8
	60.9%	11.4
Lung	51.5%	9.4
	49.5%	11.0
	36.5%	6.4
Prostate	57.2%	13.8
	52.3%	12.2
	59.7%	14.7
Colorectal	58.8%	14.0
	56.1%	12.9
	47.2%	8.5

- Progression Free Survivals fall short of desired metric-- measured in months not years
- Overwhelming unmet primary need is efficacy improvement
- Given efficacy gaps: side effects remain a secondary objective

U.S. | W. Europe | Japan

Source: MattsonJack DaVinci

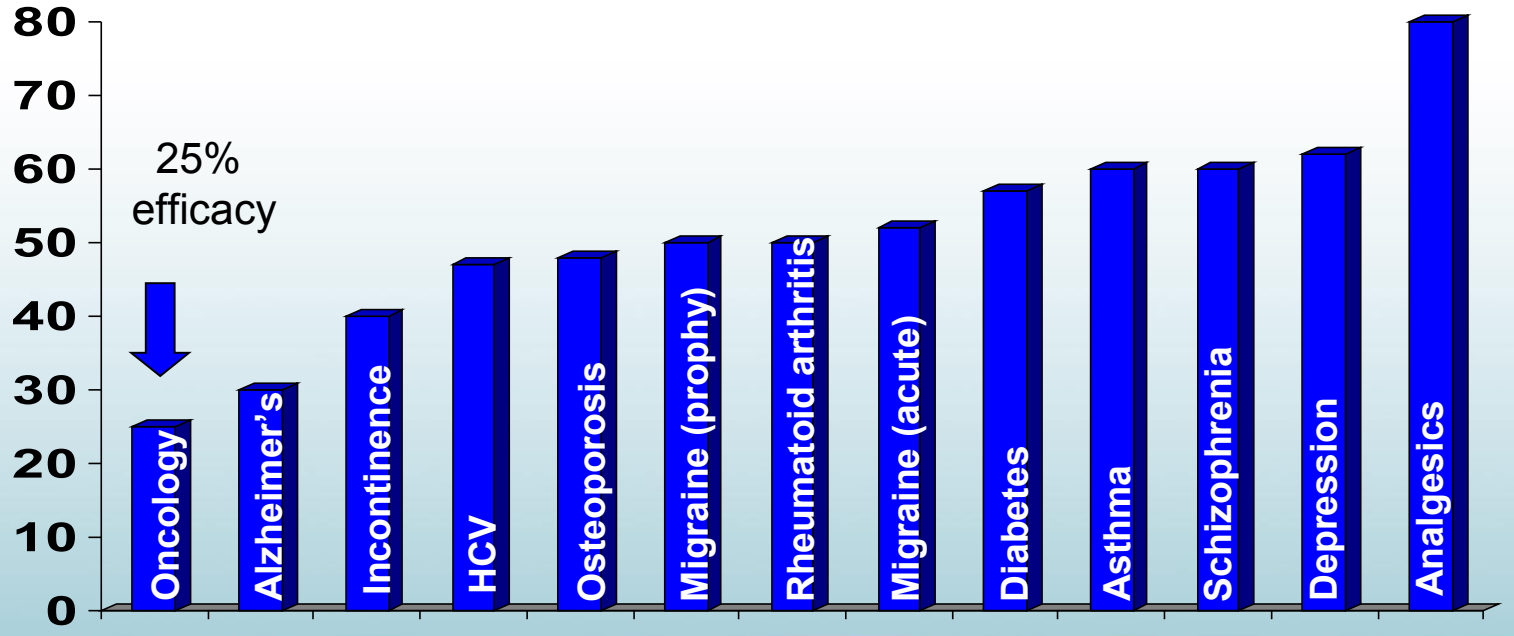
Attrition is High in the R&D Process: Clinical success rates from first-in-man to registration



Kola I & Landis J. *Nature Reviews Drug Discovery*. 3:711, 2004

Current State:
Developing New Therapies for Oncology

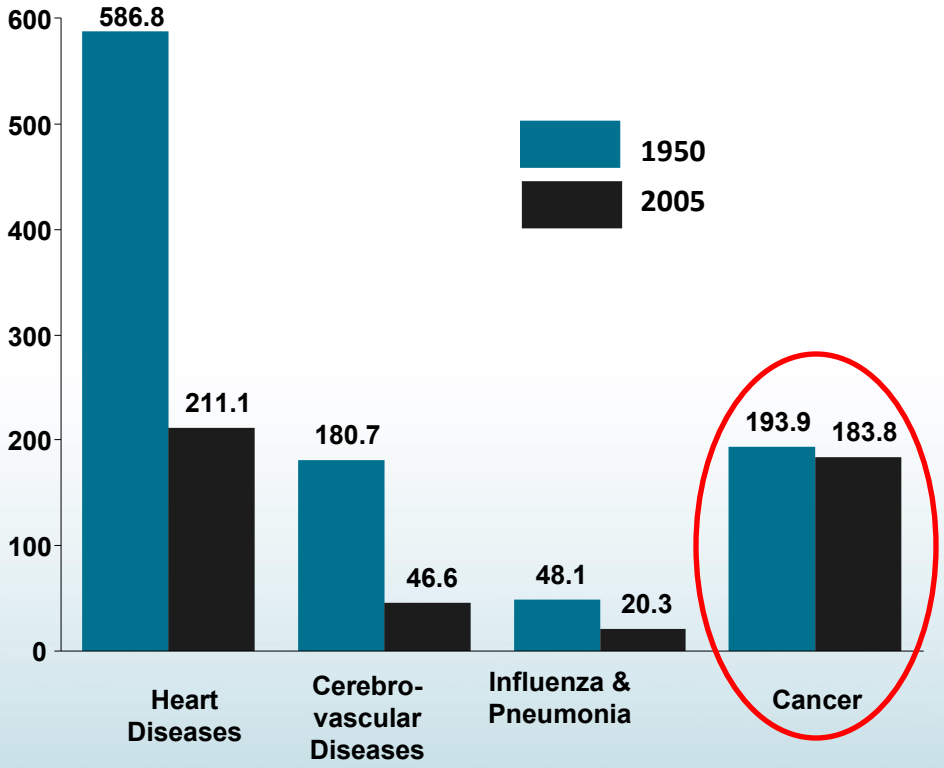
- Marketed oncology therapies are characterized by a very low efficacy rate
- We Need To Do Better!



Source: Trends in Molecular Medicine (2001)

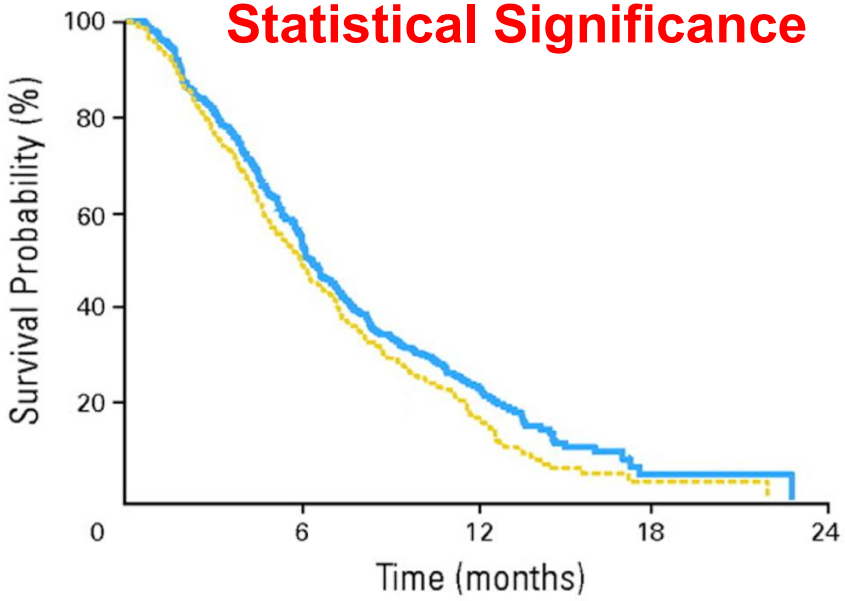
Are We Winning the War Against Cancer?

Mortality Rates Per 100,000



* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2005 Mortality Data: US Mortality Data 2005, NCHS, CDC, 2008.

Clinical Benefit vs. Statistical Significance



e.g. Survival curve used to obtain recent FDA approval for non-selected cancer patients in pancreatic cancer

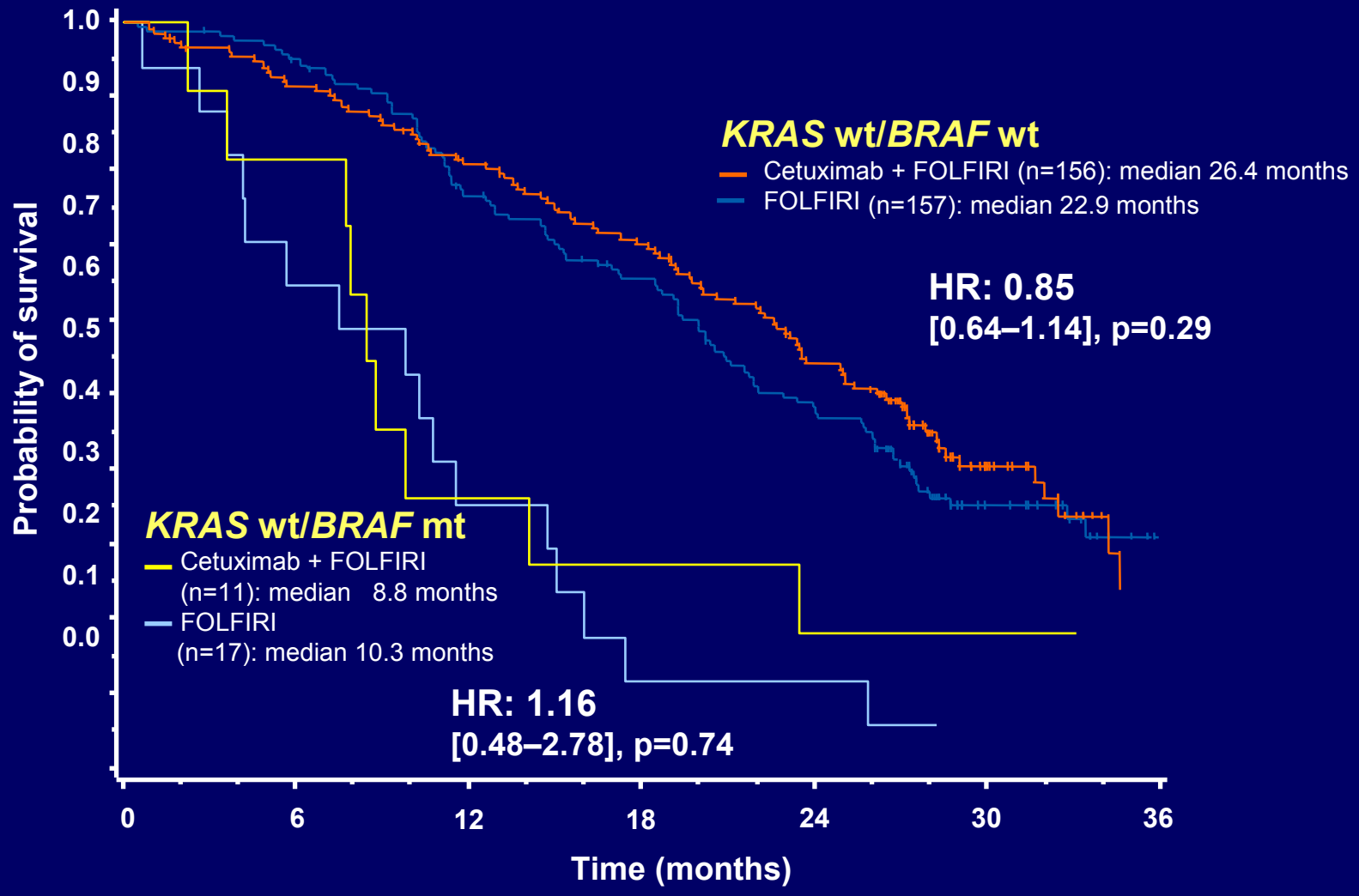
Proposal for Approval for advanced Disease

A. Sobrero J. Clin. Onc. 2009

- Median survival time < 1 y (e.g. pancreas, gastric, NSCLC), agent should give > 50% increased median survival time

- Median survival time > 2 y (e.g. breast, colorectal, ovarian..), the increment should be >30%

Overall survival in the *KRAS* wild-type/BRAF population



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Take home message:

When the evidence is weak, caution should be applied (Lancet Oncology 2010,11:805)

Merci

Si vous voulez ce set de diapos:
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