化學治療可以

- 延長轉移患者的存活期
  - @ **Primary chemotherapy**
- 減輕癌症引起的不適
  - @ **Palliative chemotherapy**
- 增加手術或放射治療的療效
  - @ **Neoadjuvant & adjuvant**
  - @ **Concommitent radiosensitizer**
- 改善臨床的治療方式

5-FU 的給藥方式

FU/LV Bolus

Mayo Clinic

LV 20 mg/m^2
5-FU 425 mg/m^2
d1-5, q 4 wks

RPMI

LV 500 mg/m^2
5-FU 600 mg/m^2
d1, weekly x6 on
x2 off

FU/LV Infusion

de Gramont

LV 200 mg/m^2 (2 h)
5-FU 400 mg/m^2
bolus
5-FU 600 mg/m^2
infusional (22 h)
d1,2, q 2wks

AIO

LV 500 mg/m^2
5-FU 2,600 mg/m^2
24h, weekly x6 on
x2 off

Continuous

Lokich

5-FU 300 mg/m^2
24 hrs, every day

大腸直腸癌治療藥物的進步(1990-)

- 口服藥物

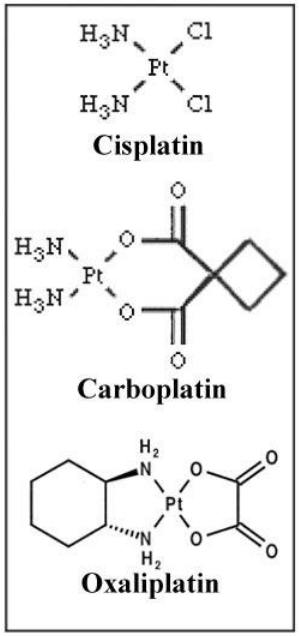
  UFT (UFUR)

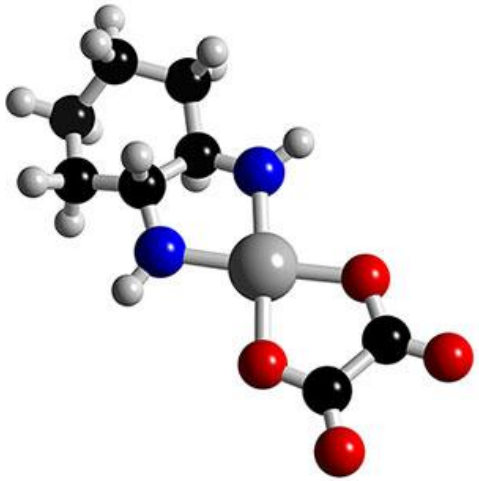
  Capecitabine(Xeloda)
- **Oxaliplatin(Eloxatin)**
- **Irinotecan(CPT-11, Camto)** **Topo-I inhibitors**

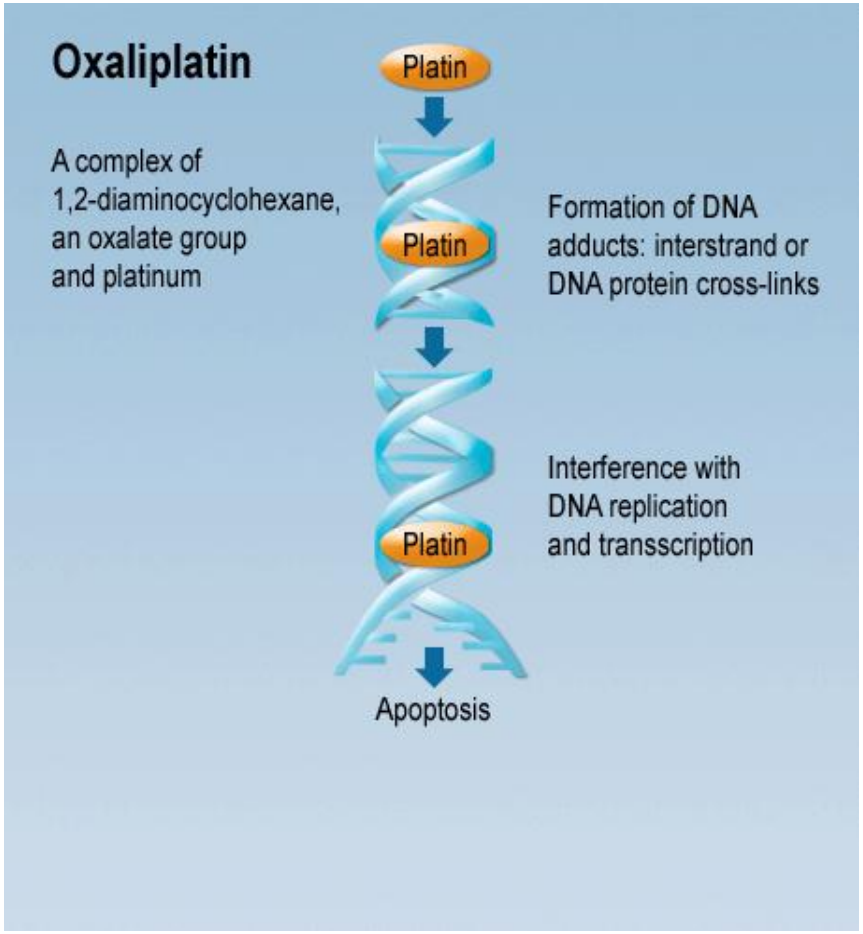
5-FU 世代:整體腫瘤緩解率

	Study treatment	Mayo Clinic regimen	p value
Capecitabine	**25.7**	**16.7**	**<0.0002**
UFT/LV	**11.7**	**14.5**	**NS**
de Gramont	**32.6**	**14.5**	**0.004**

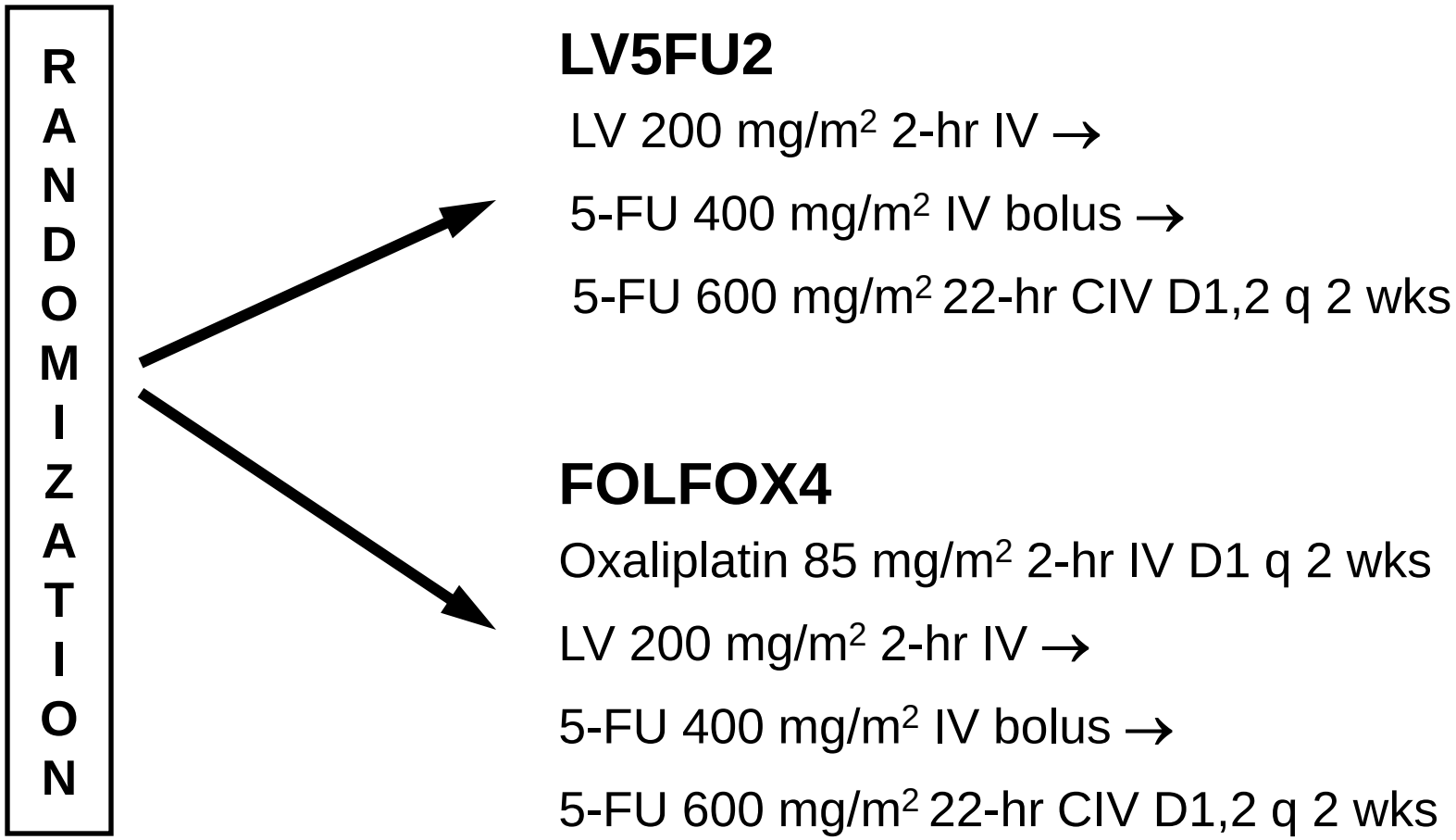
Oxaliplatin (Eloxatin)







de Gramont First-line Trial



de Gramont – Objective Response Rate

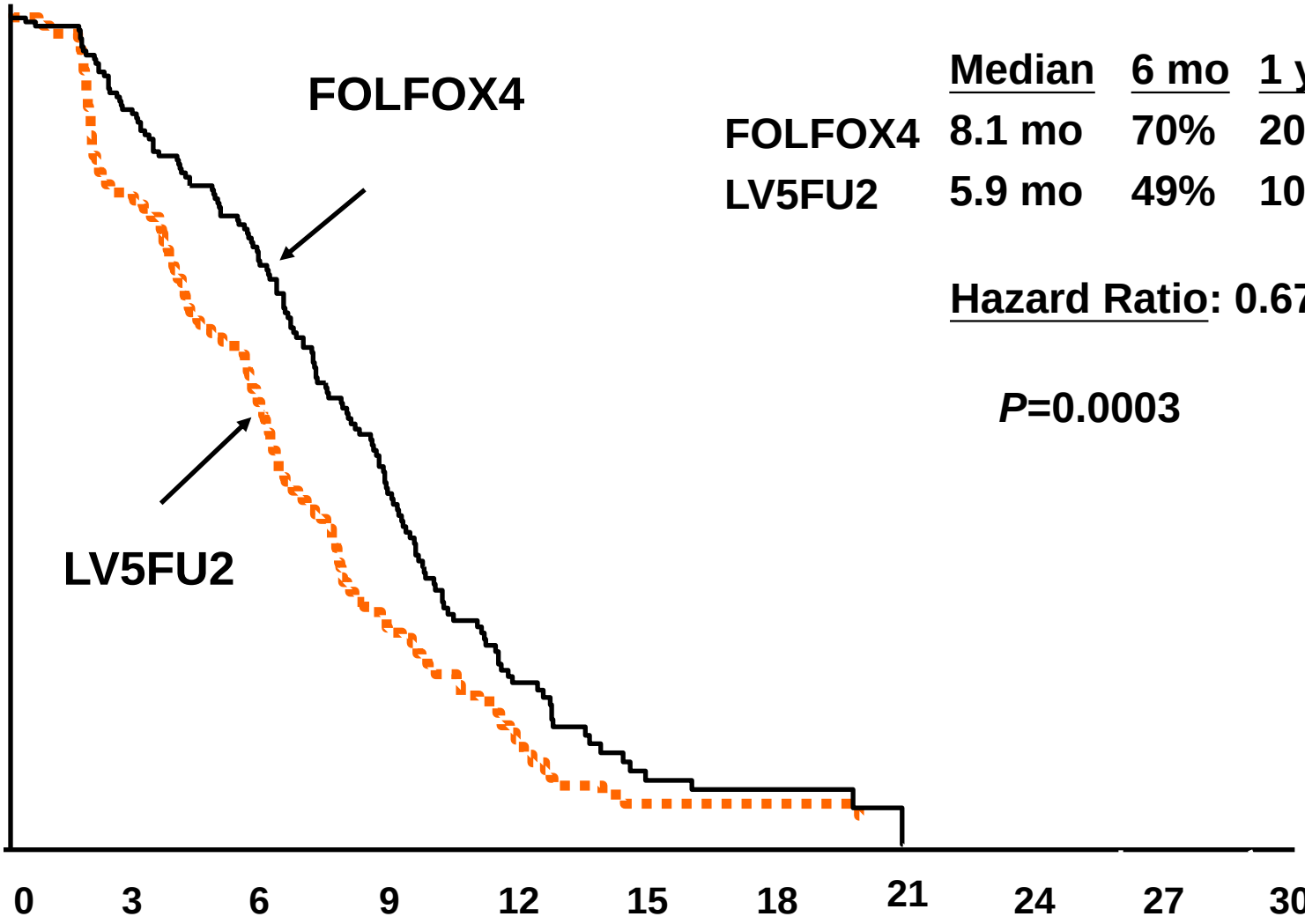
✹ 緩解率顯著提升

	RR*
• LV5FU2	21.9%
	⬇
• FOLFOX4	**49.0%**
• *P* value	< 0.001†

*** Responses evaluated every 8 weeks and confirmed at 4 weeks**

† Chi-square 2-tailed test

平均無悪化存活期 5.9 → 8.1m



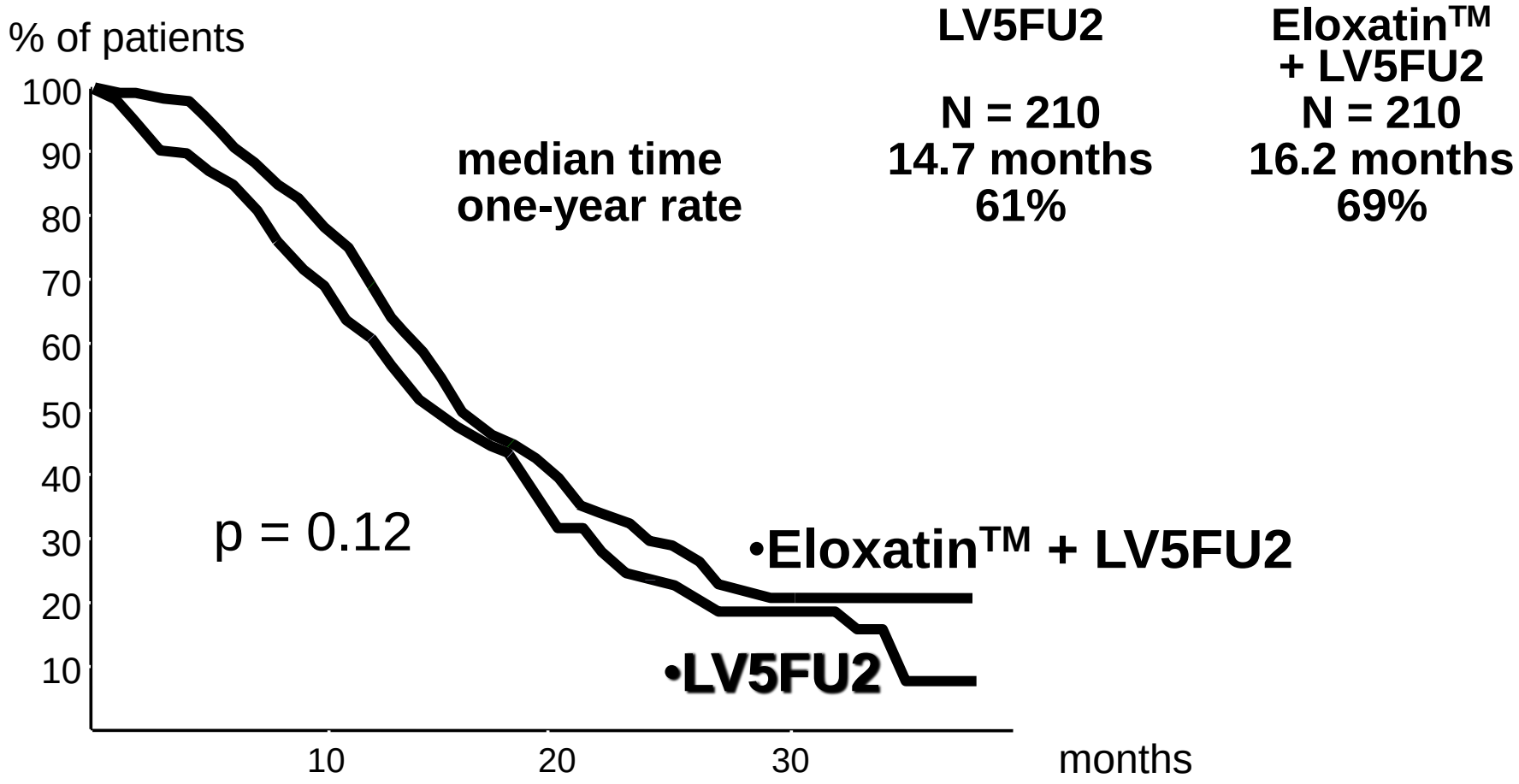
	Median	6 mo	1 yr
FOLFOX4	8.1 mo	70%	20%
LV5FU2	5.9 mo	49%	10%

Hazard Ratio: 0.67

***P*=0.0003**

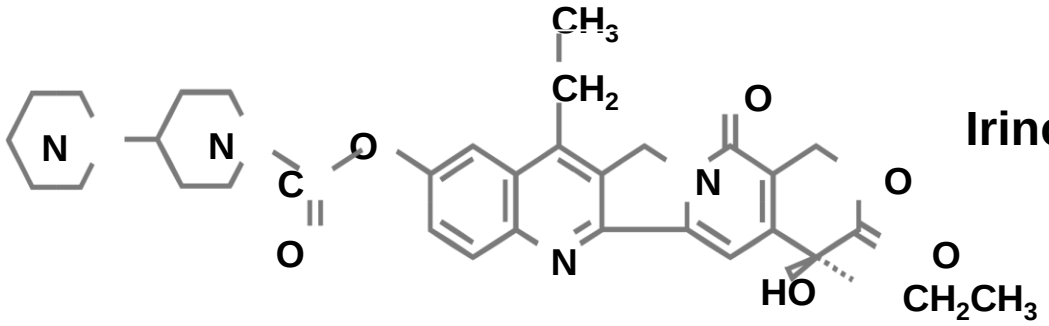
整體平均存活曲線

Median follow-up : 27.7 months



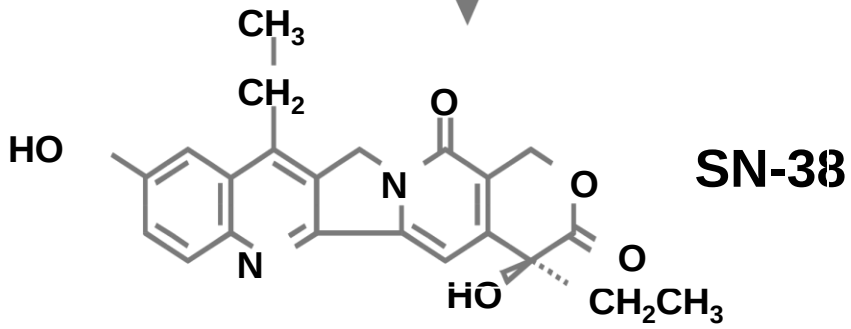
	LV5FU2	Eloxatin™ + LV5FU2
	N = 210	N = 210
median time	14.7 months	16.2 months
one-year rate	61%	69%

Irinotecan (CAMPTO)

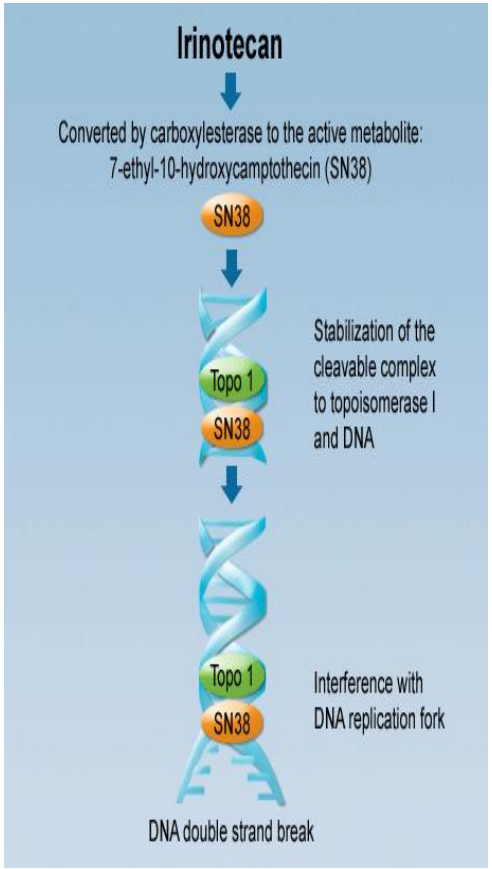


Irinotecan

Carboxylesterase



SN-38

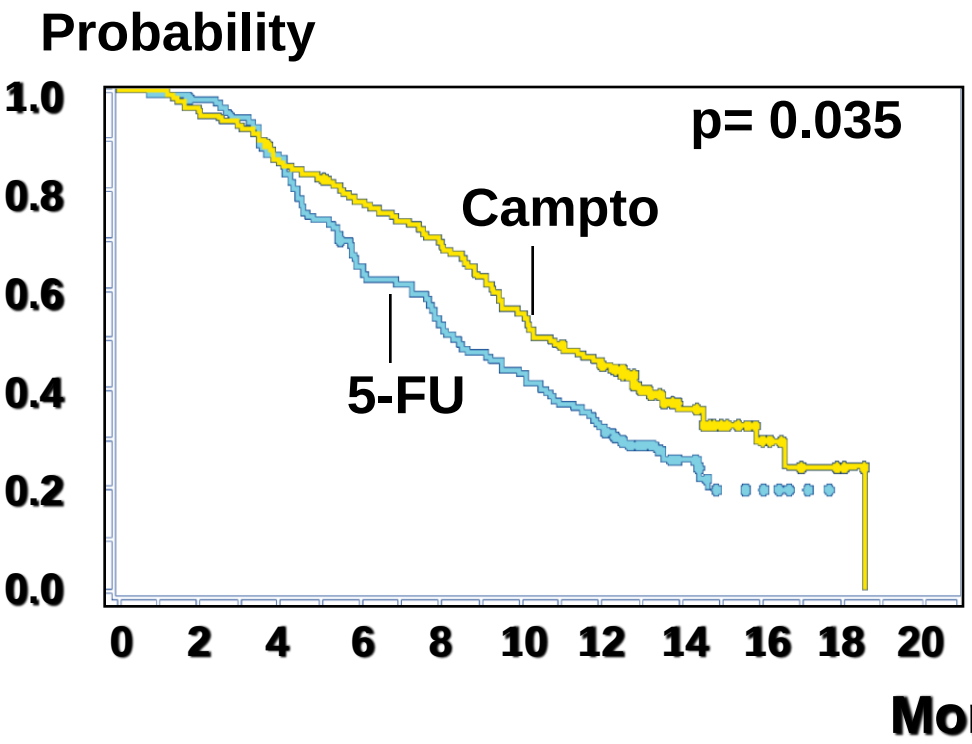


Inhibition of topoisomerase I

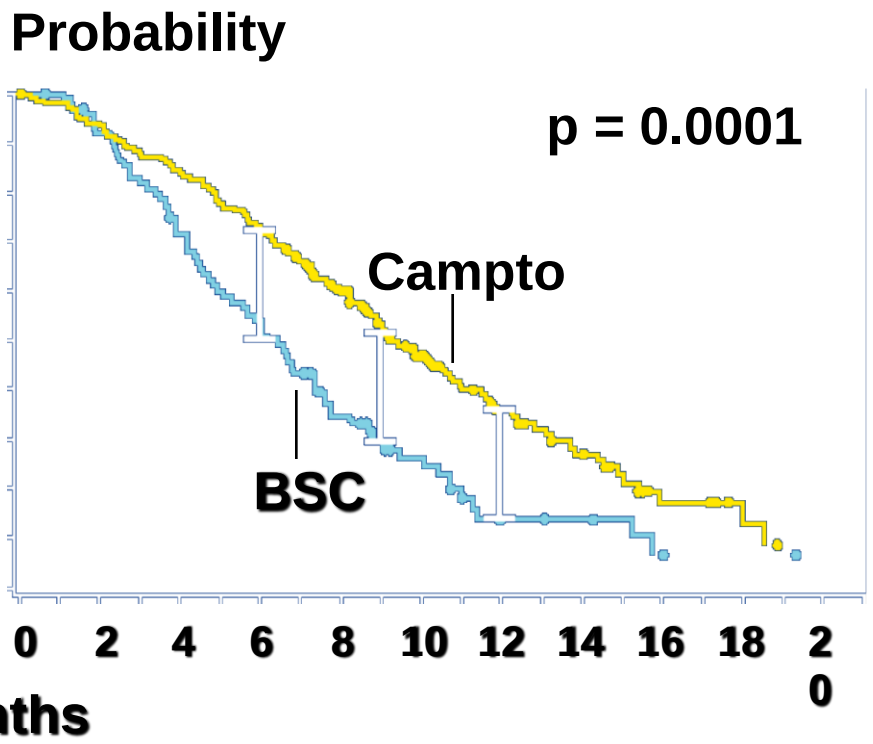
Key enzyme regulating DNA replication and cell division

Campto(CPT-11)： 5-FU 無效後的二線治療

- 單一藥物比支持療法或長時輸注5-FU均有平均存活期的顯著延長



Campto *vs* 5-FU



Campto *vs* BSC

The Lancet, 1998

Douillard Study 第一線治療

RANDOMIZED

Campto + 5-FU / FA
(weekly AIO schedule or q 2wks De Gramont schedule)
(N=199)

VERSUS

5-FU / FA
(weekly AIO schedule or q 2wks De Gramont schedule)
(N=188)

Choice of 5-FU/FA regimen decided by each investigator before commencing study
AIO= Association of medical oncology of the German Cancer Society

Douillard et al Lancet 2000; 355: 1041 – 1047.

Douillard Study: 臨床療效的比較

	Campto+ *i*FL	***i*FL**	**P**
緩解率	49%	31%	<0.001
Time to Progression	6.7 mos	4.4 mos	<0.001
平均存活	**17.4mos**	**14.1mos**	**.031**

*i*FL=infusion 5FU/FA

Douillard et al Lancet 2000; 355: 1041 – 1047.

嚴重的藥物不良反應 NCI Grade 3/ 4 Toxicity

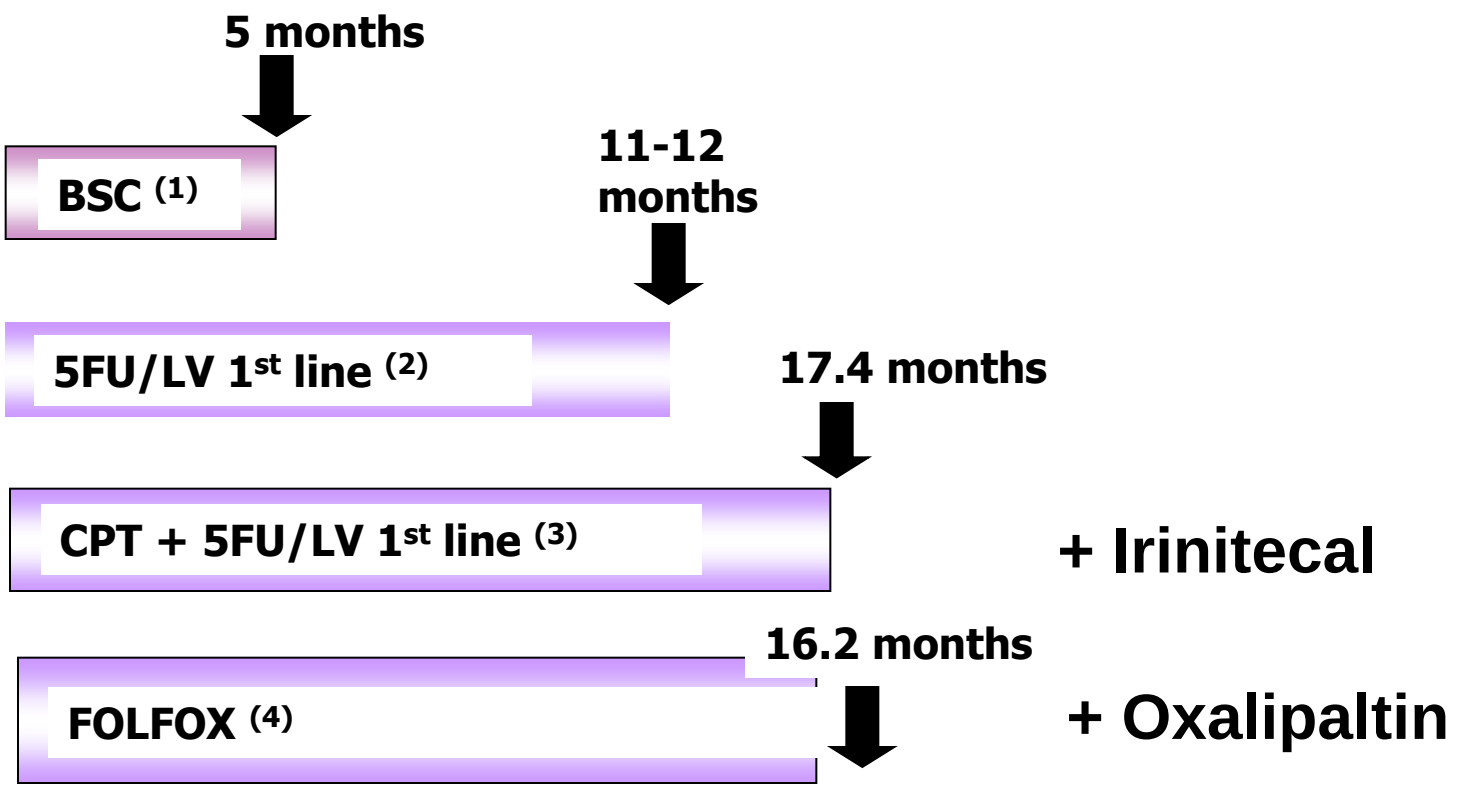
% of patients	Campto+ *i*FL	*i*FL	P
腹瀉 Diarrhea	22	10	.028
Asthenia	7	1	.011
Nausea	4	2	NS
Vomiting	5	2	NS
中性球低下 Neutropenia	42	11	.001
Leukopenia	17	4	.001
Infection with G3/4 neutropenia	2.1	0	NS

*i*FL=infusion 5FU/FA

Douillard et al Lancet 2000; 355: 1041 – 1047.

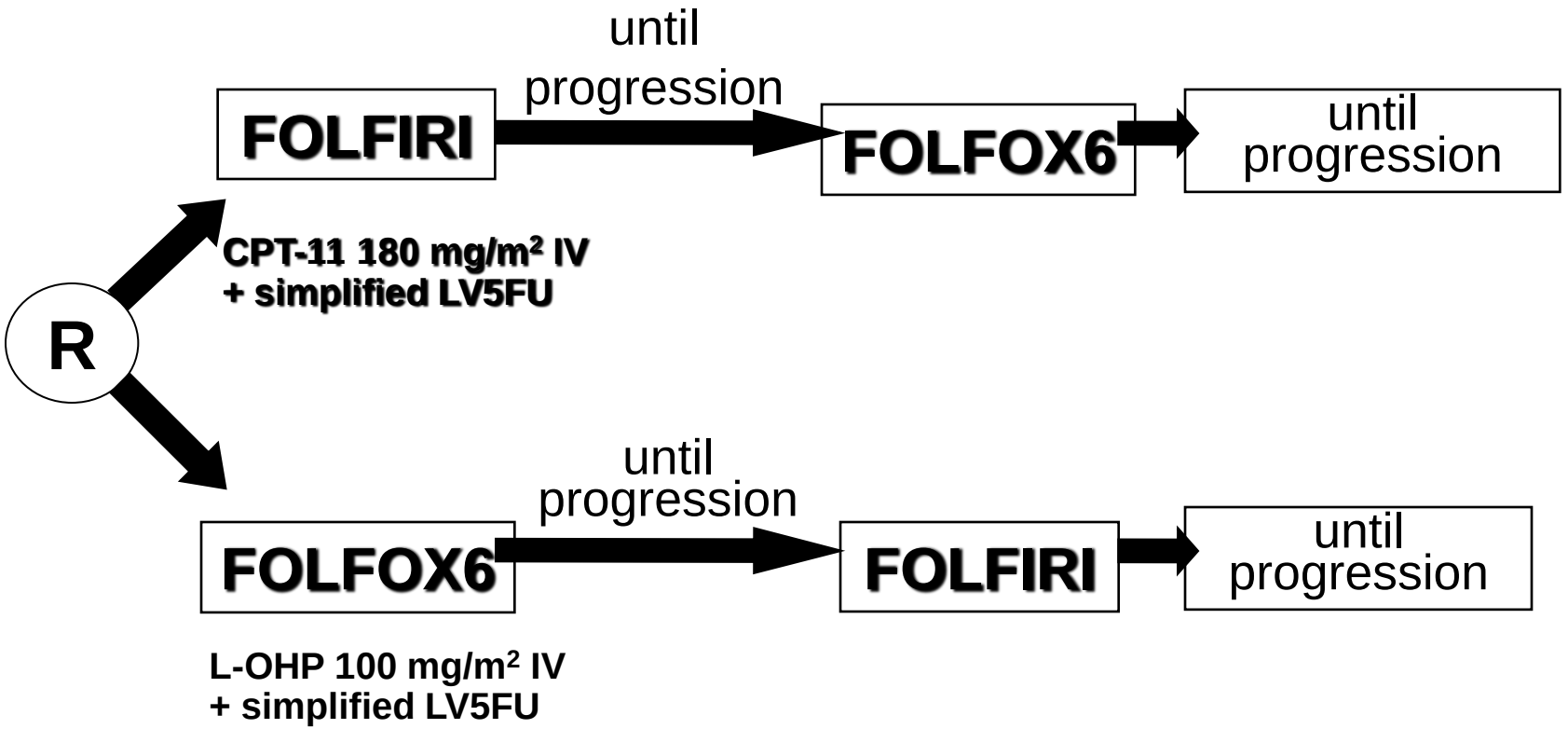
晚期大腸直腸癌治療：存活期延長

平均存活(月)



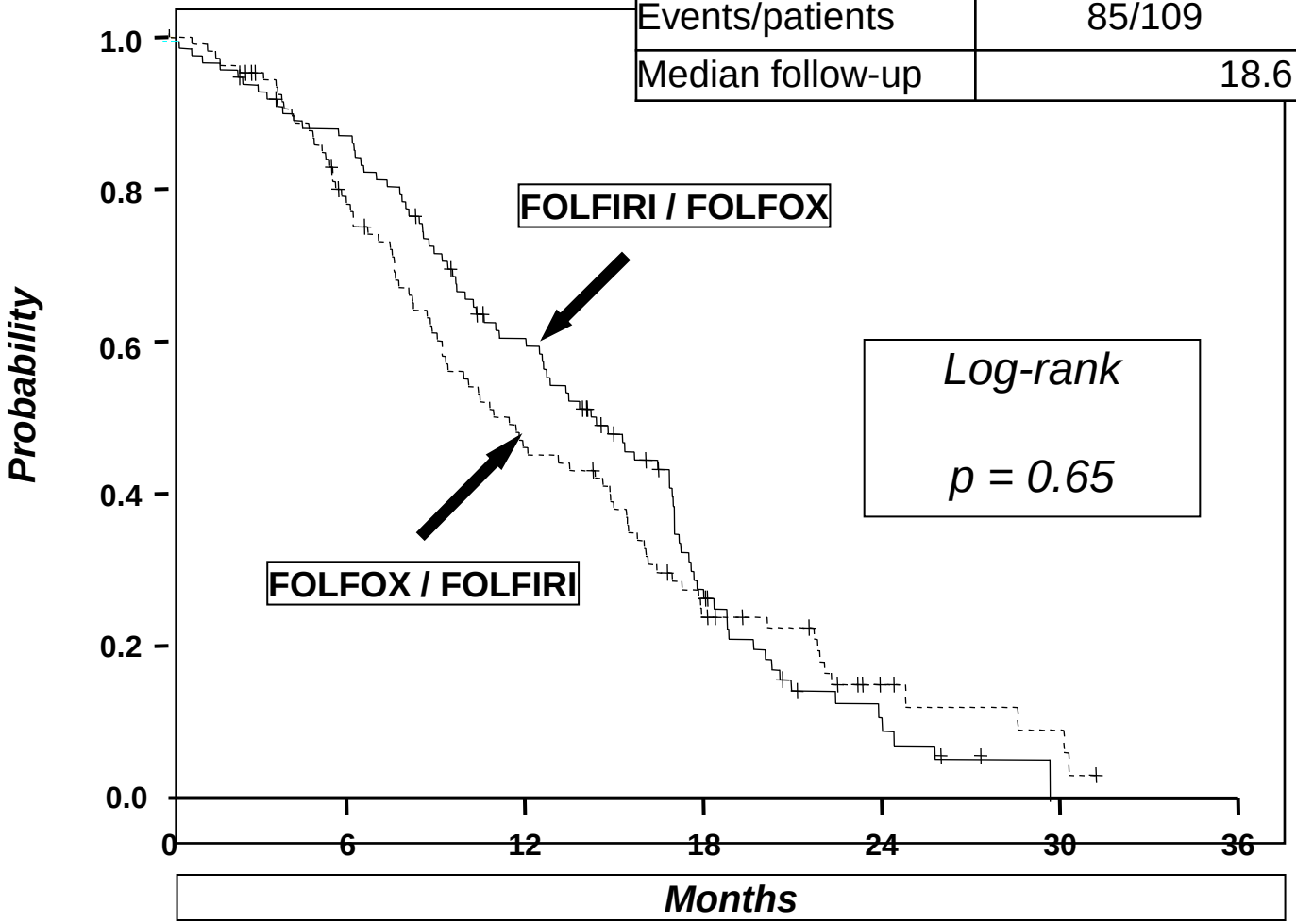
(1) Scheithauer & al : B. Med J. 1993
(2) Meta-analysis Group in Cancer. J Clin Oncol 16:301, 1998.
(3) Douillard & al : Lancet 2000
(4) De Gramot : ASCO 1998

Tournigand Study



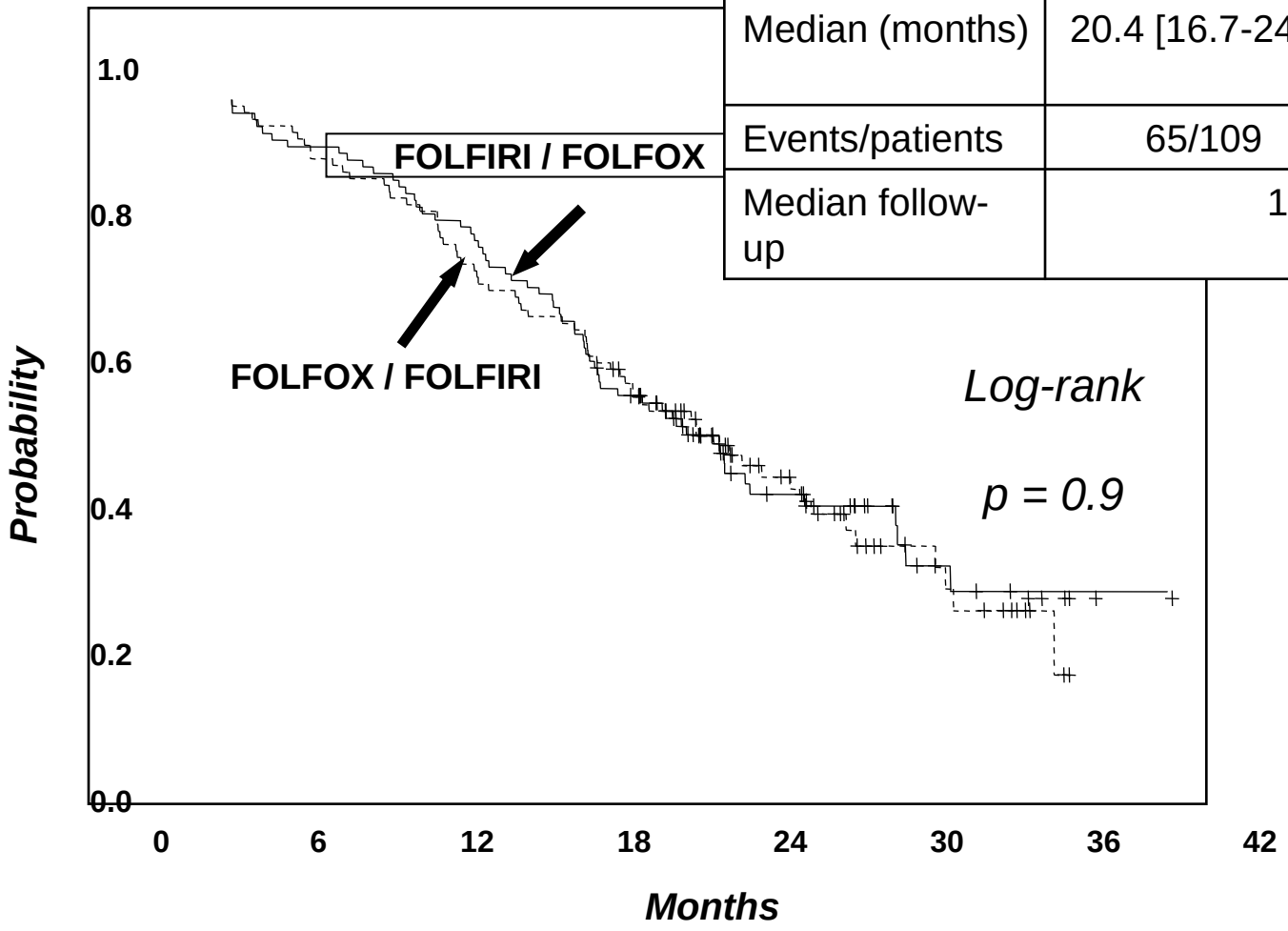
平均悪化時間 Time to progression

	FOLFIRI/FOLFOX	FOLFOX/FOLFIRI
Median (months)	14.4 [12.5-17.0]	11.5 [9.2-14.6]
Events/patients	85/109	86/111
Median follow-up	18.6 months	



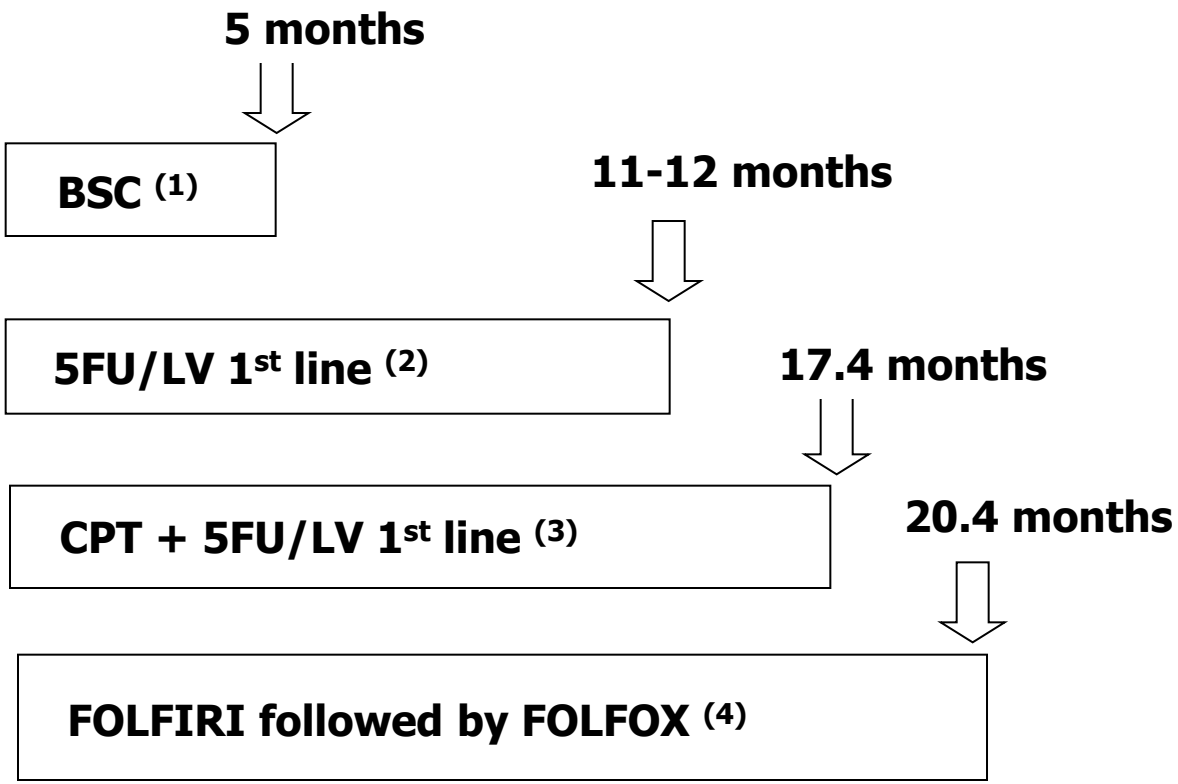
平均存活Overall survival

	FOLFIRI/FOLFOX	FOLFOX/FOLFIRI
Median (months)	20.4 [16.7-24.9]	21.5 [17.3-24.8]
Events/patients	65/109	67/111
Median follow-up	18.6 months	



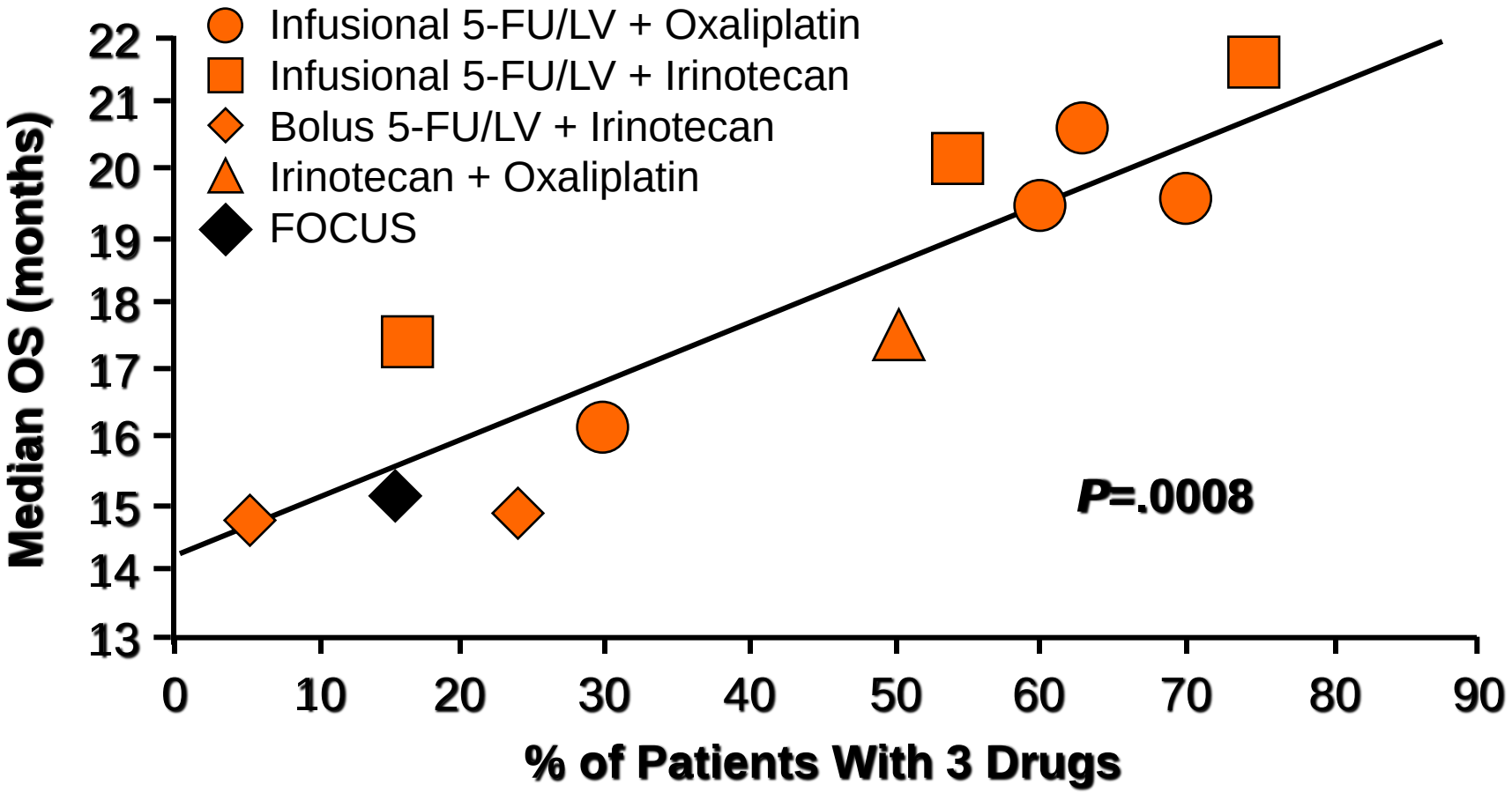
晚期大腸直腸癌：存活期延長

Survival Benefit



(1) Scheithauer & al : B. Med J. 1993
(2) Meta-analysis Group in Cancer. J Clin Oncol 16:301, 1998.
(3) Douillard & al : Lancet 2000
(4) Tournigand & al : ASCO 2001

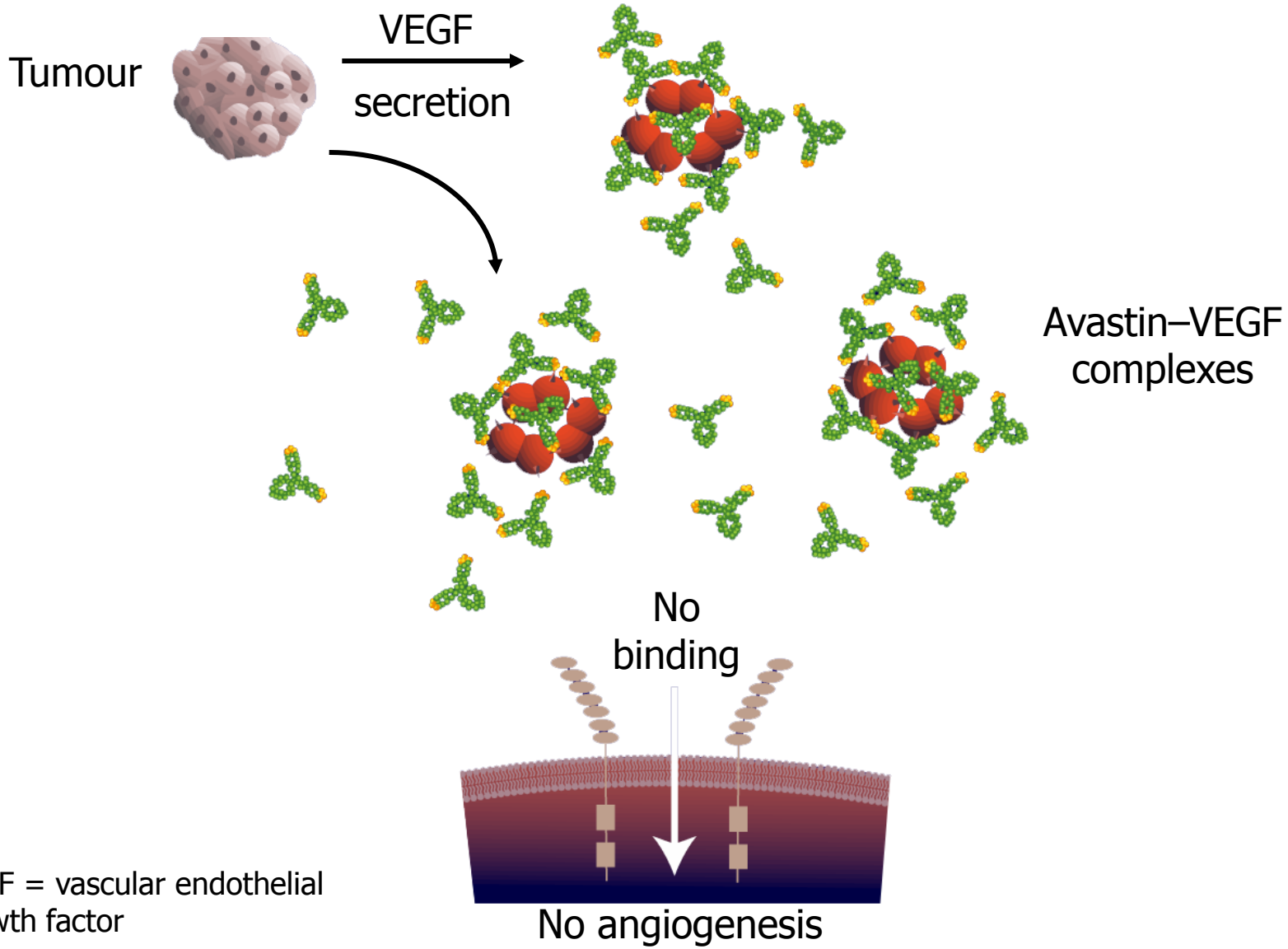
Survival correlates with availability of all 3 cytotoxic agents



"Median overall survival correlates with the % of patients who receive all 3 drugs in the course of their disease" (*P*=.0008)

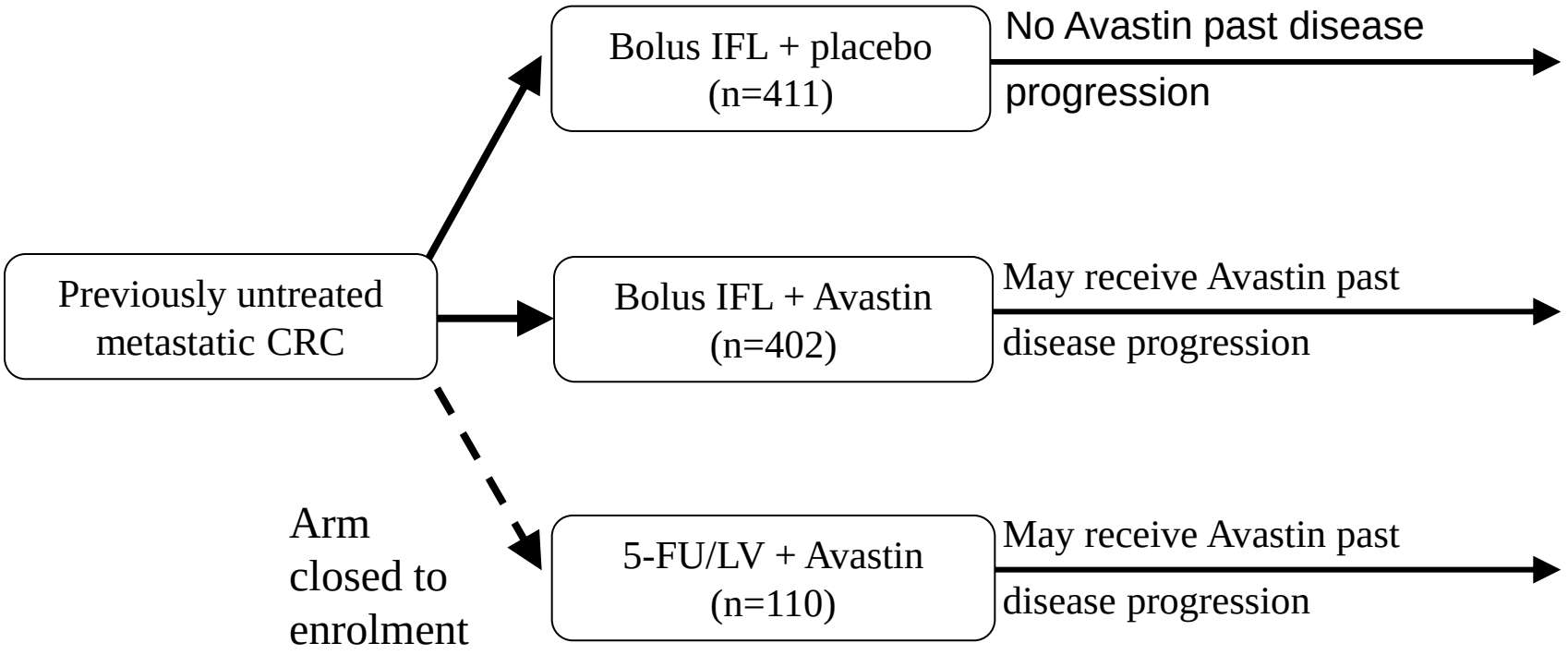
Grothey et al. *J Clin Oncol*. 2004;22;1209-1214.

Avastin : mechanism of action



VEGF = vascular endothelial growth factor

Phase III trial of IFL ± Avastin in metastatic CRC (AVF2107g)



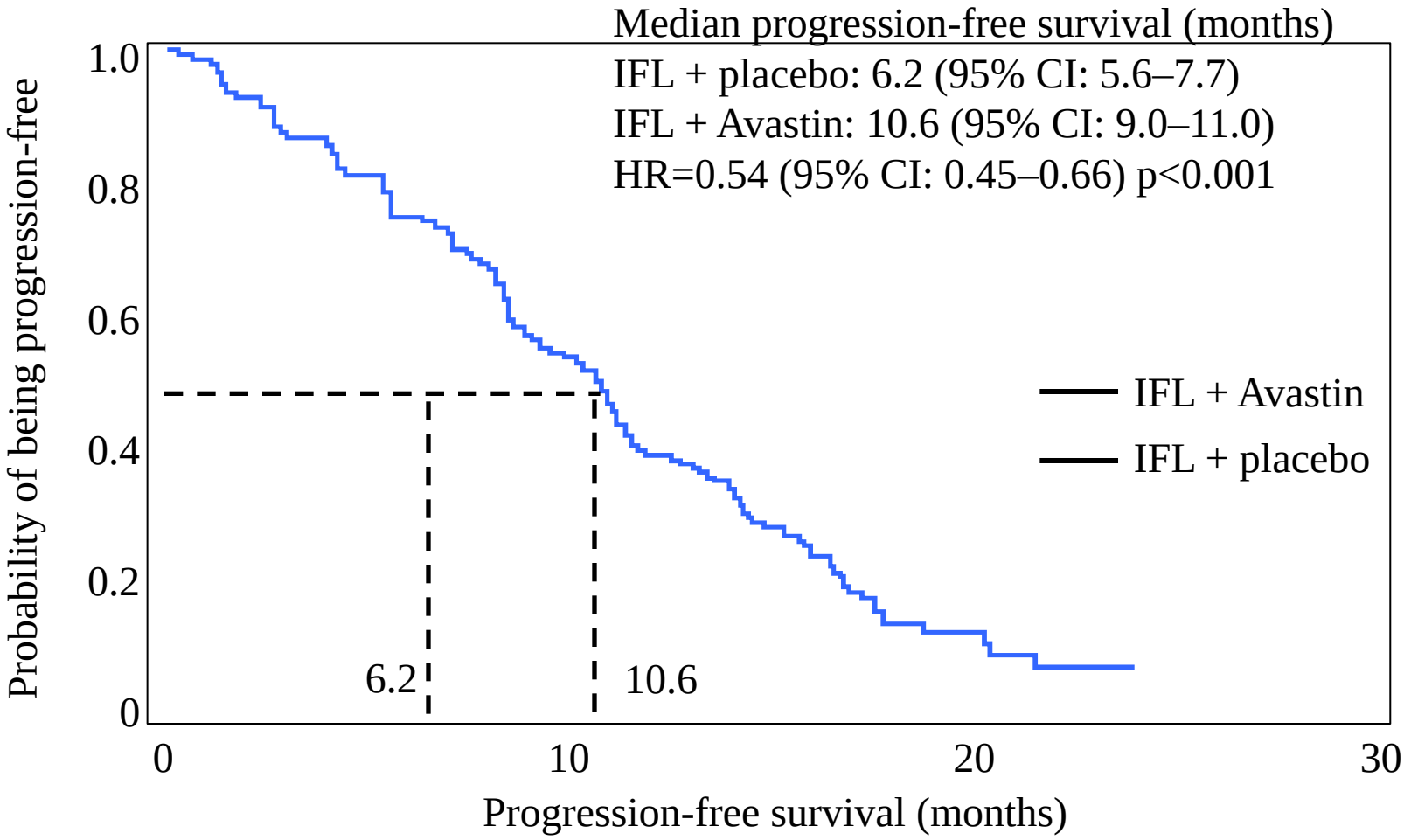
IFL
bolus 5-FU 500mg/m^2
LV 20mg/m^2
irinotecan 125mg/m^2
given 4/6 weeks

5-FU/LV
bolus 5-FU 500mg/m^2
LV 500mg/m^2
given 6/8 weeks

Avastin
5mg/kg every 2 weeks

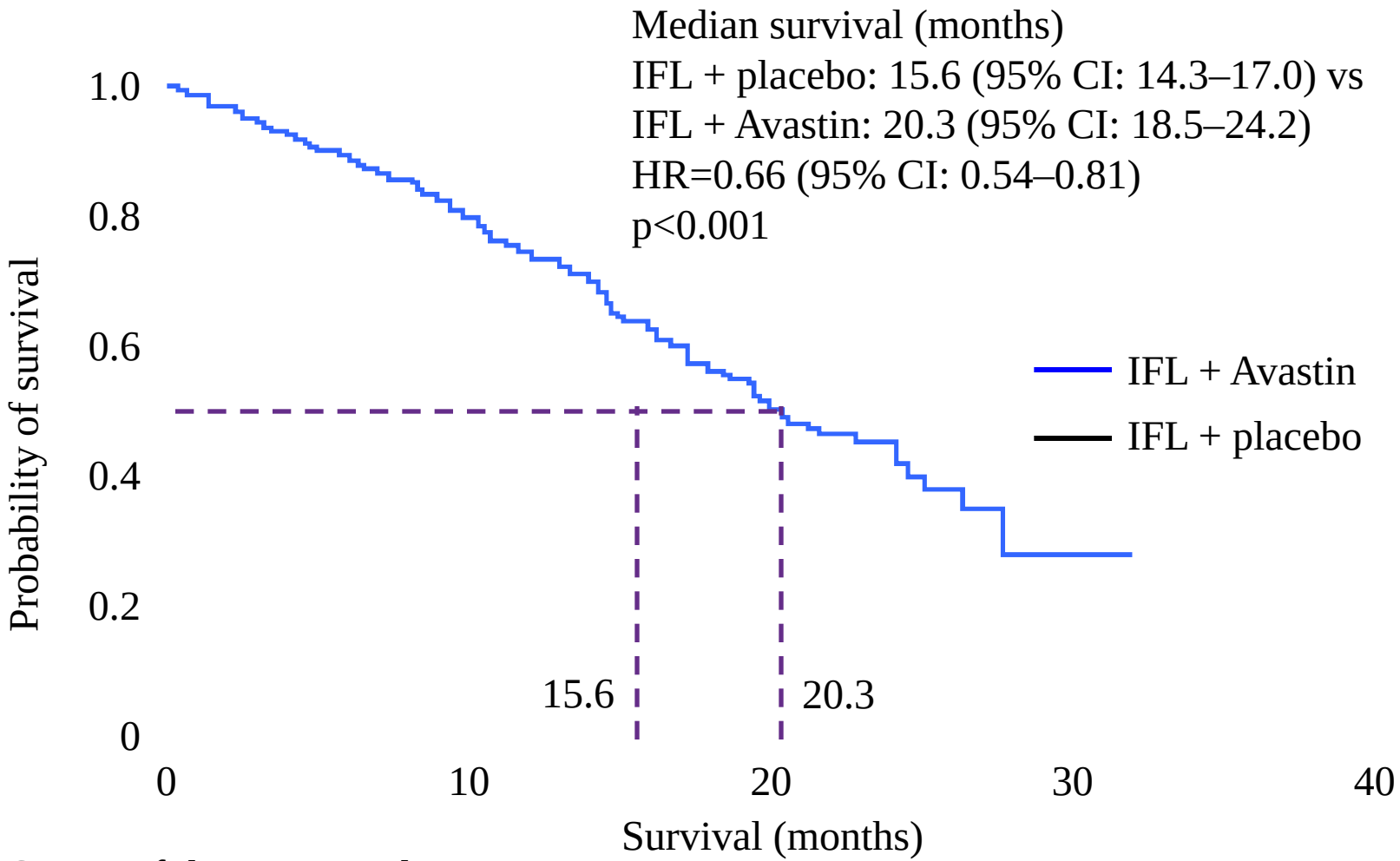
Hurwitz H, et al. N Engl J Med 2004;350:2335–42

Phase III trial of IFL ± Avastin in metastatic CRC (AVF2107g): progression-free survival



Hurwitz H, et al. N Engl J Med 2004;350:2335–42

Phase III trial of IFL ± Avastin in metastatic CRC (AVF2107g): survival

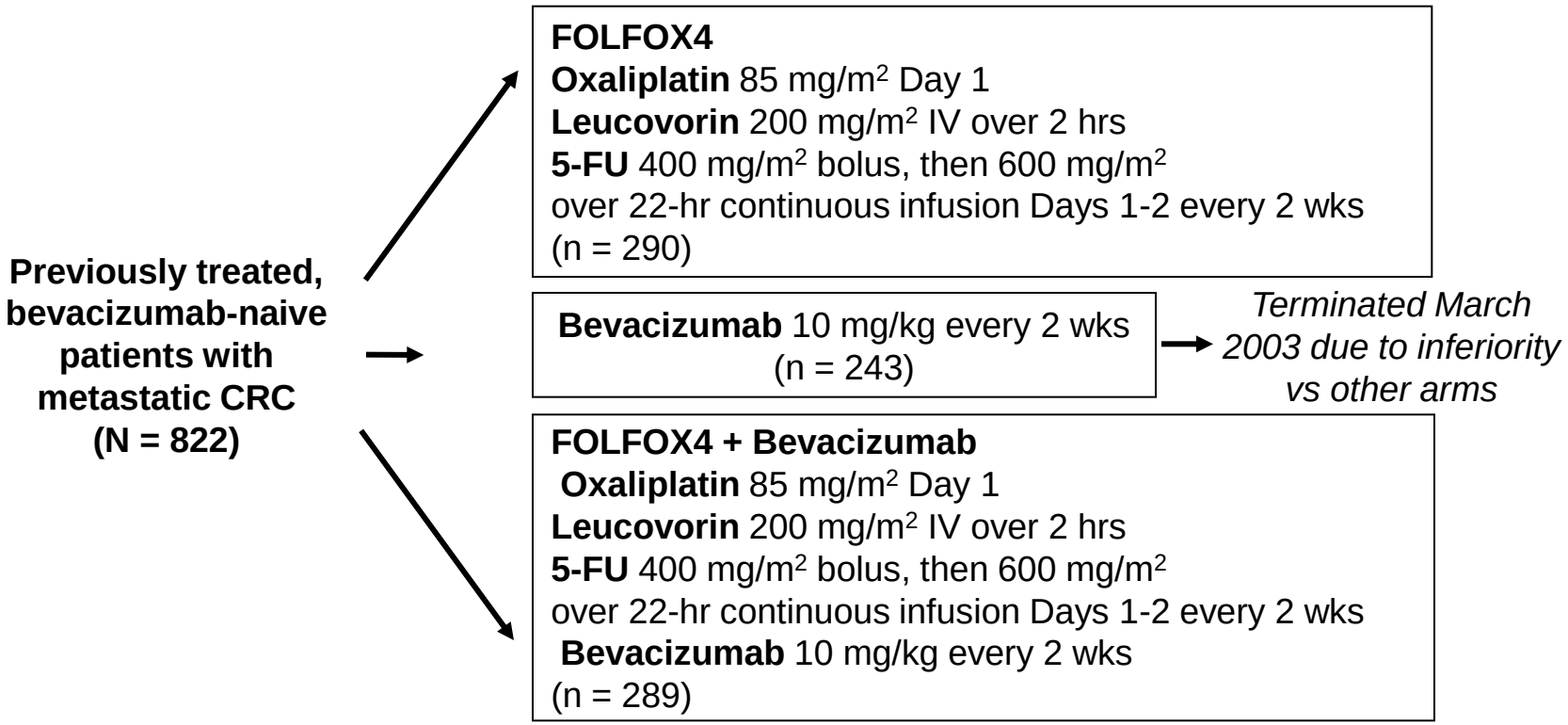


CI = confidence interval
HR = hazard ratio

Hurwitz H, et al. N Engl J Med 2004;350:2335–42

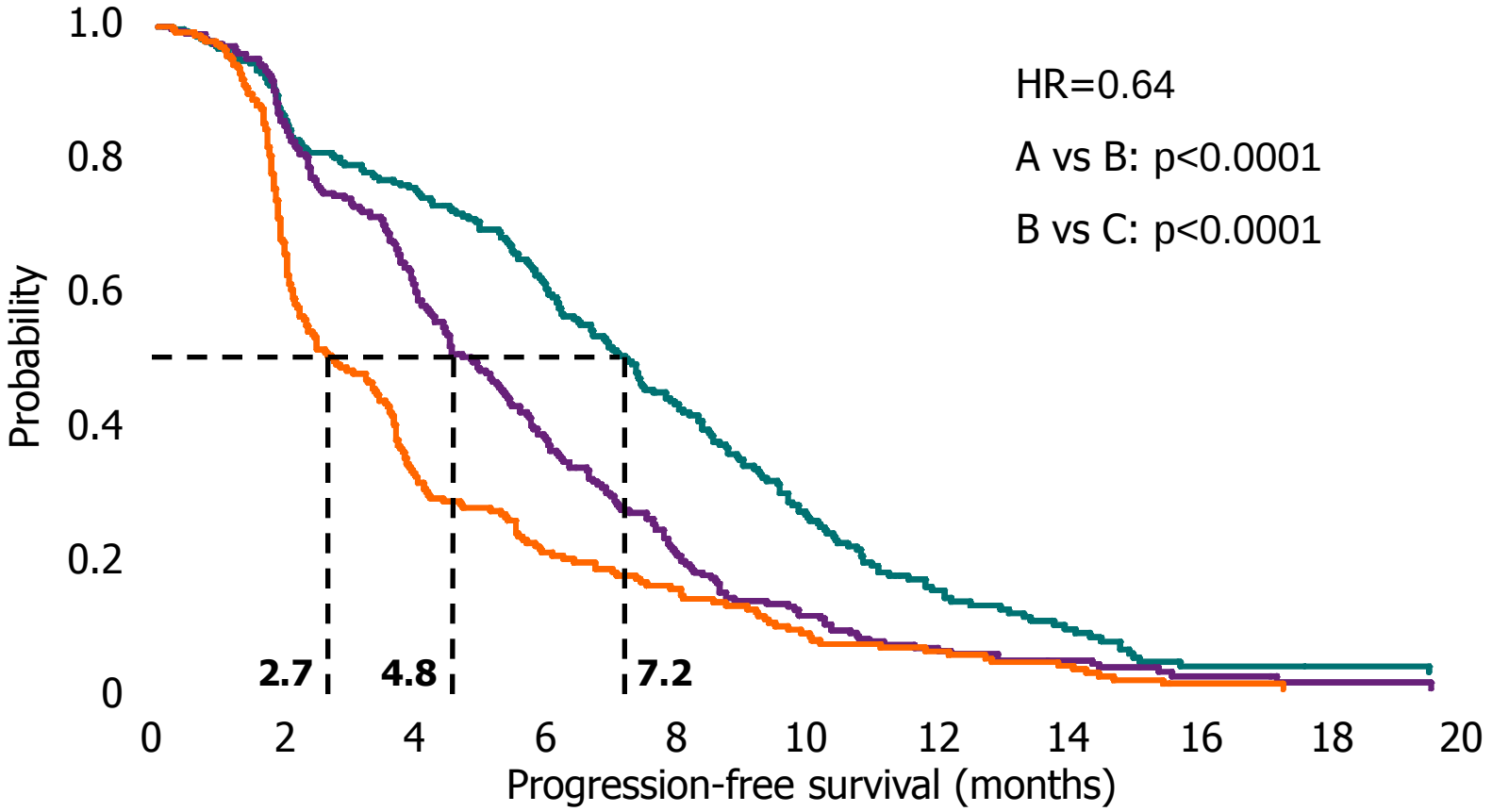
Bevacizumab for Previously Treated Metastatic CRC

- ECOG E3200: Randomized, phase 3 trial



Giantonio et al. ASCO 2005. Abstract 2.

E3200: progression-free survival



	Total	Fail	Cens	Median
A: FOLFOX4 + bevacizumab	273	228	45	7.2
B: FOLFOX4	273	241	32	4.8
C: Bevacizumab	229	215	14	2.7

Giantonio BJ, et al. J Clin Oncol 2005;23(June 1 Suppl.):1s (Abstract 2)

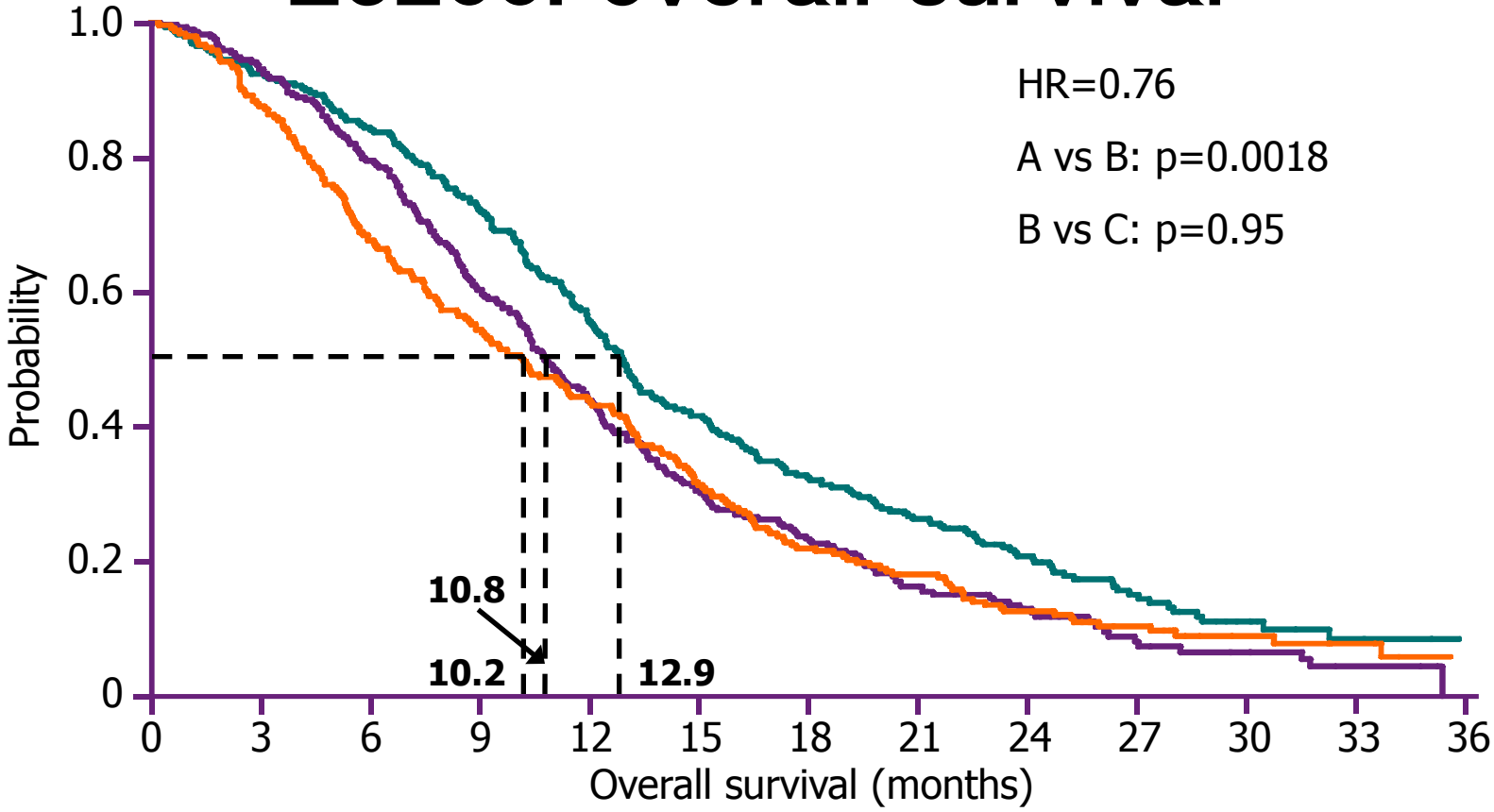
E3200: response rates

	FOLFOX4 + bevacizumab (n=271)	FOLFOX4 (n=271)	Bevacizumab (n=230)
Overall response (%)*	21.8	9.2	3.0
Complete response (%)	1.9	0.7	0
Partial response (%)	19.9	8.5	3.0
Stable disease (%)	51.7	45.0	29.1

*FOLFOX + bevacizumab versus FOLFOX: $p<0.0001$

Giantonio BJ, et al. J Clin Oncol 2005;23(June 1 Suppl.):1s (Abstract 2)

E3200: overall survival

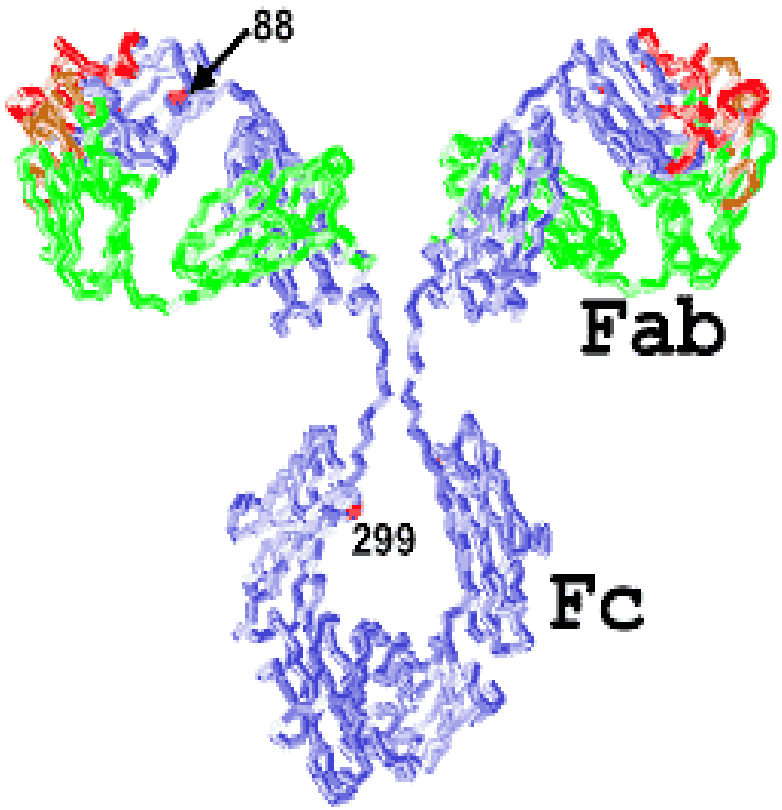


	Total	Dead	Alive	Median
A: FOLFOX4 + bevacizumab	289	246	43	12.9
B: FOLFOX4	290	257	33	10.8
C: Bevacizumab	243	216	27	10.2

HR = hazard ratio

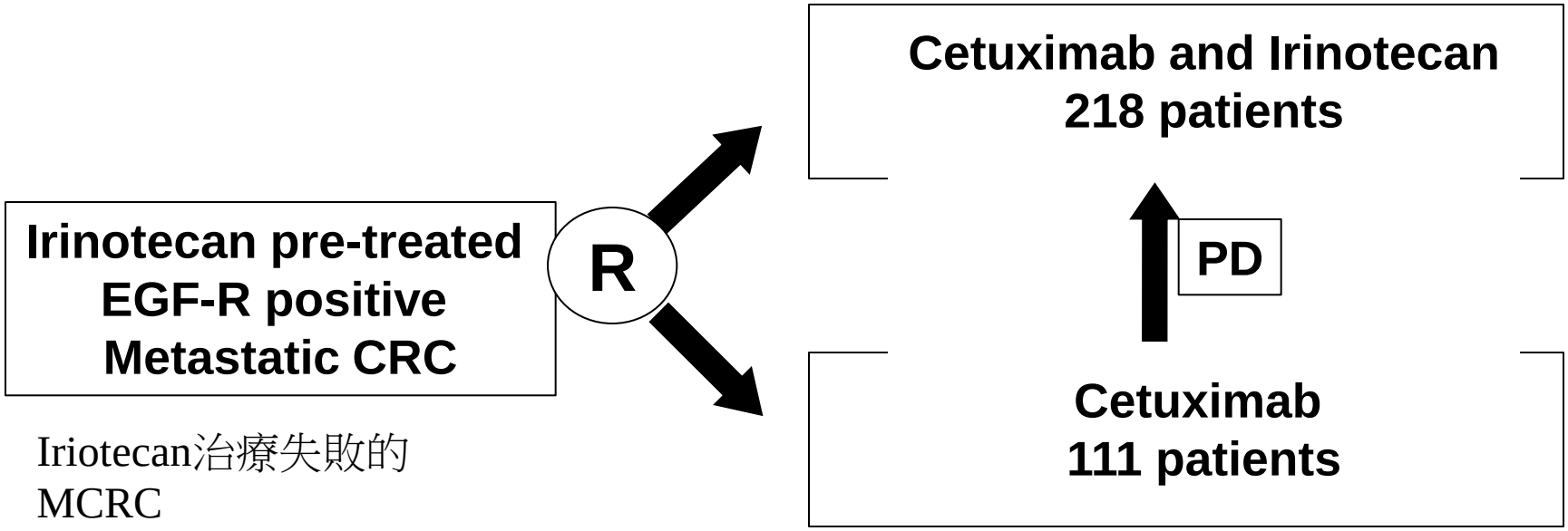
Giantonio BJ, et al. J Clin Oncol 2005;23(June 1 Suppl.):1s (Abstract 2)

Cetuximab (Erbitux™)



- Cetuximab is an IgG1 MAb that targets EGFR
- Binding blocks EGFR signaling and inhibits proliferation, angiogenesis and metastasis, and stimulates apoptosis and differentiation
- The main toxicity is an acne-like rash that generally improves during treatment, and usually does not preclude continued treatment

Cetuximab in Colorectal Cancer ("Bond Trial")

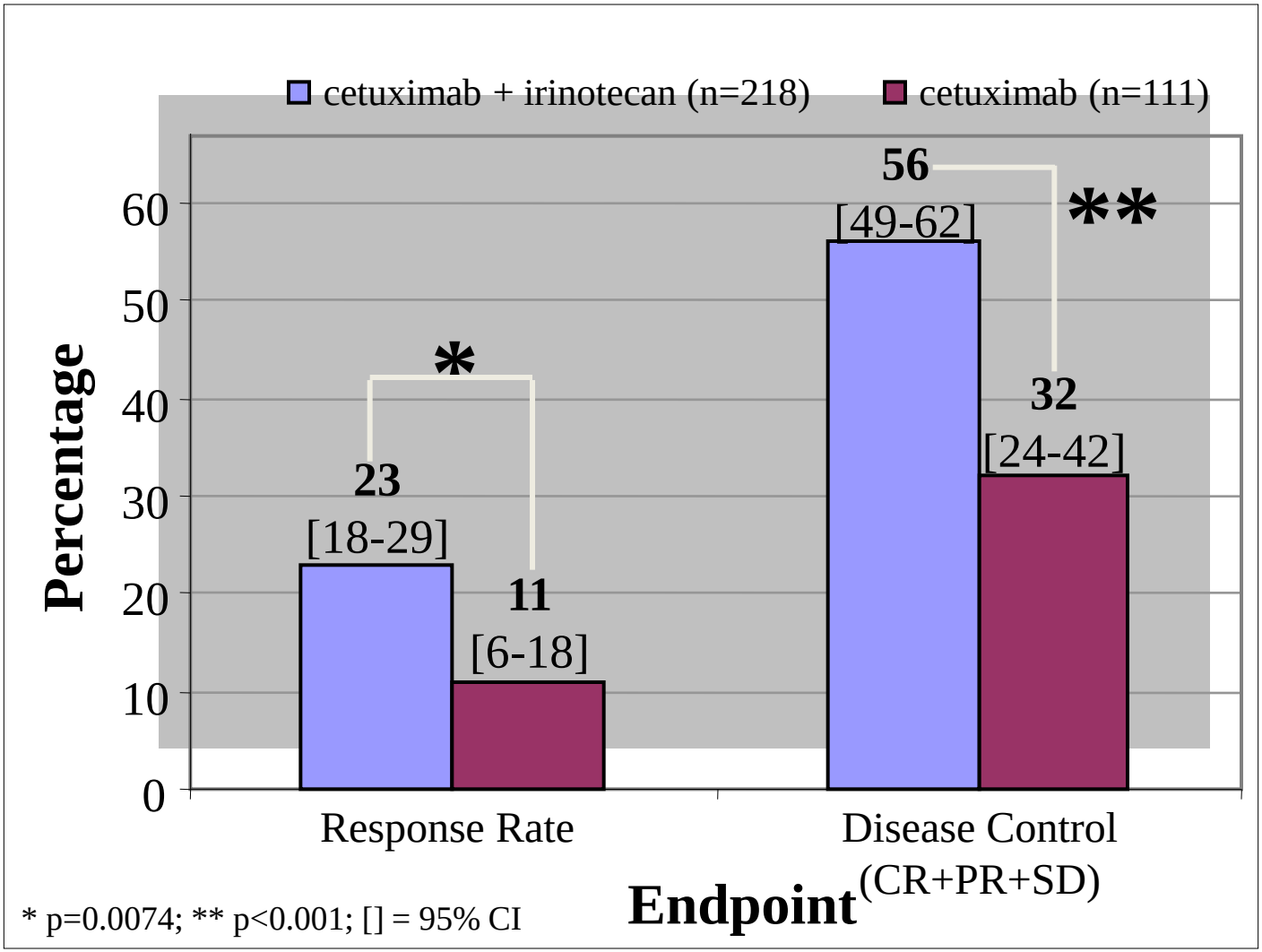


Iriotecan治療失敗的
MCRC

*** 577 patients screened 329 patients included in a 2:1 randomization**

BOND = Bowel Oncology with cetuximab Antibody

BOND study: Response Rate

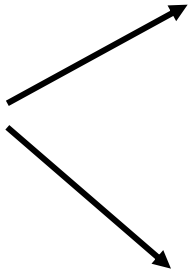


Cunningham D …Van Cutsem E. N Eng J Med 2004

The BOND-2 Study

Metastatic colorectal cancer patients refractory to irinotecan

(N = 81)



Bevacizumab/Cetuximab + Irinotecan*
Cetuximab 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly
Bevacizumab 5 mg/kg every other week
Irinotecan at same dose and schedule given just before study entry
(n = 41)

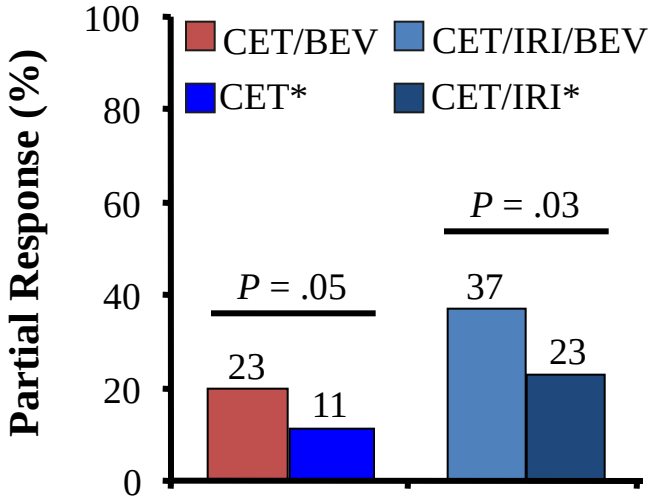
Bevacizumab/Cetuximab*
Cetuximab 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly
Bevacizumab 5 mg/kg every other week
(n = 40)

*Patients received cetuximab on Day 1 (plus irinotecan, if randomized to that arm) and bevacizumab on Day 2.

Saltz L, et al. ASCO 2005. Abstract 3508.

BOND-2 Efficacy Results

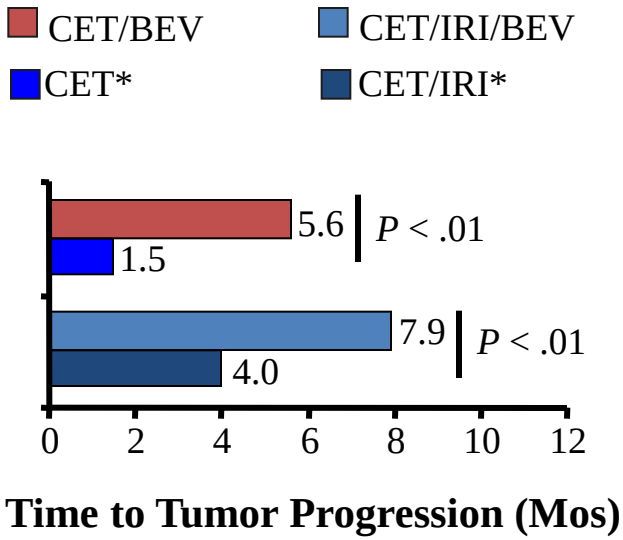
- Significant response for bevacizumab + cetuximab
  - Addition of irinotecan improved responses



*Historical controls.

Bevacizumab extends time to tumor progression vs historical controls

Median TTP



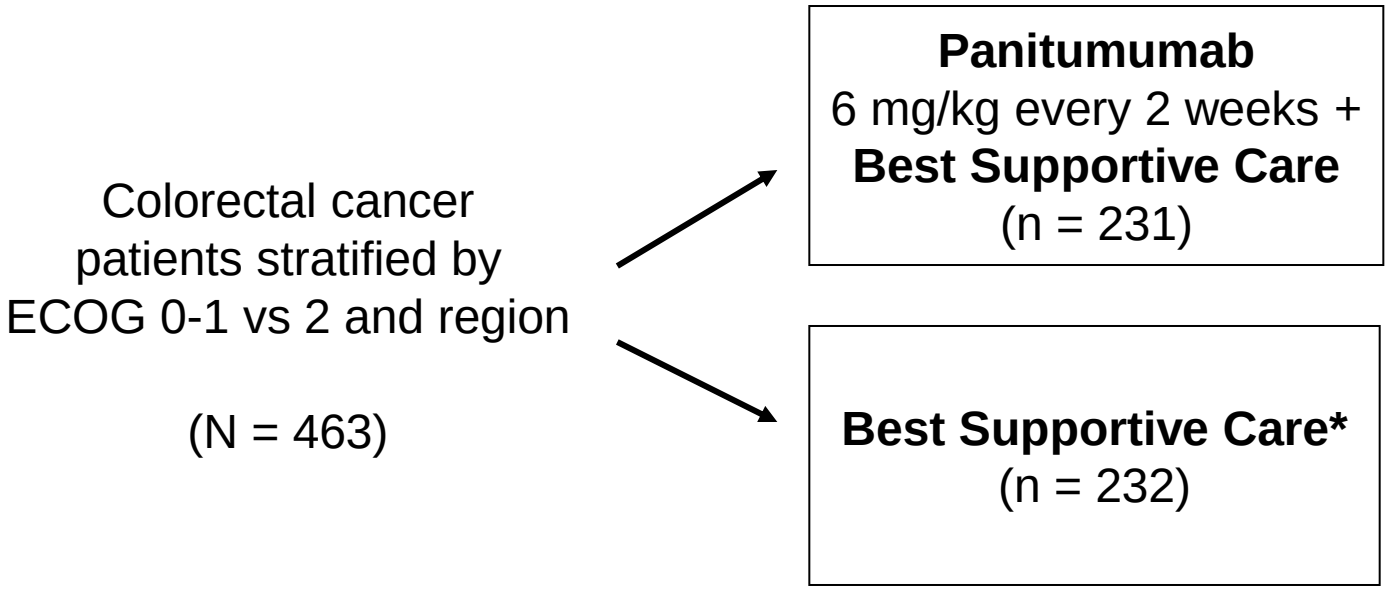
Saltz L, et al. ASCO 2005. Abstract 3508.

Metastatic CRC Survival > 20 months

Regimen	N	PFS	RR	OS	author
FOLFOX 6	**111**	**8.0**	**54**	**20.4**	Tournigand JCO2004
FOLFIRI	**109**	**8.5**	**56**	**21.5**	Tournigand JCO2004
AIO Irinotecan	**215**	**8.5**	**62**	**20.1**	Köhne ECCO 2003
IFL Bevacuzimab	**403**	**10.6**	**45**	**20.3**	Hurwitz NEJM 2004
FOLFOX4	**262**	**9.2**	**59**	**20.0**	OPTIMOX ASCO 2004
FOLFOX4	**152**	**10.1**	**47**	**20.5**	Goldberg ASCO 2004
FOLFOX7	**264**	**9.0**	**59**	**21.6**	OPTIMOX ASCO 2004

de Gramont 2005

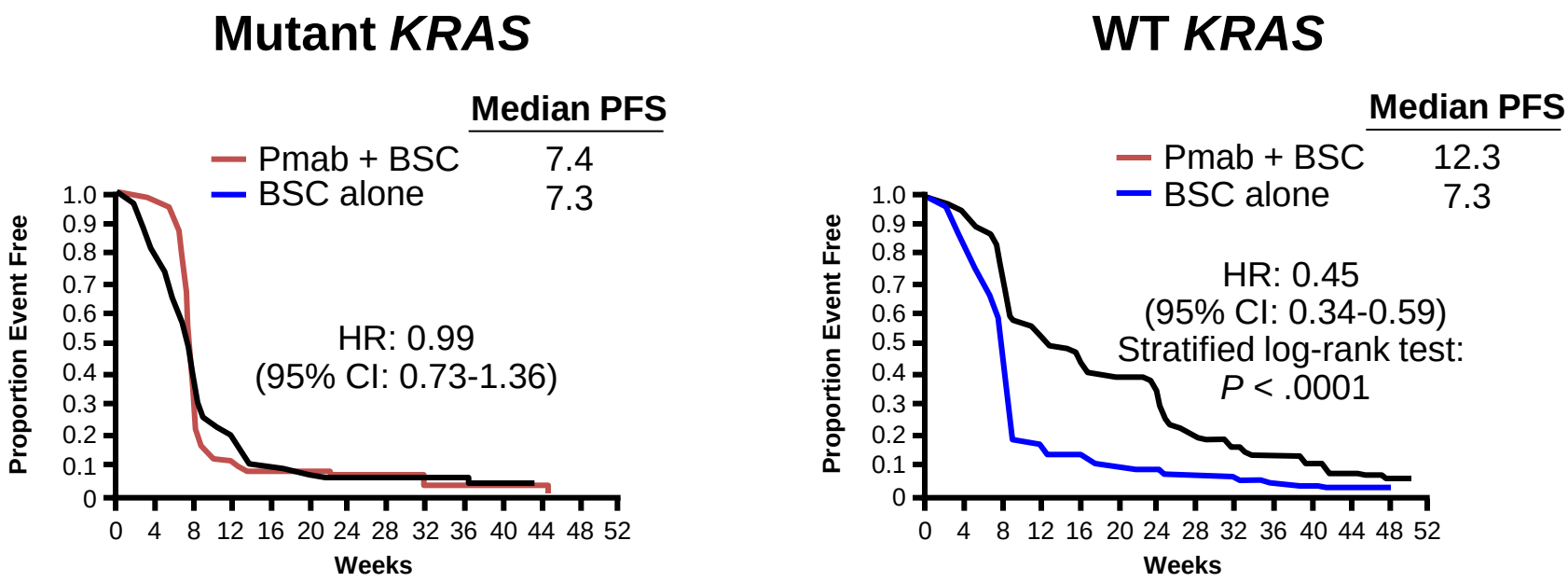
KRAS Status and Response to Panitumumab: Phase III Trial Analysis



*Optional crossover to panitumumab upon disease progression.

Amado RG, et al. GI Cancers Symposium 2008. Abstract 278.

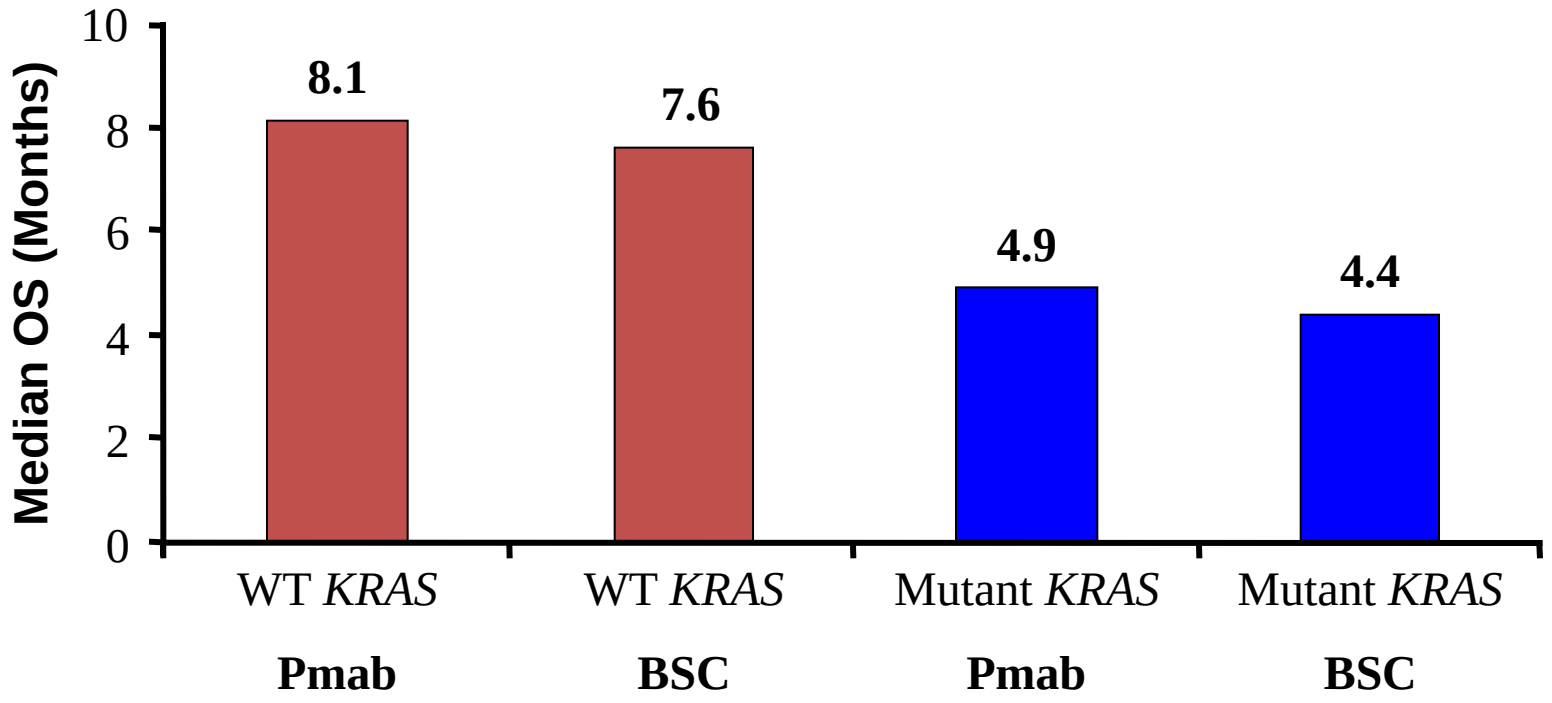
PFS by *KRAS* Status and Treatment



- The relative effect of panitumumab vs best supportive care was significantly greater in patients with WT vs mutant *KRAS*
- The quantitative-interaction test comparing the magnitude of the relative treatment effect on PFS between WT and mutant *KRAS* was statistically significant ($P < .0001$)
- PFS was significantly greater for panitumumab treatment compared with best supportive care in the WT KRAS group (stratified log-rank test: $P < .0001$).

Amado RG, et al. GI Cancers Symposium 2008. Abstract 278.

OS by *KRAS* Status and Treatment



Amado RG, et al. GI Cancers Symposium 2008. Abstract 278.

輔助性化學治療

Colorectal Cancer
Adjuvant Chemotherapy

大腸直腸癌輔助性化學治療的演進

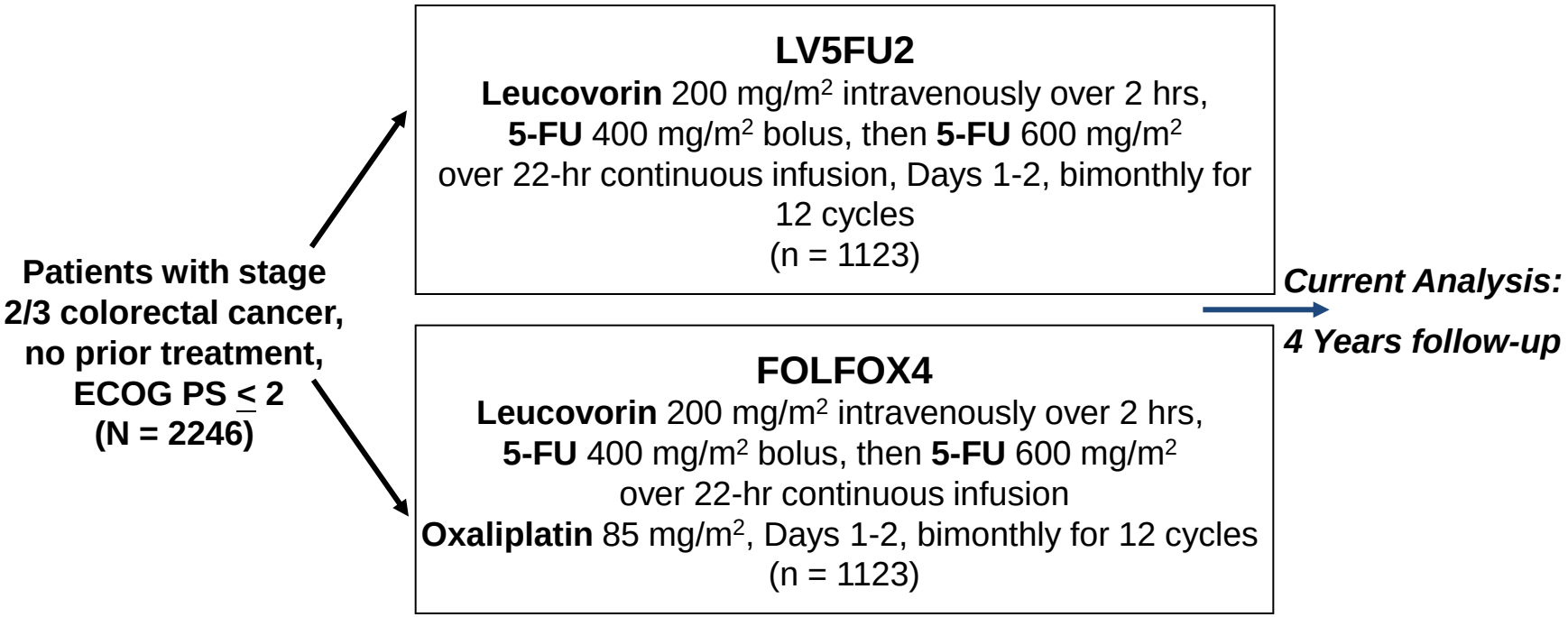
1990 FU/levamosole better than nothing
1994 FU/LV better than nothing
1998 FU/LV better than FU/levamisole
1998 6 months=12 months(IV form)
1998 HD LV = LD LV
1998 Weekly = monthly schedules
2001 Elderly benefit from Chemotherapy
2003 FOLFOX > 5FU/LV
2004 NSABP C06 Result (Oral Form=IV)
2004 FOLFOX approval FDA or EU

輔助性化學治療的新藥研究

- Intravenous chemotherapy- New combination
  - Oxaliplatin contained
    - MOSAIC trial
    - NSABP C07 trial
  - Irinotecan contained
    - CALGB 89803 (NCIC CO.15) trial
    - ACCORD-2 trial
    - PETACC- 3 trial

Oxaliplatin Plus LV5FU2 for Stage 2/3 Colon Cancer

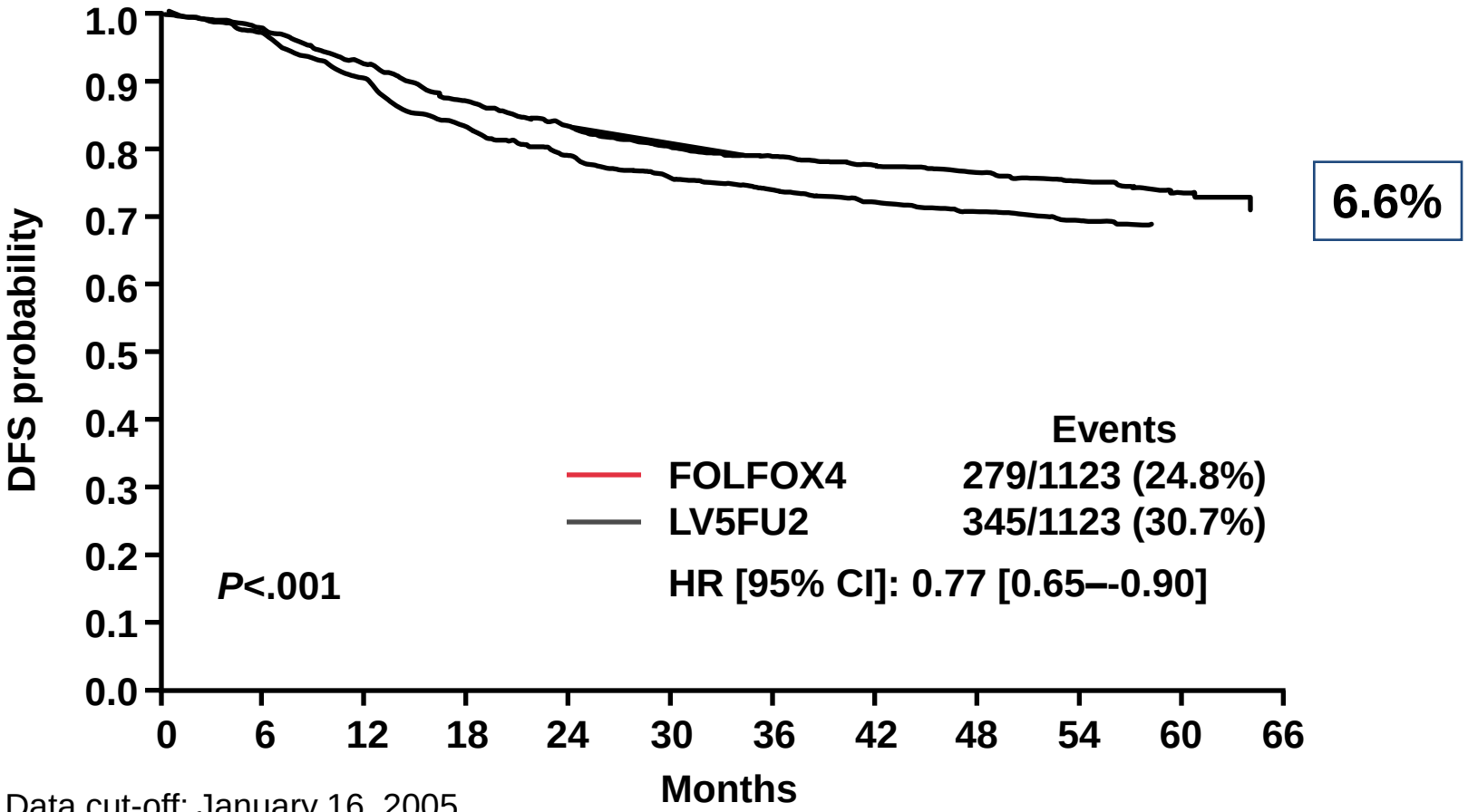
- MOSAIC: Multicenter, international trial



ECOG, Eastern Cooperative Oncology Group; 5-FU, fluorouracil, PS performance scale

de Gramont et al. ASCO 2005. Abstract 3501.

MOSAIC trial
Disease-free survival



Data cut-off: January 16, 2005

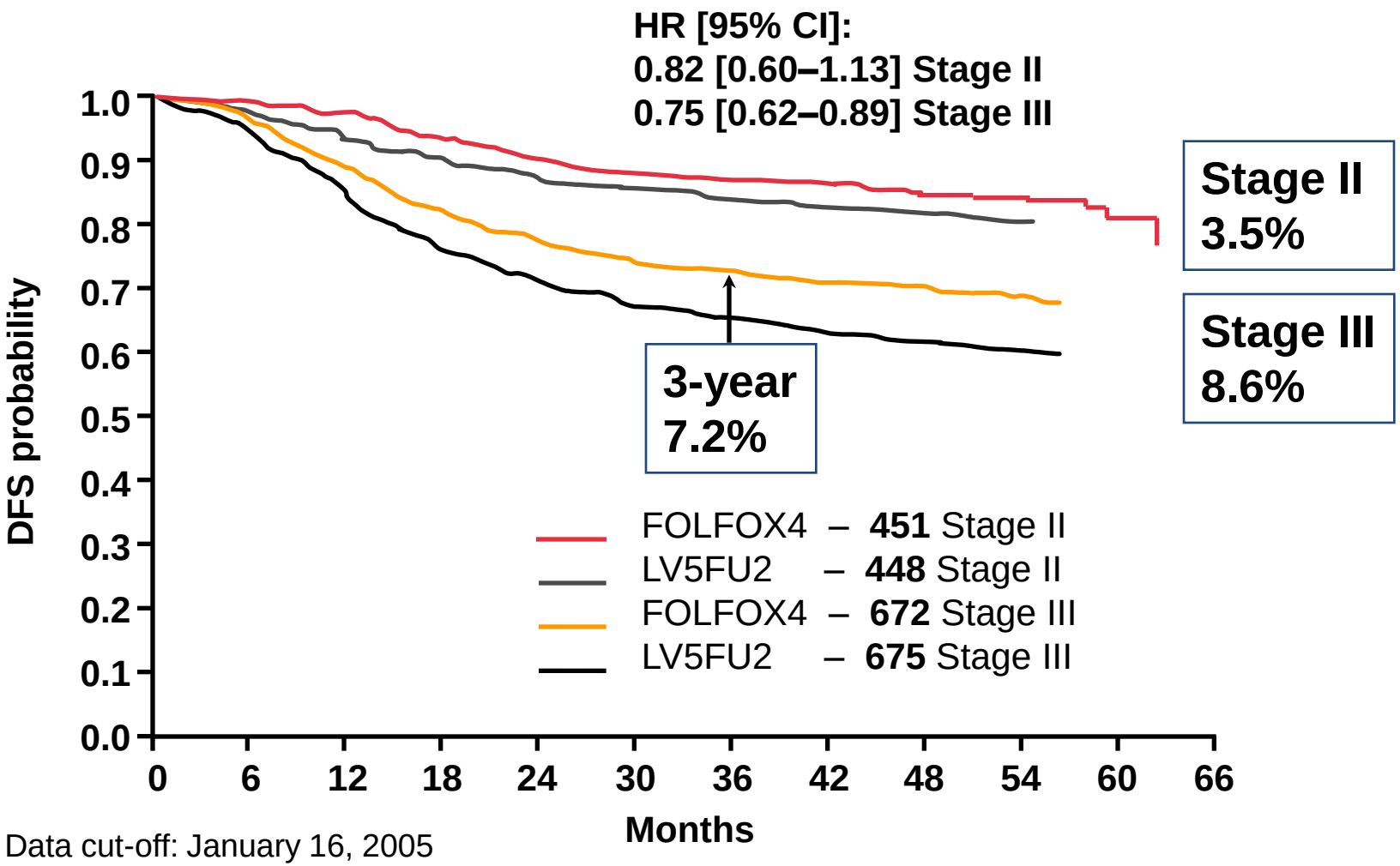
De Gramont A et al, ASCO 2005, Abstract 3501.

MOSAIC trial
Disease-free survival

Update	Median follow-up (months)	FOLFOX4 DFS	LV5FU2 DFS	Difference
April 2003[1]	37.9	78.2%	72.9%	5.3%
June 2004[2]	48.6	75.9%	69.1%	6.8%
Jan 2005	**56.2**	**76.4%**	**69.8%**	6.6%

1. Andre et al. *N Eng J Med* 2004;**350**: 2343–2351. 2. De Gramont A et al, ASCO 2005, Abstract 3501.

Disease-free survival *(ITT)* – *stage II and stage III patients*

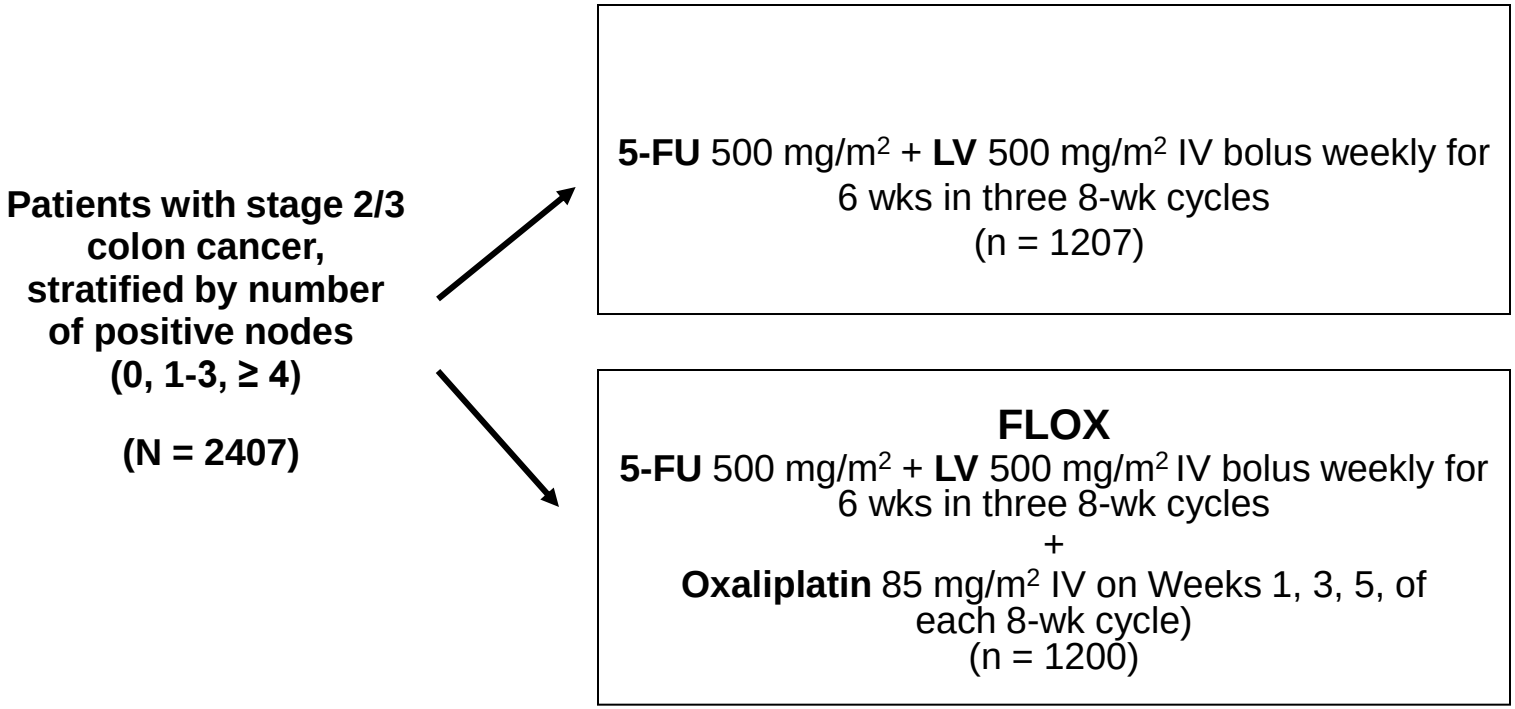


Data cut-off: January 16, 2005

De Gramont A et al, ASCO 2005, Abstract 3501.

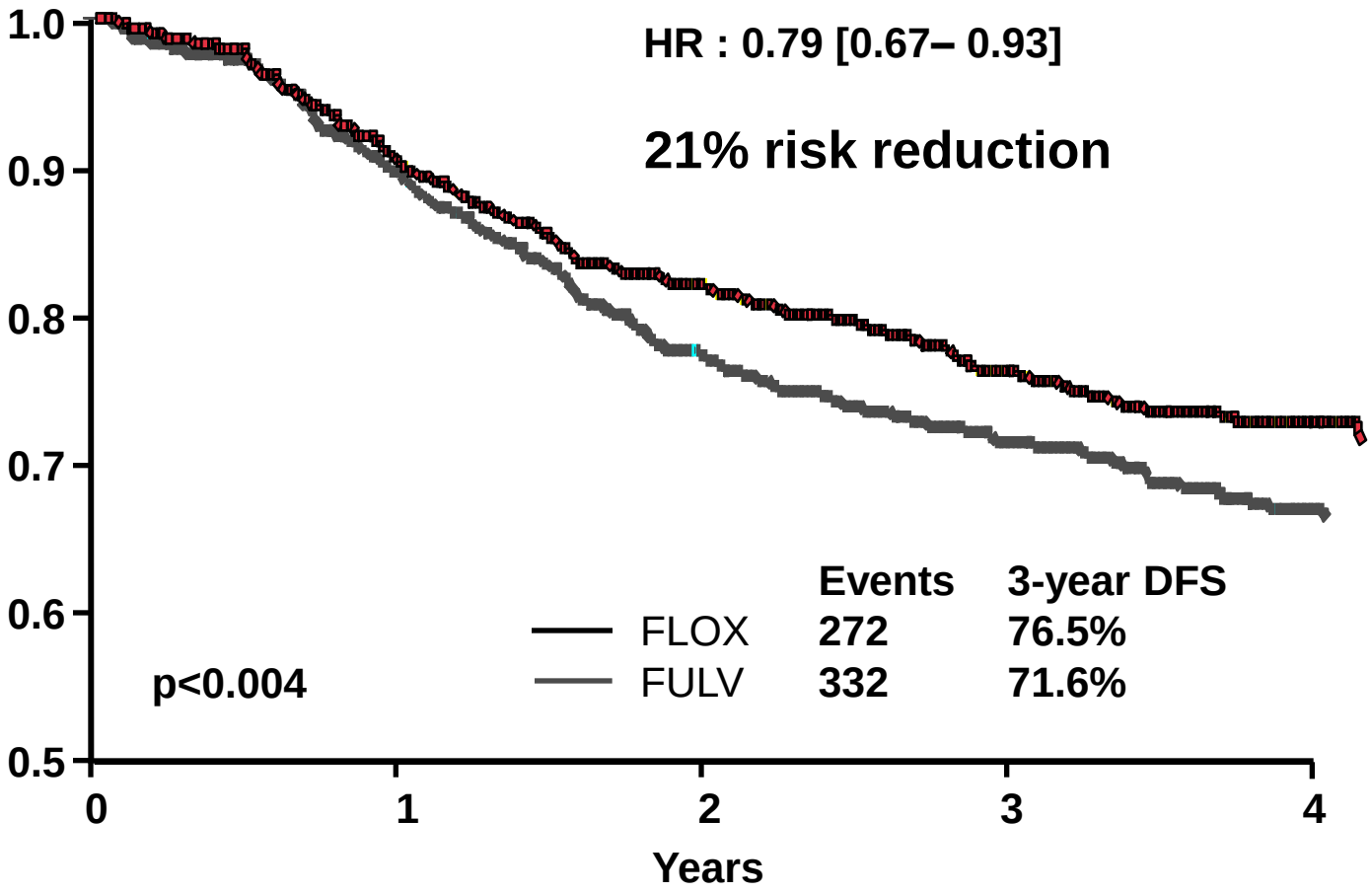
Oxaliplatin Plus FULV for Stage 2/3 Colon Cancer

- NSABP C07: Phase 3 randomized trial



Wolmark et al. ASCO 2005. Abstract LBA3500.

NSABP C-07 (FLOX vs FULV)
3-year disease-free survival



Wolmark N et al, ASCO 2005, Abstract LBA3500.

臨床療效的比較 Efficacy Endpoints

	Arm A		Arm B		
	FOLFIRI n = 109	FOLFOX n = 81	FOLFOX n = 111	FOLFIRI n = 69	*p value*
緩解率 ORR (CR) %	**56 (3)**	15	**54 (5)**	4	***0.68***
ORR + SD %	79	63	81	35	
Median overall TTP mos	14.4		11.5		***0.65***
平均存活期(月)	**20.4**		**21.5**		***0.9***
Absence of progression at 15 months	49		40		

Many options, many questions…