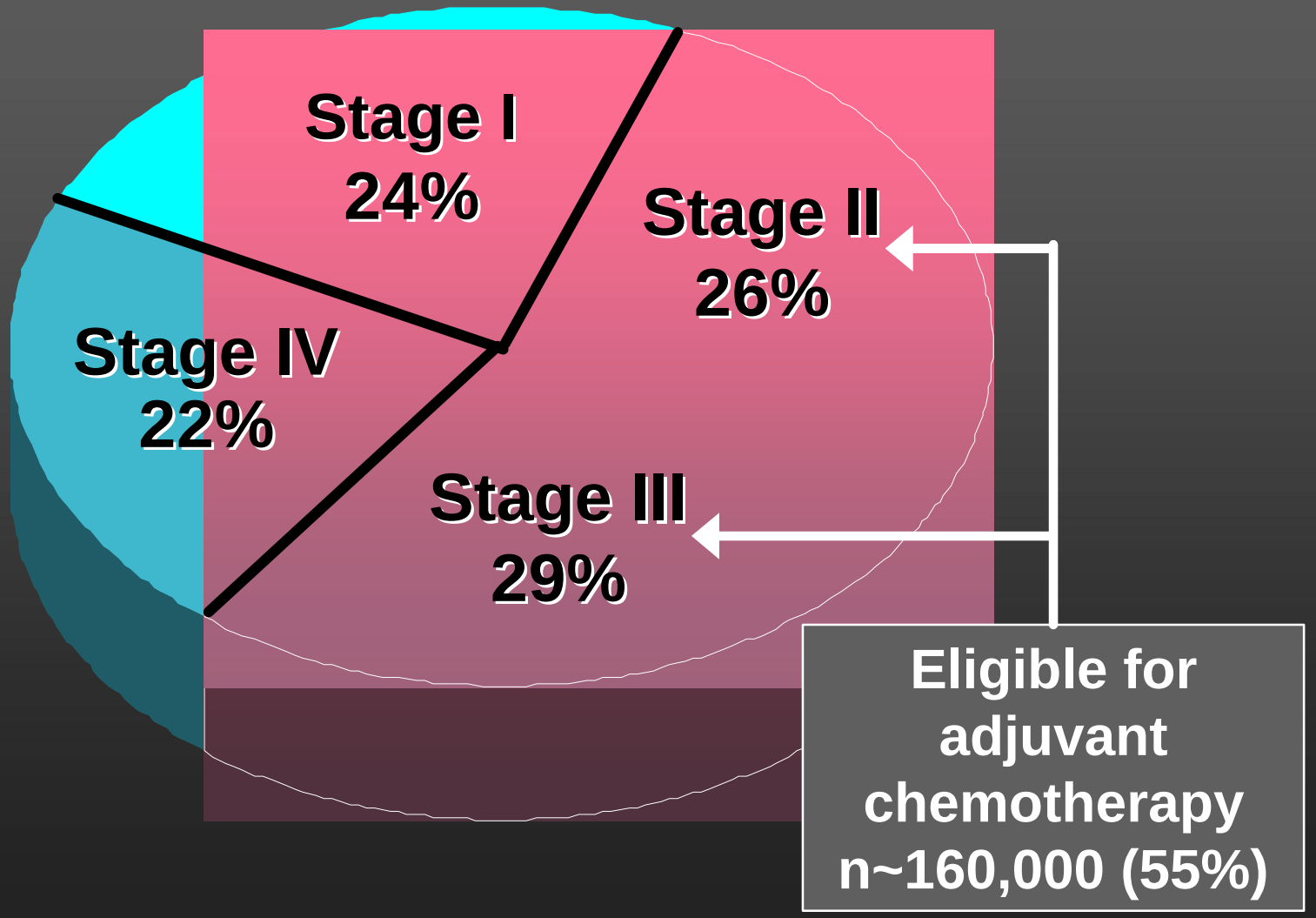
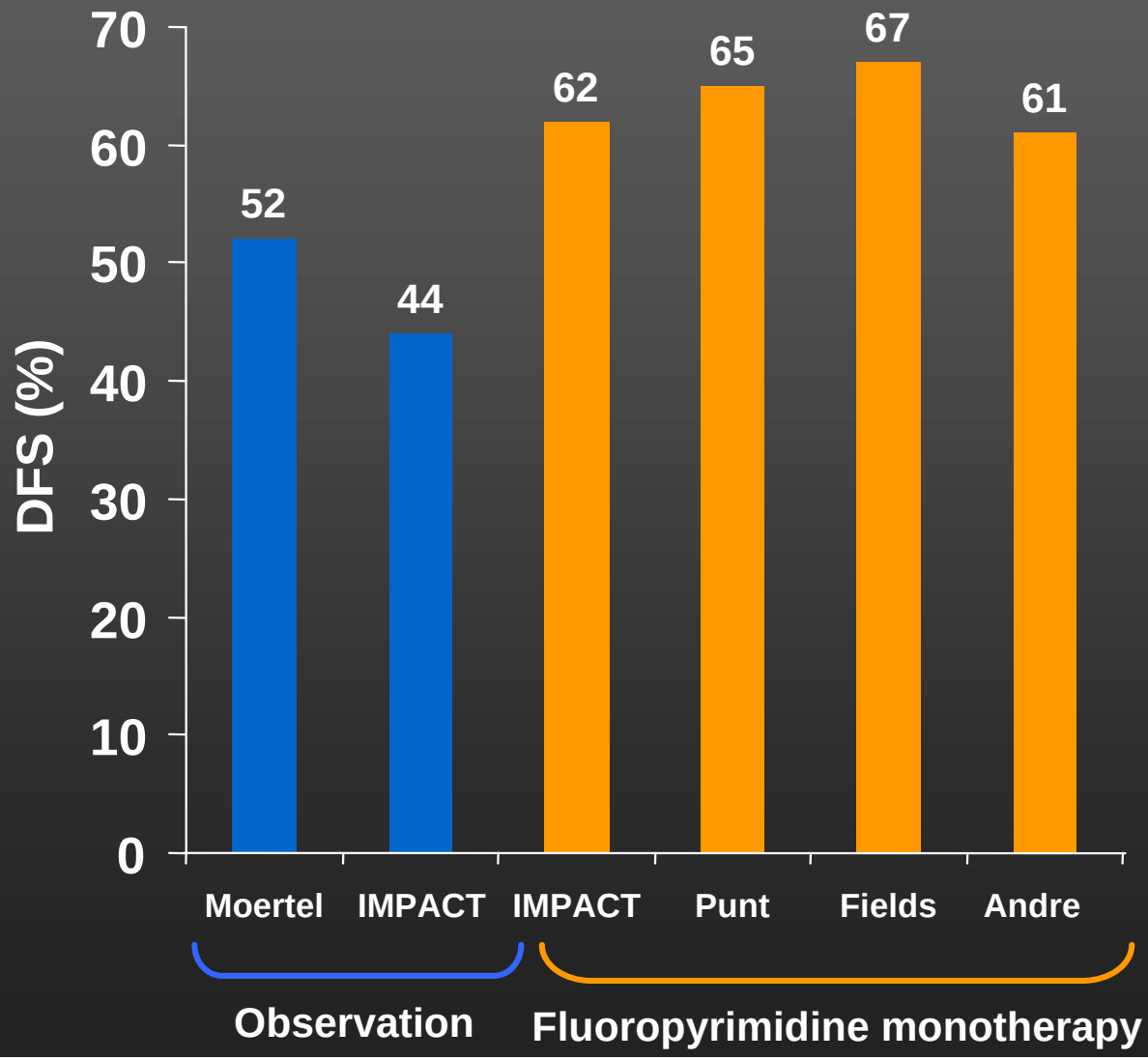
Systemic adjuvant chemotherapy in colon cancer

Prof.Dr.Hans-Joachim Schmoll
Director, Department of
Haematology and Oncology
Martin Luther University
Halle, Germany

Incidence of colorectal cancer in the U.S. and Western Europe 2006 (n~300,000)



3-year DFS in stage III CRC
5FU +/- FA



X-ACT trial in adjuvant treatment of stage III colon cancer

Recruitment 1998–2001

Capecitabine
1250mg/m² twice daily, d1–14, q21d
n=1004

Chemo-naïve stage III, resection £8 weeks

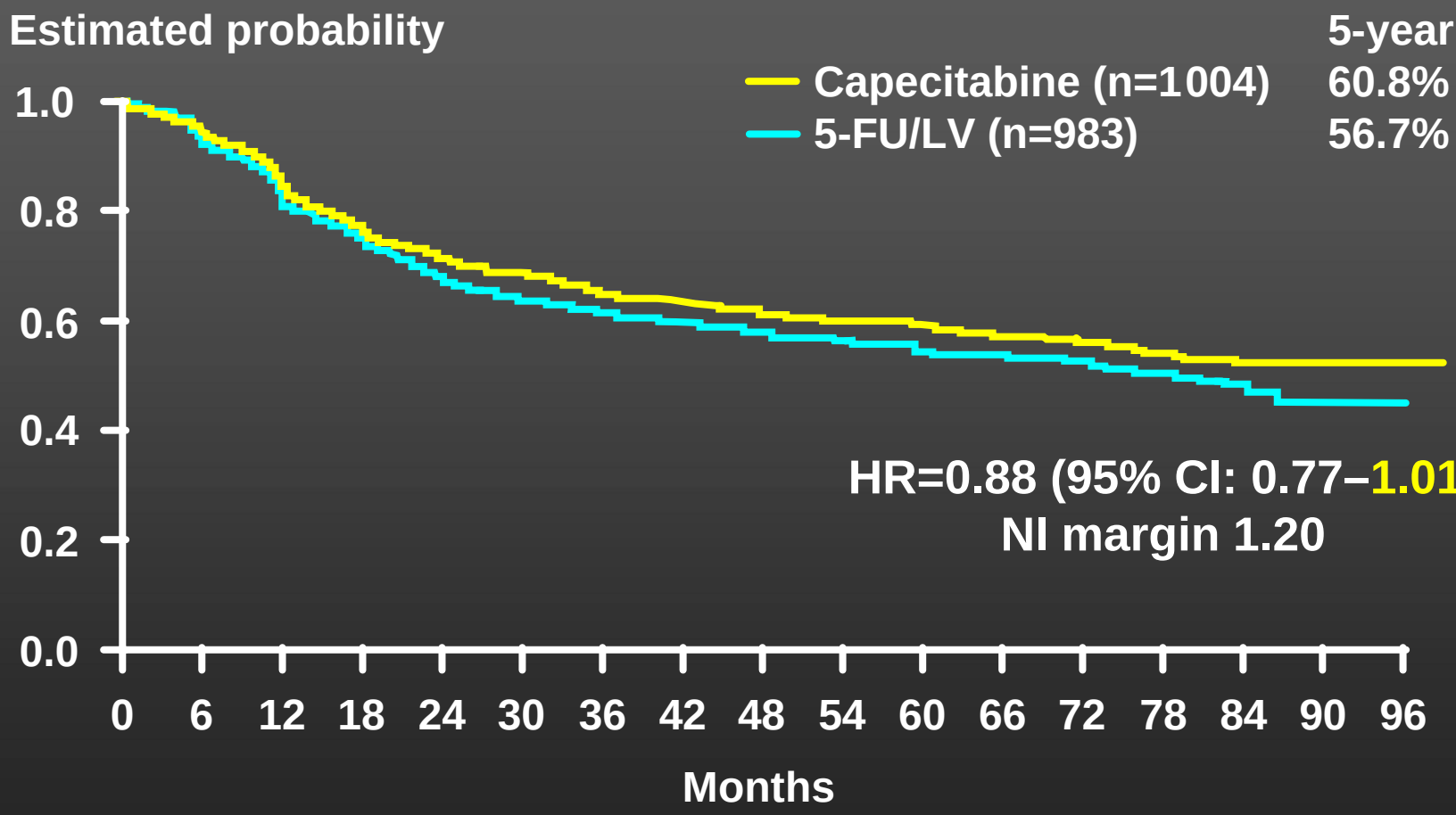
24 weeks

Bolus 5-FU/LV
5-FU 425mg/m² plus LV 20mg/m², d1–5, q28d
n=983

- 1° endpoint: disease-free survival (DFS)
- 2° endpoints
  - overall survival (OS)
  - relapse-free survival (RFS)
  - tolerability (NCIC CTG)
  - pharmacoeconomics
  - QoL

Twelves et al., ECCO 2007

Disease-free survival:
5-year update – median follow-up 6.8 years

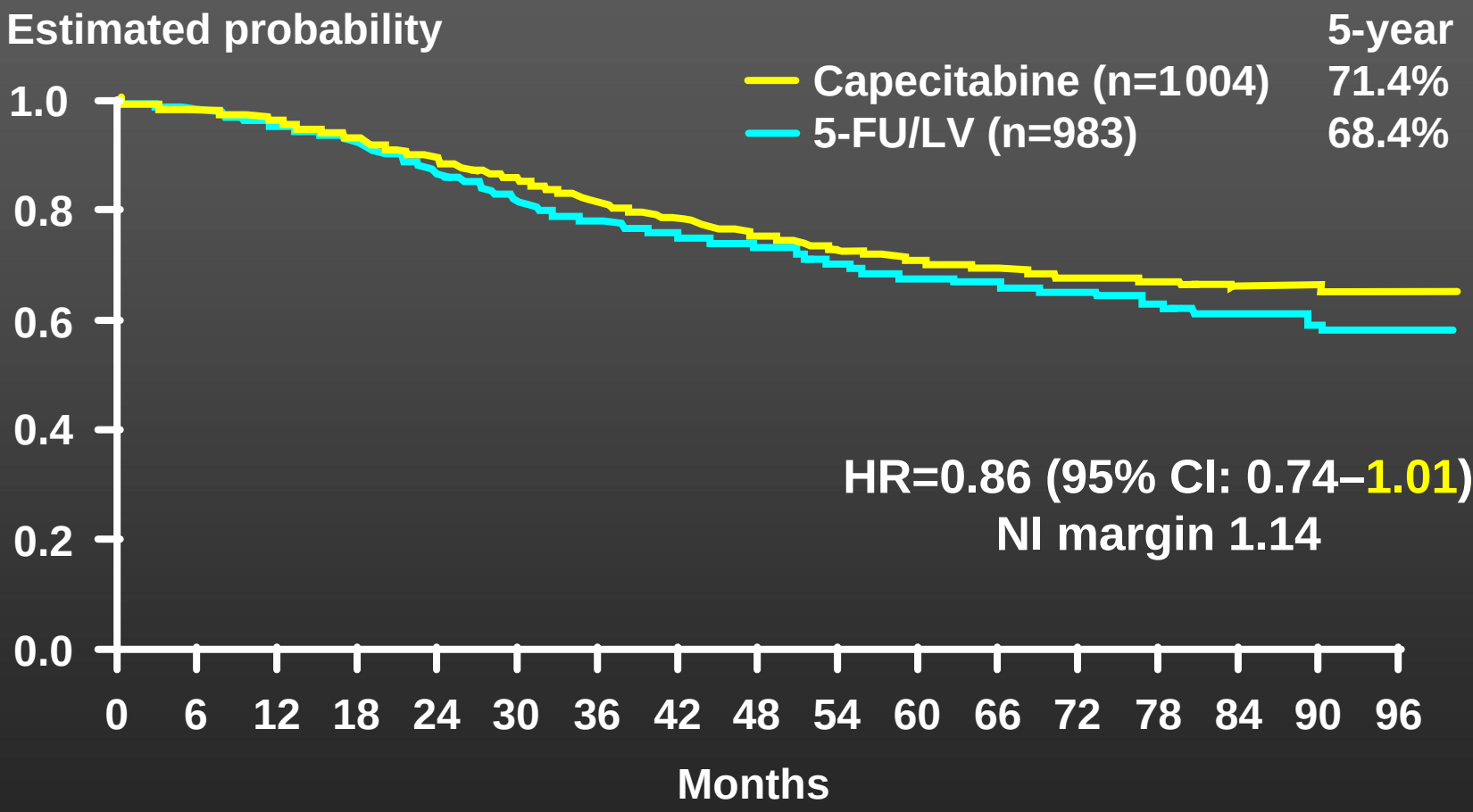


Test of non-inferiority p<0.0001
Test of superiority p=0.0682

ITT population

Twelves et al., ECCO 2007

Overall survival:
5-year update – median follow-up 6.8 years

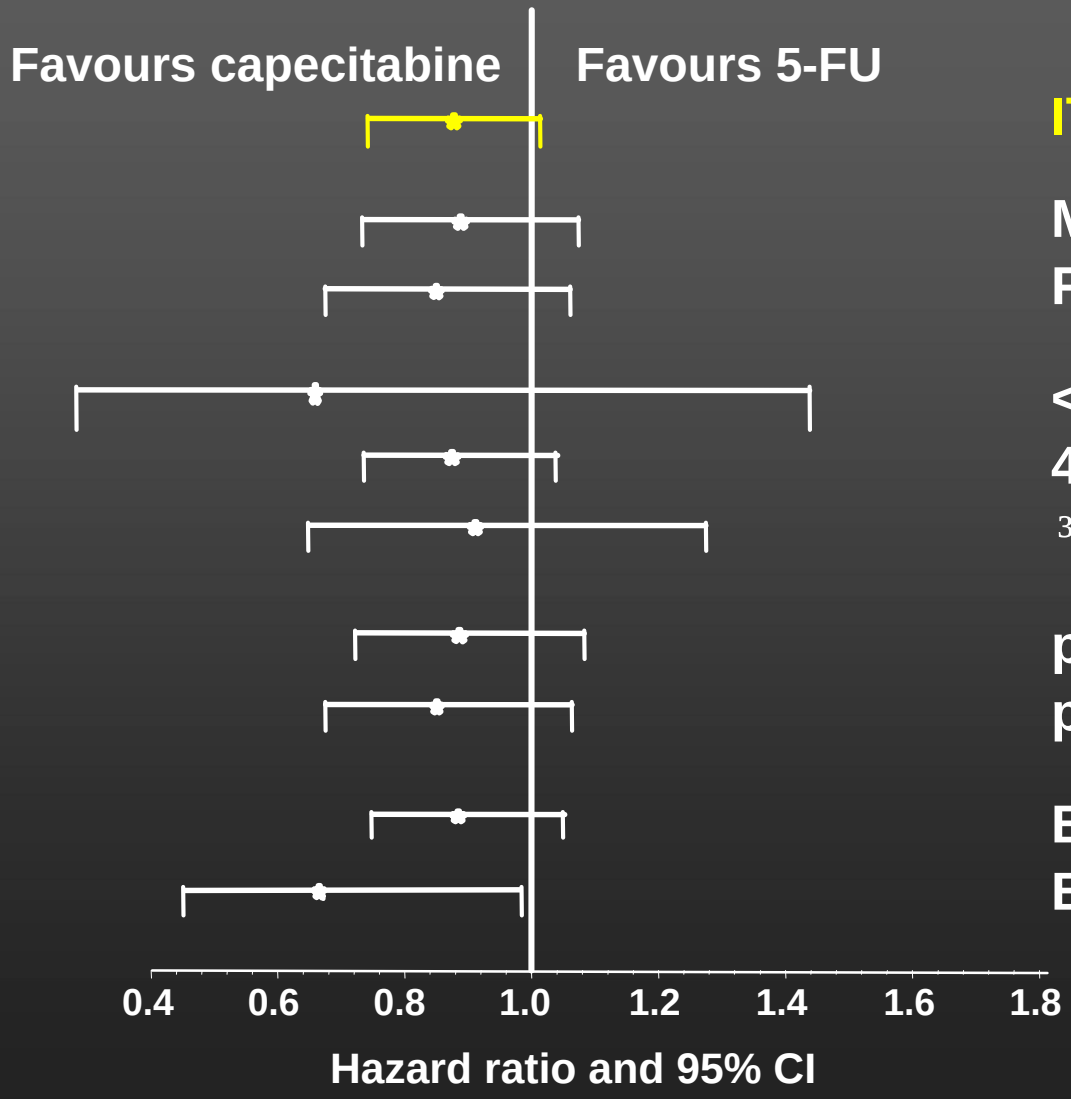


Test of non-inferiority p=0.000116
Test of superiority p=0.06

ITT population

Twelves et al., ECCO 2007

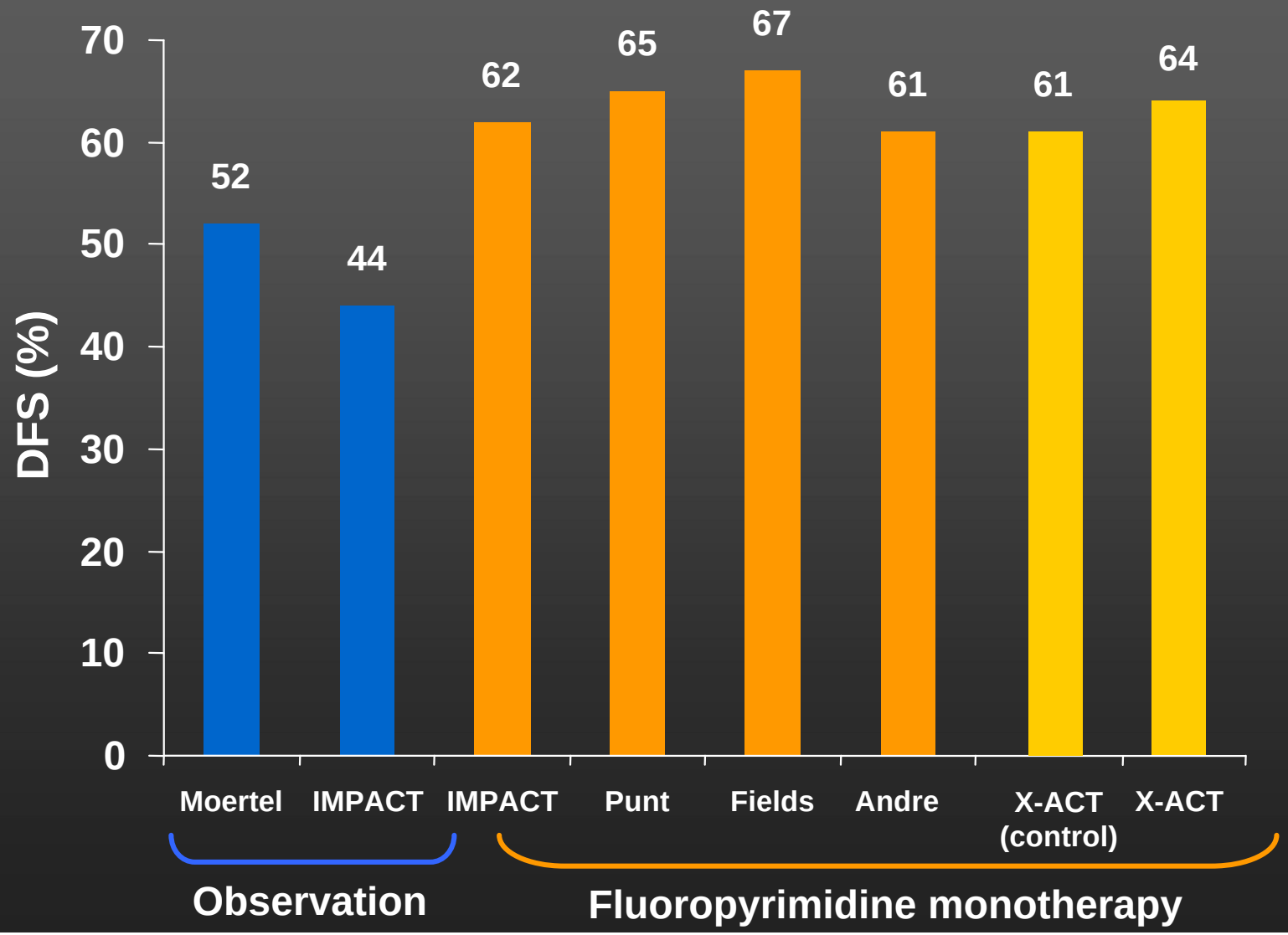
5-year overall survival subgroup analysis



		n
ITT population		**1987**
Male		1074
Female		912
<40		76
40–69	years old	1513
³70		396
pN1		1389
pN2		593
Baseline CEA <ULN		1672
Baseline CEA >ULN		155

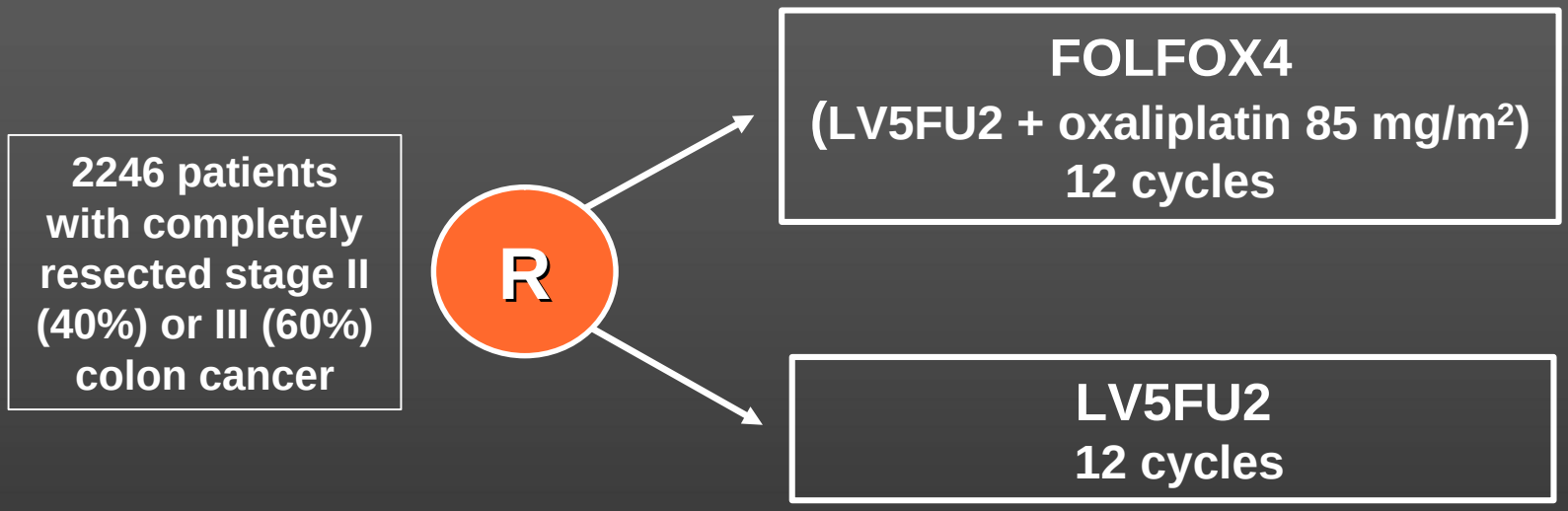
Twelves et al., ECCO 2007

3-year DFS in stage III CRC



MOSAIC and NSABP C04

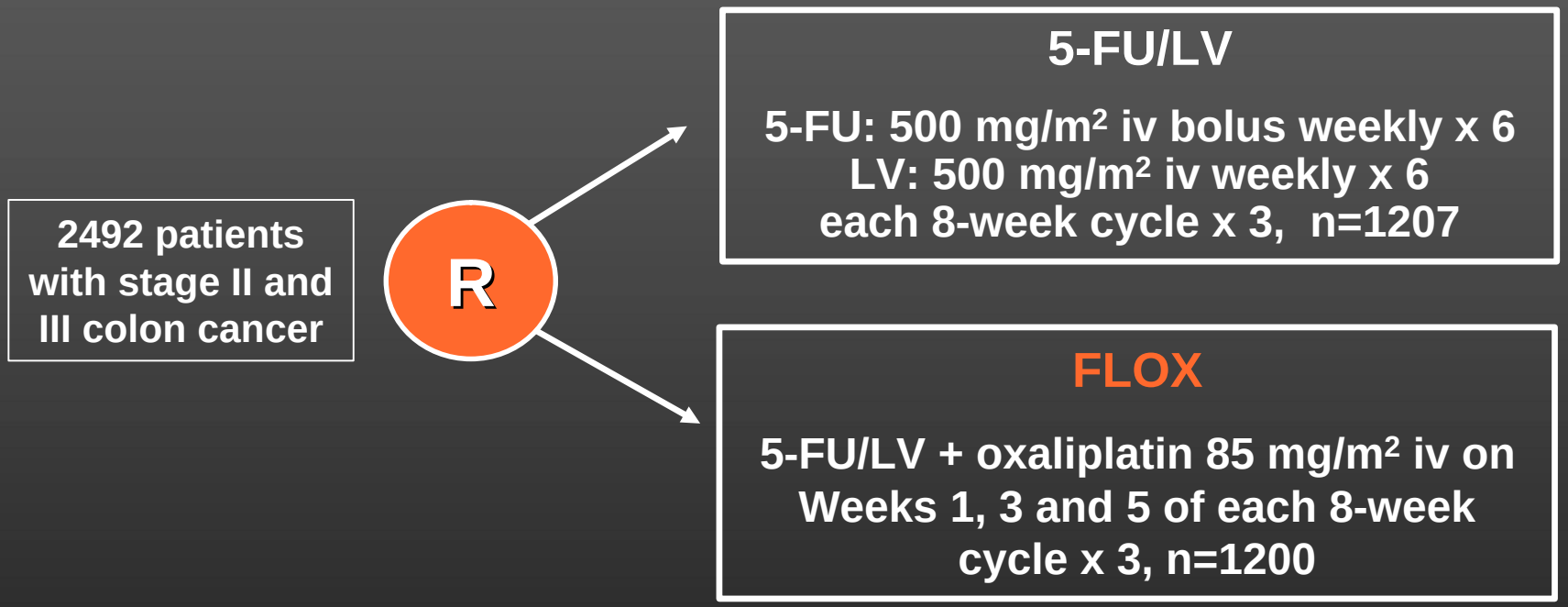
Oxaliplatin combinations: MOSAIC



- Primary endpoint: DFS
- Secondary endpoints: safety, OS

André T et al. N Engl J Med 2004;350:2343–2351.

Oxaliplatin combinations: NSABP C-07



- **Primary endpoint: 3-year DFS**

Wolmark N, et al. ASCO 2005 (Abstract LBA3500).

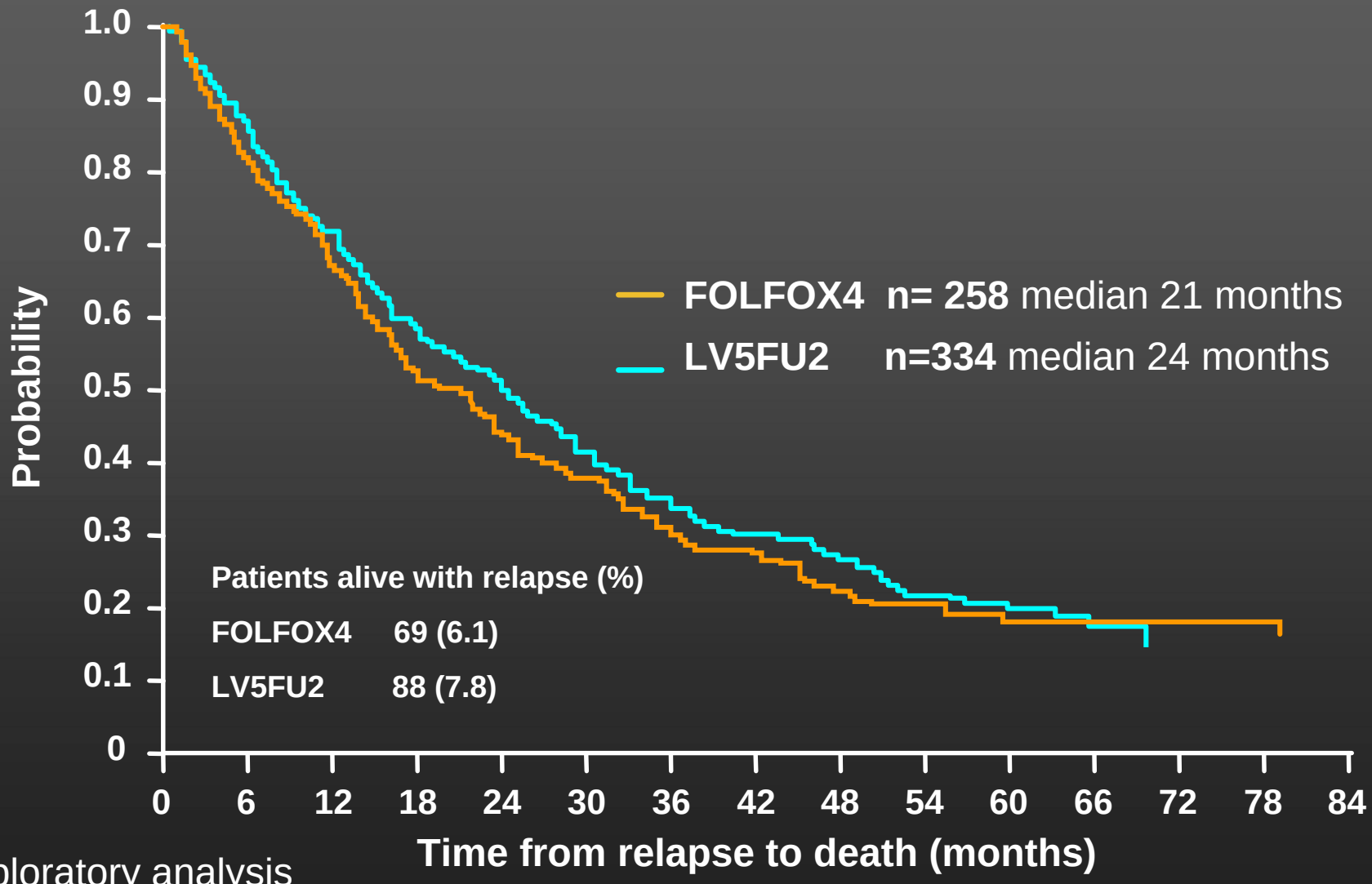
3-year DFS (stage II and III)

	3-year DFS	?	HR
C-07	76.5%	4.9%	0.79
MOSAIC	78.2%	5.3%	0.77

Mosaic: Disease-free Survival - 2007 Update

Data cut-off: June 2006	5-year DFS %			
	FOLFOX4	LV5FU2	HR [95% CI]	p-value
ITT (overall population)	73.3	67.4	0.80 [0.68–0.93]	0.003
Stage III	66.4	58.9	0.78 [0.65–0.93]	0.005
Stage II	83.7	79.9	0.84 [0.62–1.14]	0.258
High-risk stage II n=576	82.1	74.9	0.74 [0.52–1.06]	—
Low-risk stage II n=323	86.3	89.1	1.22 [0.66–2.26]	—

Time from Relapse to Death



Exploratory analysis

Treatment for Recurrence

	FOLFOX4	LV5FU2
Number of patients with relapse	258	334
Any chemotherapy (%)	73.3	76.9
Oxaliplatin-based regimen* (%)	28.5	29.0
Irinotecan-based regimen* (%)	45.0	32.6
Other, including biologics (%)	14.3	13.5

* first-line

Exploratory analysis

Data cut-off: June 2006

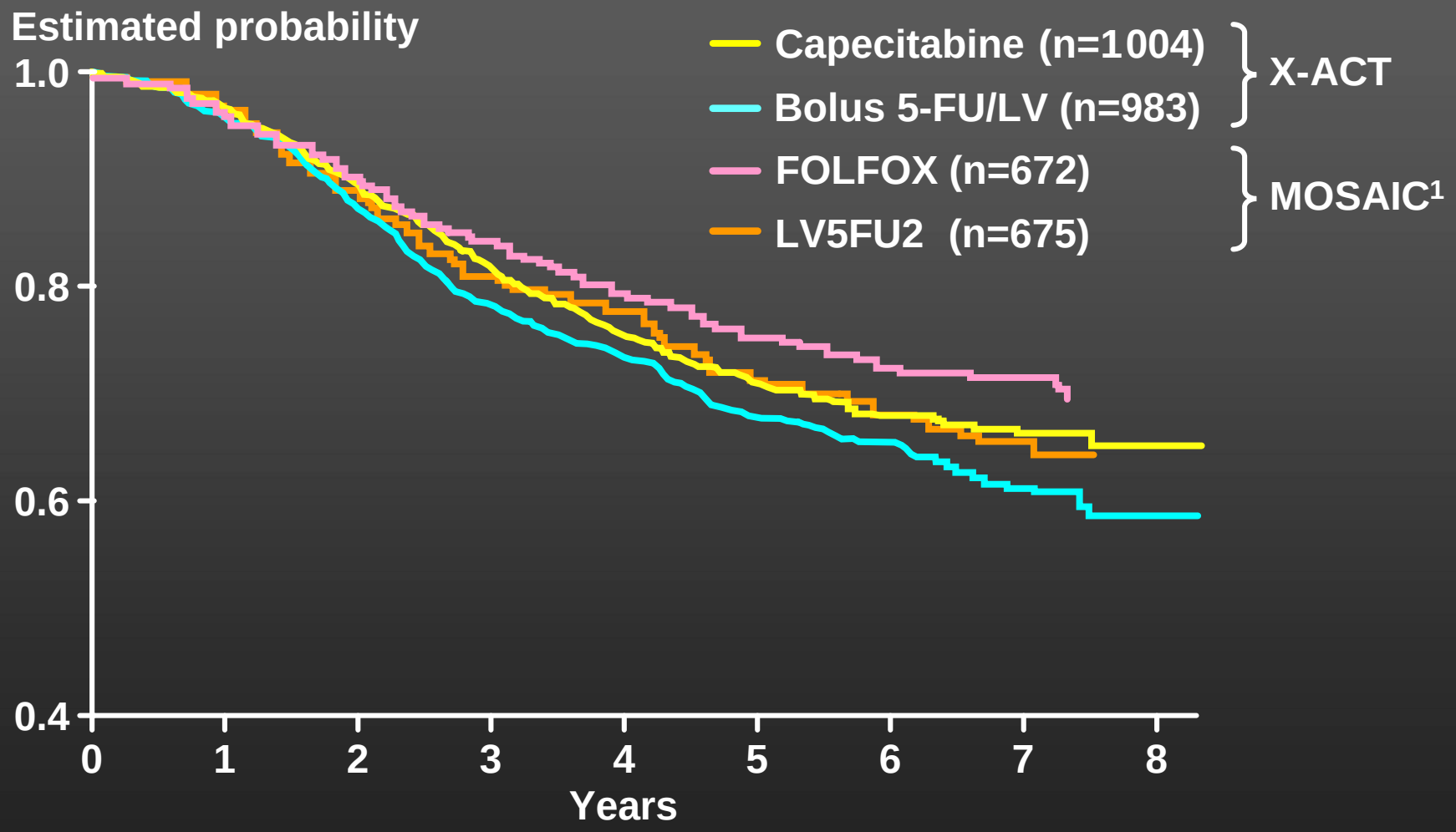
Deaths other than Colon Cancer

	FOLFOX4	LV5FU2
Total number	48	30
Other cancers	21 (44%)	11 (37%)
GI cancers	4	2
Urologic cancers	5	0
Lung cancers	4	2
Breast-Gynecologic	3	2
Hematological	2	2
Other cancers	3	3
Cardio-vascular	18 (37%)	11 (37%)
Pneumopathy	3	2
Other	2	3
Unknown	4	3

Exploratory analysis

De Gramont et al, , ASCO 2007

X-ACT and MOSAIC: overall survival in stage III patients



ITT population

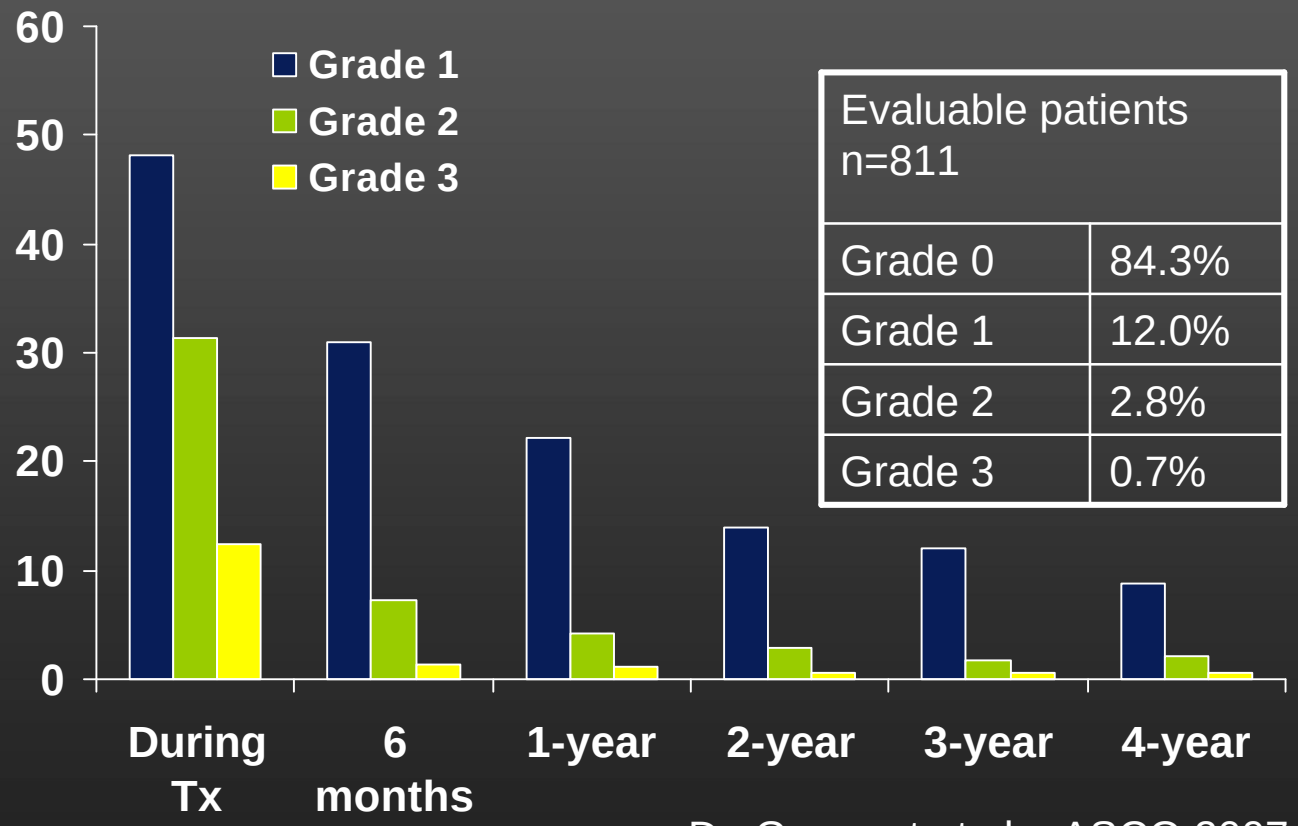
De Gramont et al., ASCO 2007; Twelves et al., ECCO 2007

MOSAIC: Long-term Safety

Second cancer

	FOLFOX	LV5FU2
(% patients)	5.3	5.7

Peripheral Sensory Neuropathy



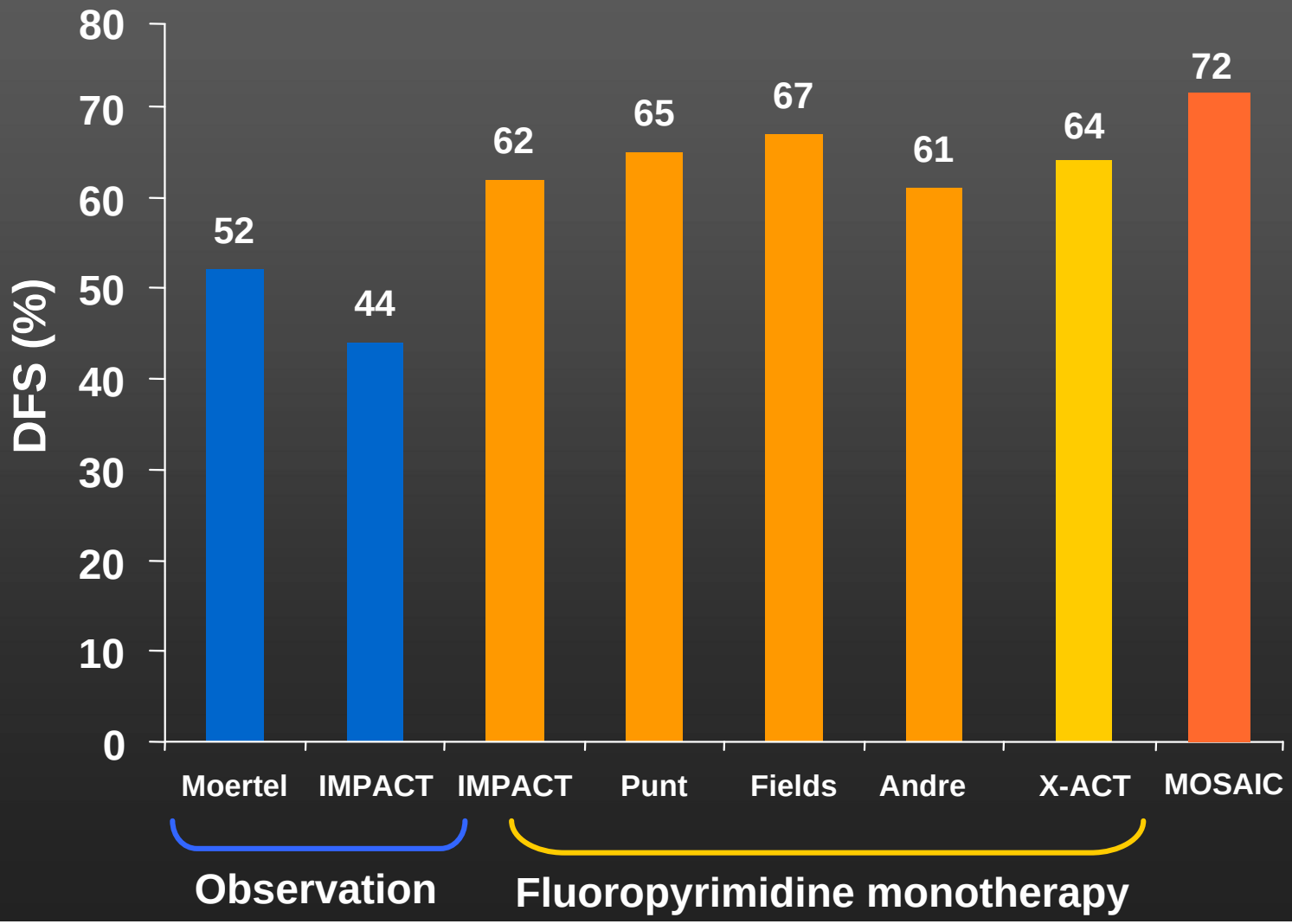
Evaluable patients n=811	
Grade 0	84.3%
Grade 1	12.0%
Grade 2	2.8%
Grade 3	0.7%

De Gramont et al, , ASCO 2007

DFS in Phase III studies of adjuvant combination chemotherapy

	Bolus 5-FU	Infusional 5-FU
Oxaliplatin	NSABP C-07 +	MOSAIC +
Irinotecan	CALGB C89803 -	PETACC-3 - ACCORD-02 -

3-year DFS in stage III CRC



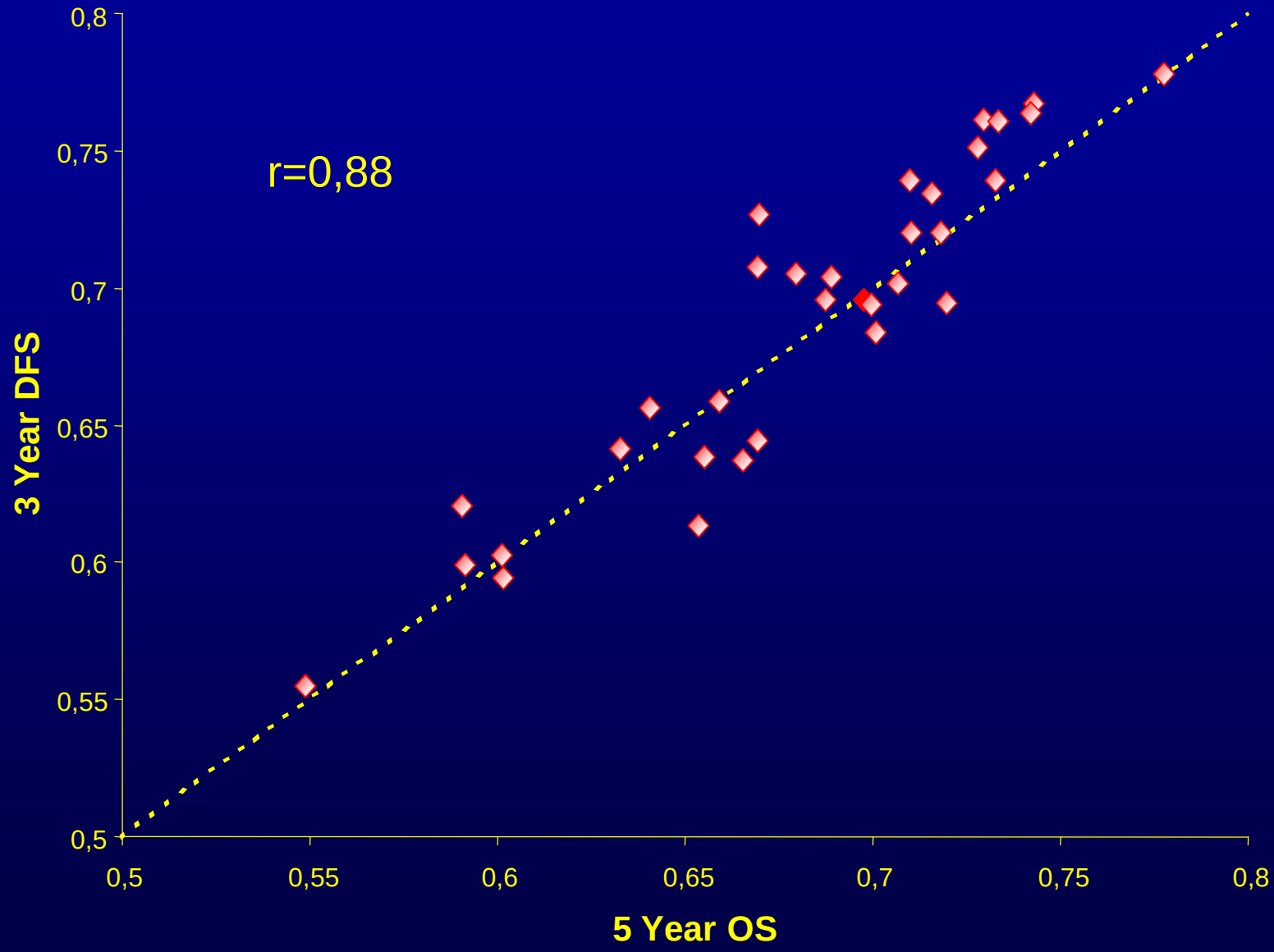
…is DFS improvement „good enough“ to define the standard?

ACCENT-Group - Trials Included

No Treatment Control		Active Control	
Trial	N	Trial	N
N784852	247	NSABP C03	1081
INT 0035	926	NSABP C04	2151
N874651	408	NSABP C05	2176
Siena	239	N894651	915
NCIC	359	N914653	878
FFCD	259	SWOG 9415	1078
NSABP C01	773	INT 0089	3547
NSABP C02	718	GERCOR	905
GIVIO	867	**QUASAR**	**3517**

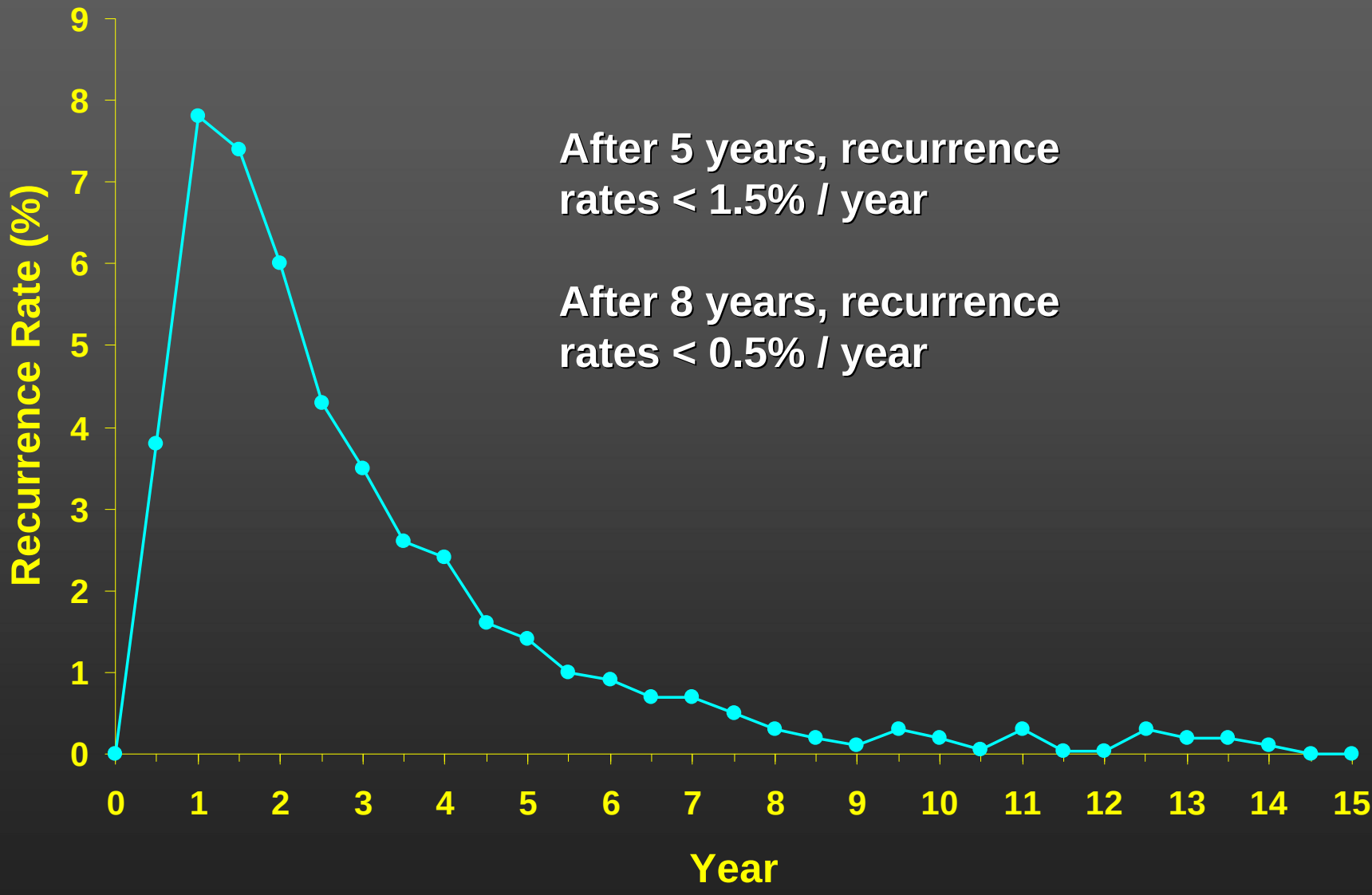
Total: 17 trials; 17,381 pts

3 Year DFS vs 5 Year OS



Sargent, et al. J Clin Oncol 2005;23:8664–8670

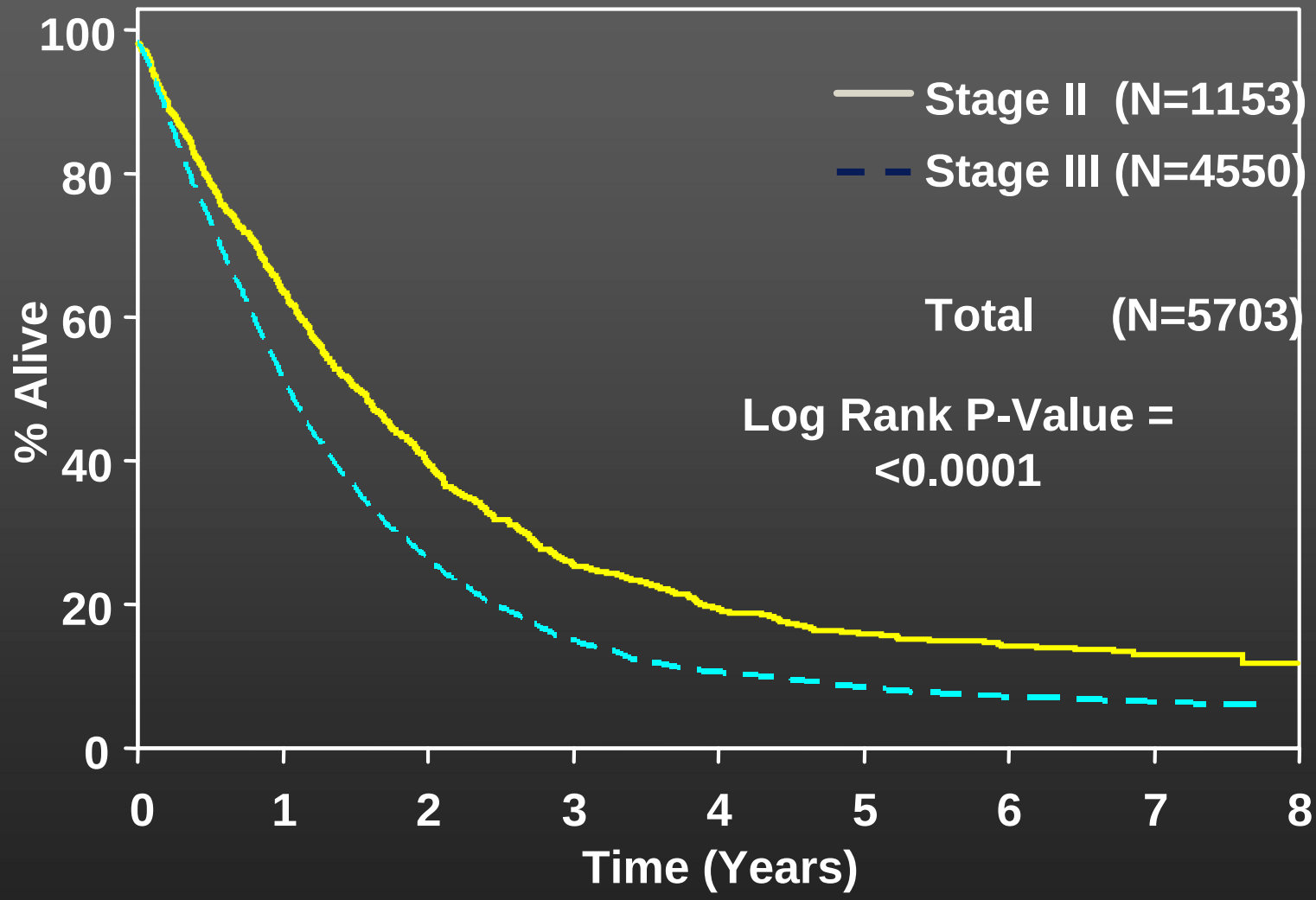
Recurrence Rate by time from randomization (all pts)



After 5 years, recurrence rates < 1.5% / year

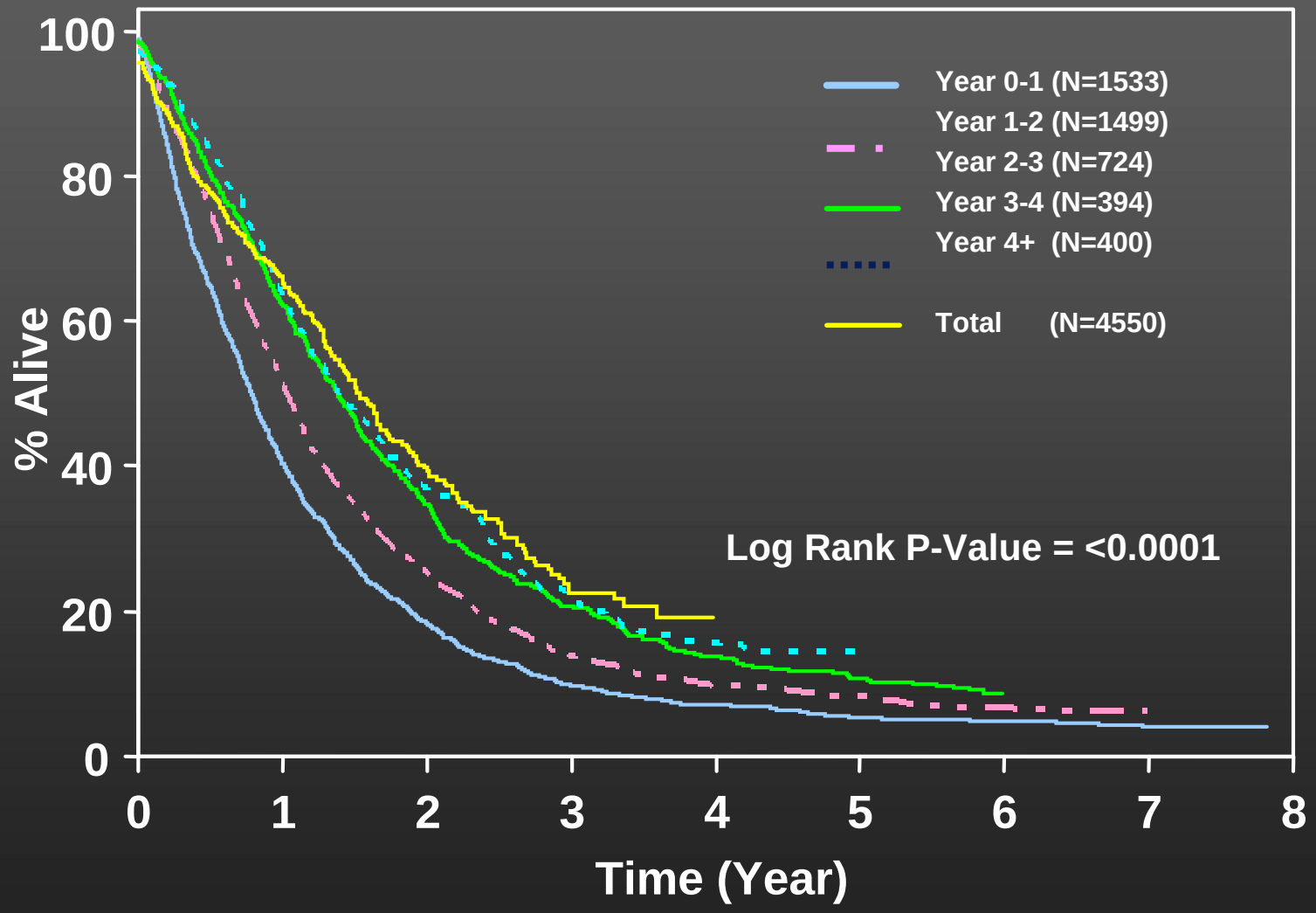
After 8 years, recurrence rates < 0.5% / year

Time from Recurrence to Death by Stage



O´Connell et al., ASCO 2007

Time from Recurrence to Death by Year of Recurrence for Stage III Patients



XELOX

NO16968 study

Stage III colon cancer

XELOX (n=938)

Capecitabine 1000mg/m² bid d1–14 q3w
+ oxaliplatin 130mg/m² i.v. d1 q3w

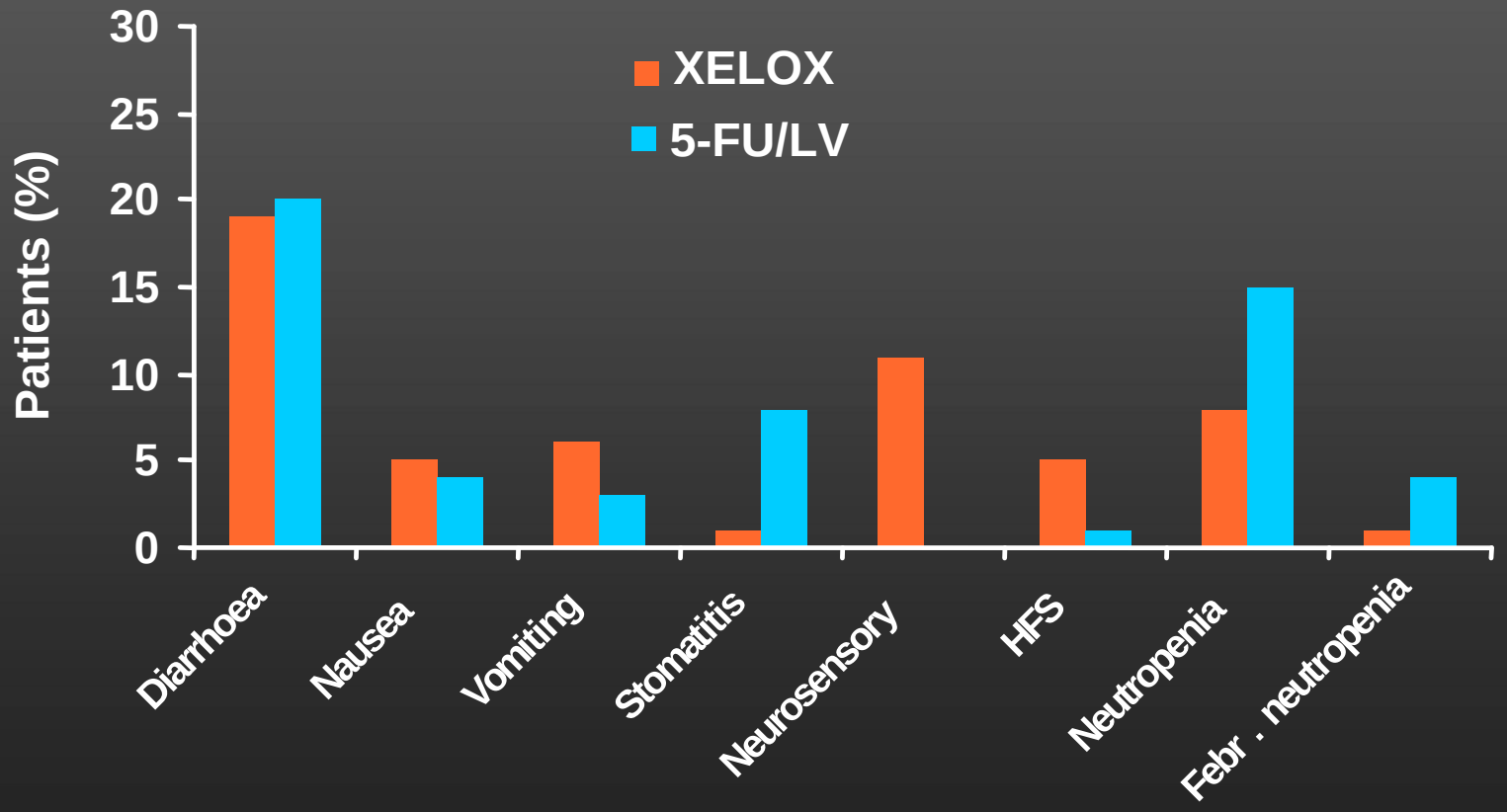
5-FU/LV (n=926)

- **Mayo Clinic bolus 5-FU/LV**
- **Roswell Park bolus 5-FU/LV**

- XELOX is feasible and safe[1]
  - similar tolerability to bolus 5-FU/LV and FOLFOX4
  - better tolerability than FLOX
- Efficacy data are due at end of 2008

Schmoll et al, J Clin Oncol 2007

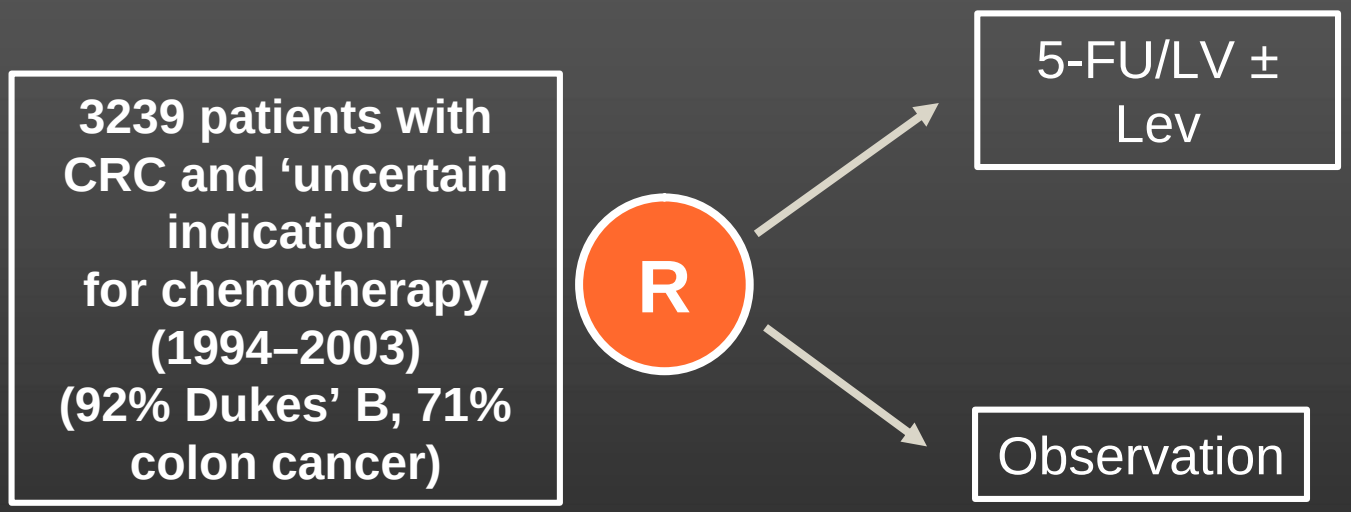
XELOX *vs* bolus 5-FU/LV: main grade 3–4 treatment-related toxicities



Schmoll et al, J Clin Oncol 2007

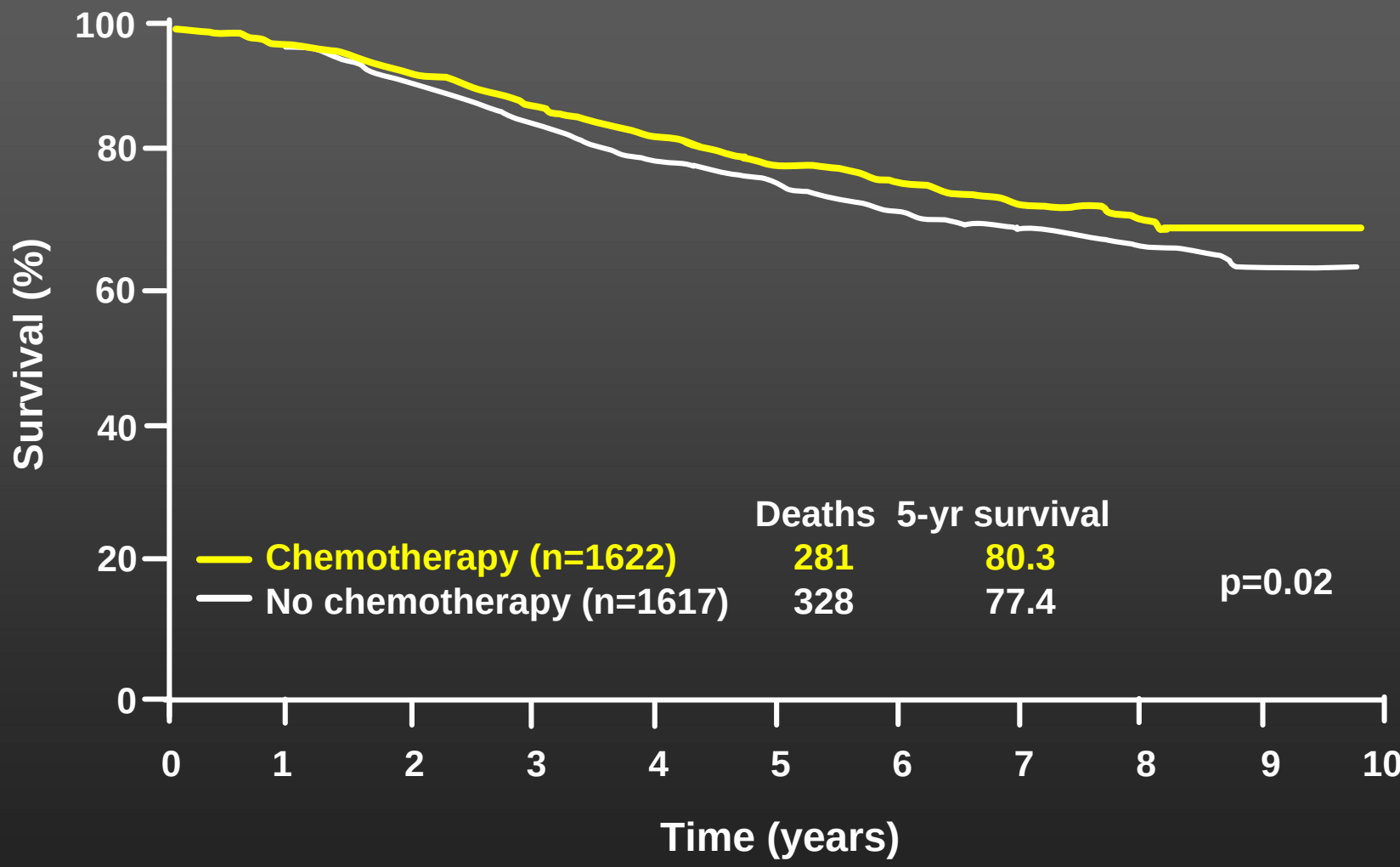
Stage II

QUASAR



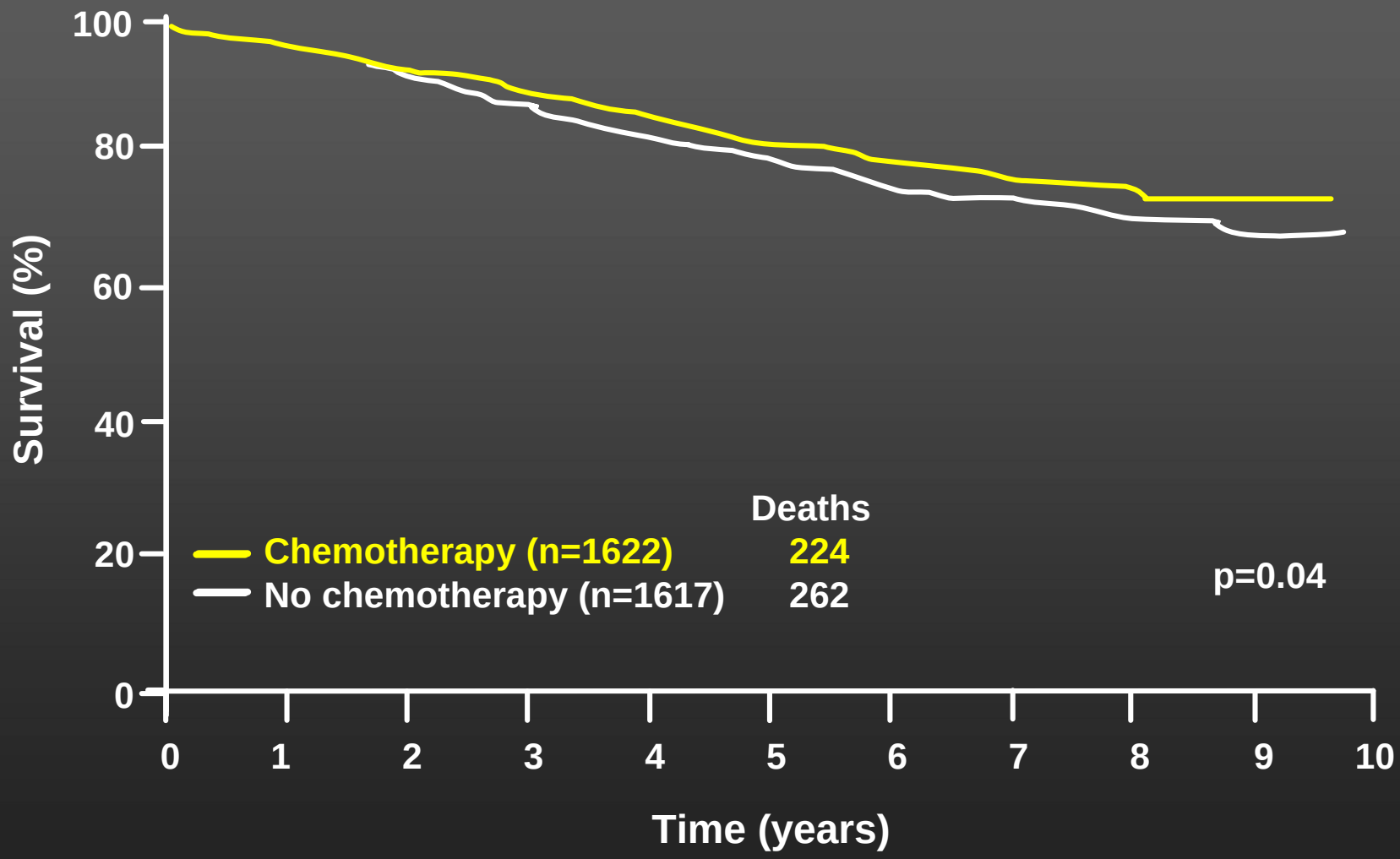
Gray et al. ASCO 2004 (Abstract 3501).

QUASAR: survival in ITT population



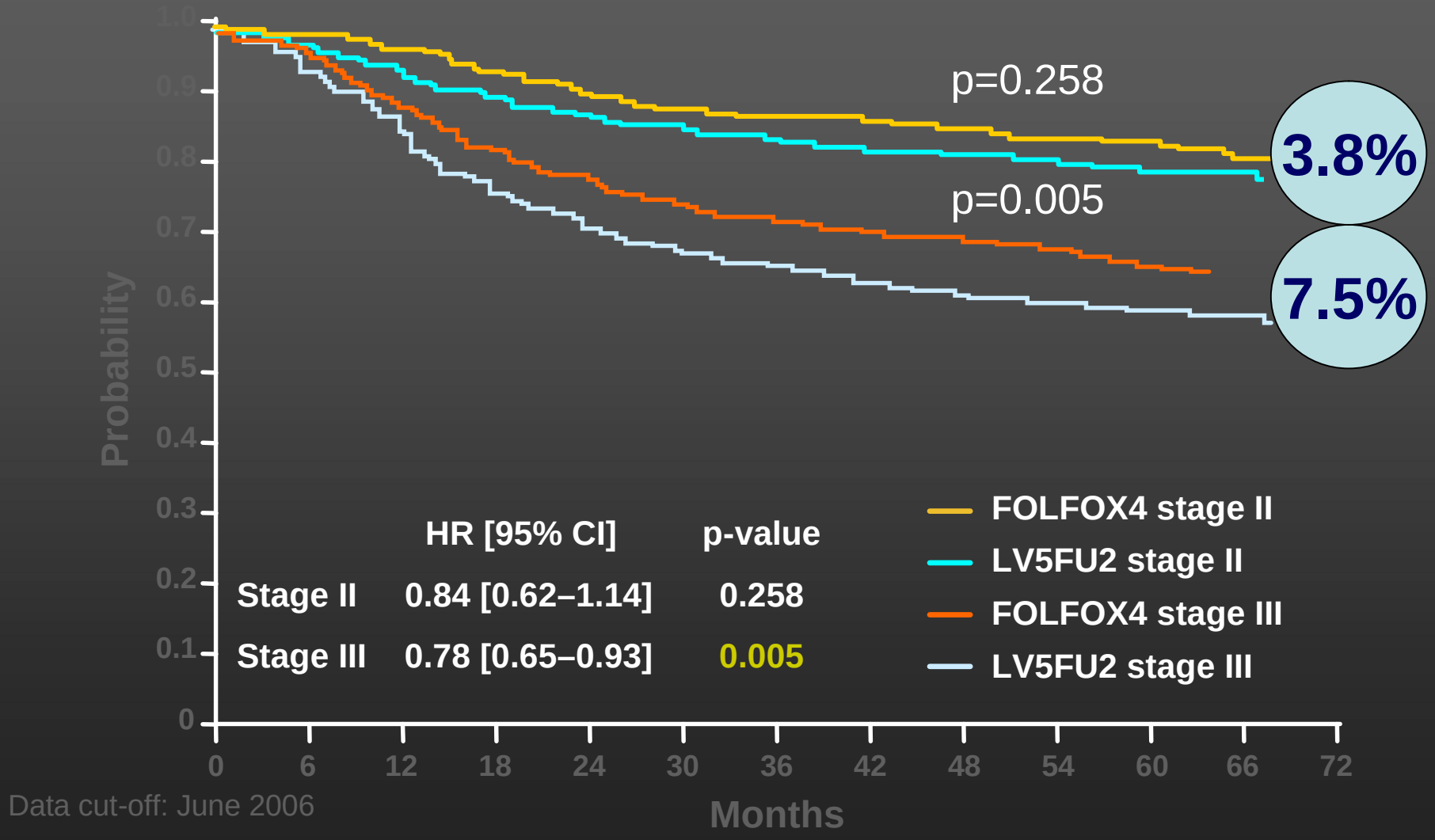
Gray et al. ASCO 2004 (Abstract 3501).

QUASAR: survival in stage II patients



Gray et al. ASCO 2004 (Abstract 3501).

Mosaic: Disease-free Survival
Stage II and III

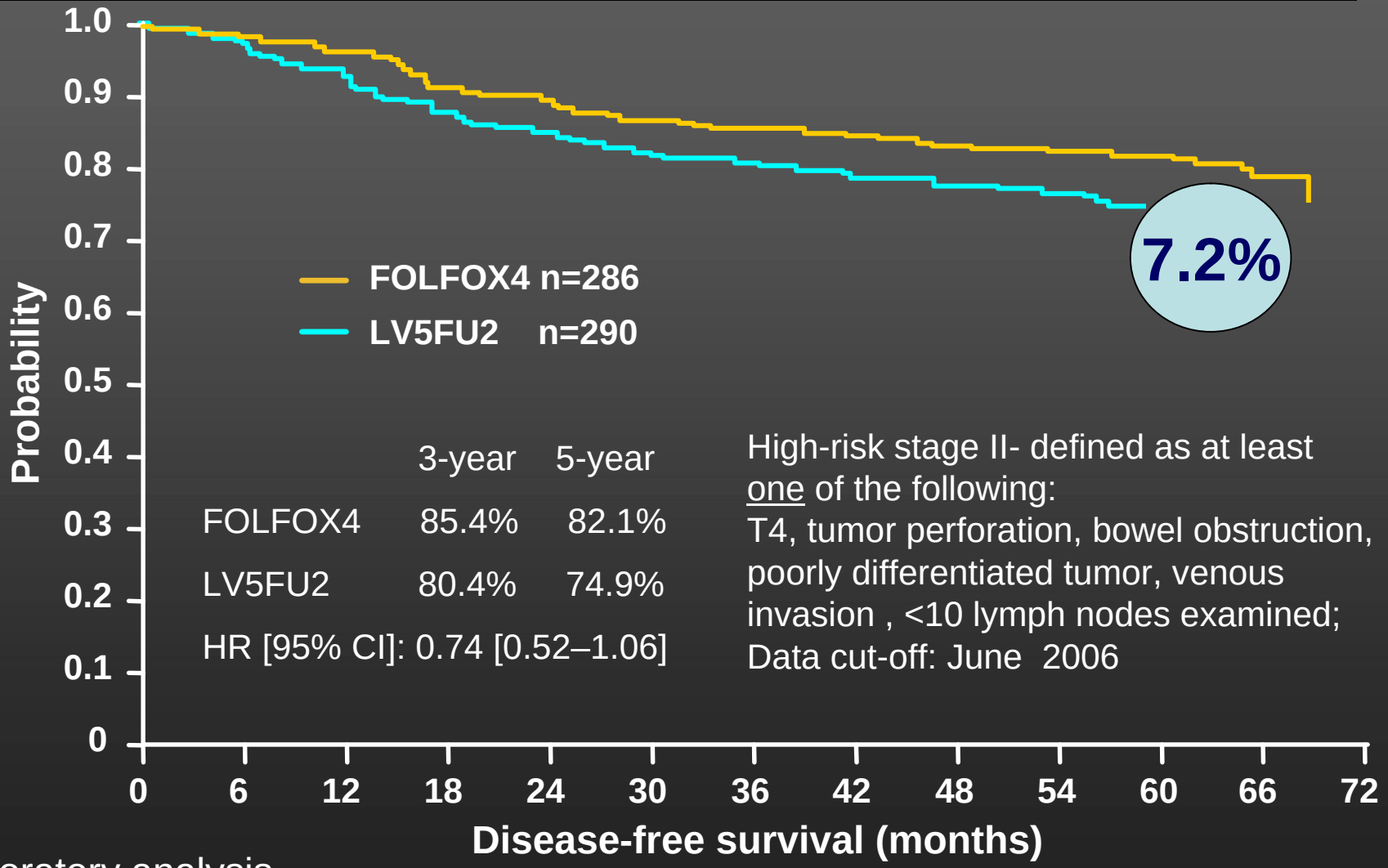


Data cut-off: June 2006

MOSAIC:
high-risk stage II patients

- 64% of stage II patients were defined as high-risk:
  - T4
  - Bowel obstruction
  - Tumour perforation
  - Poorly differentiated tumour
  - Venous invasion
  - Number of examined lymph nodes <10

Disease-free Survival: High-risk Stage II Patients



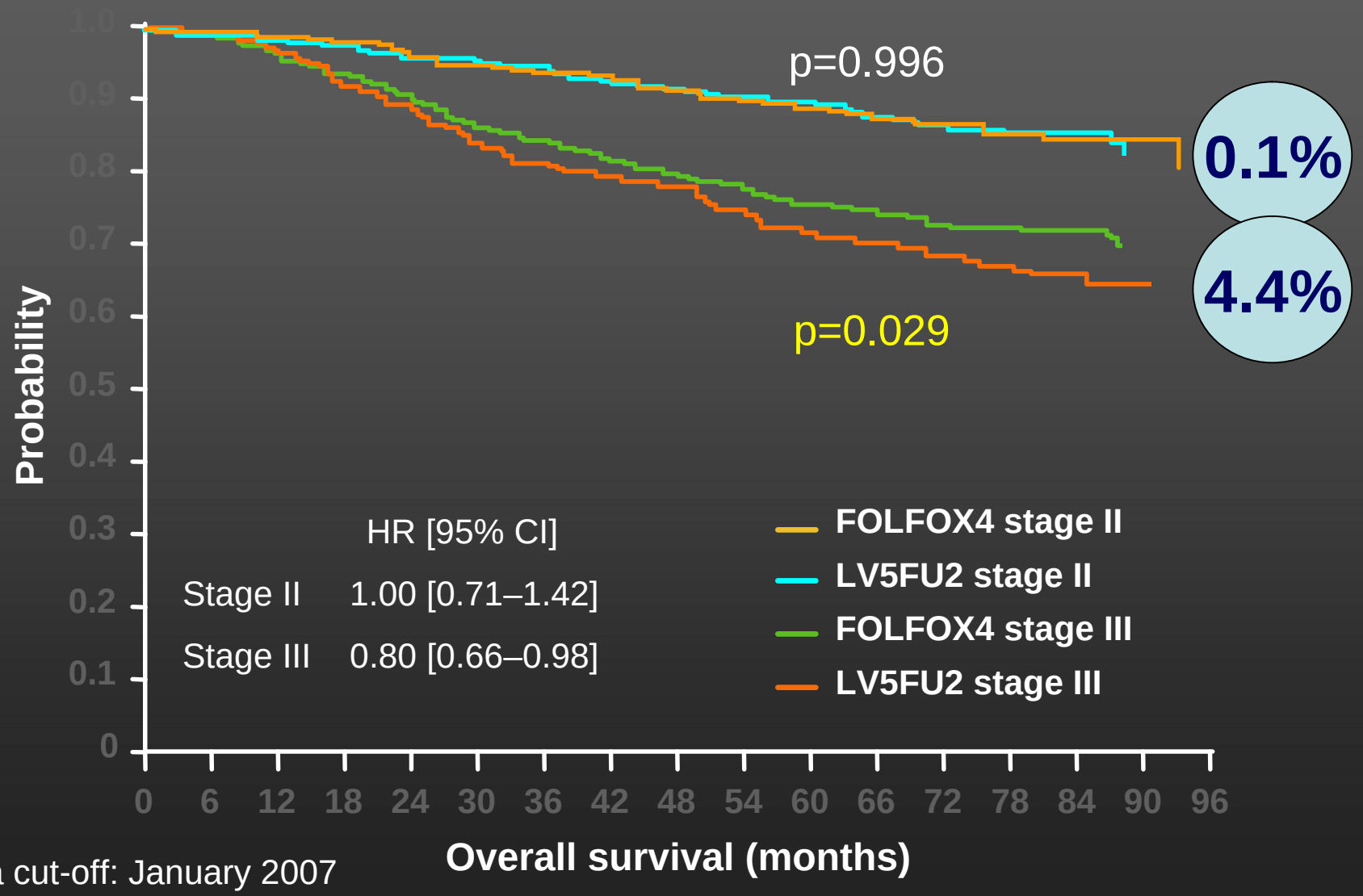
	3-year	5-year
FOLFOX4	85.4%	82.1%
LV5FU2	80.4%	74.9%

HR [95% CI]: 0.74 [0.52–1.06]

High-risk stage II- defined as at least one of the following:
T4, tumor perforation, bowel obstruction, poorly differentiated tumor, venous invasion , <10 lymph nodes examined;
Data cut-off: June 2006

Exploratory analysis

Overall Survival: Stage II and Stage III



Data cut-off: January 2007

New guidelines for adjuvant treatment of colon cancer: NCCN 2006

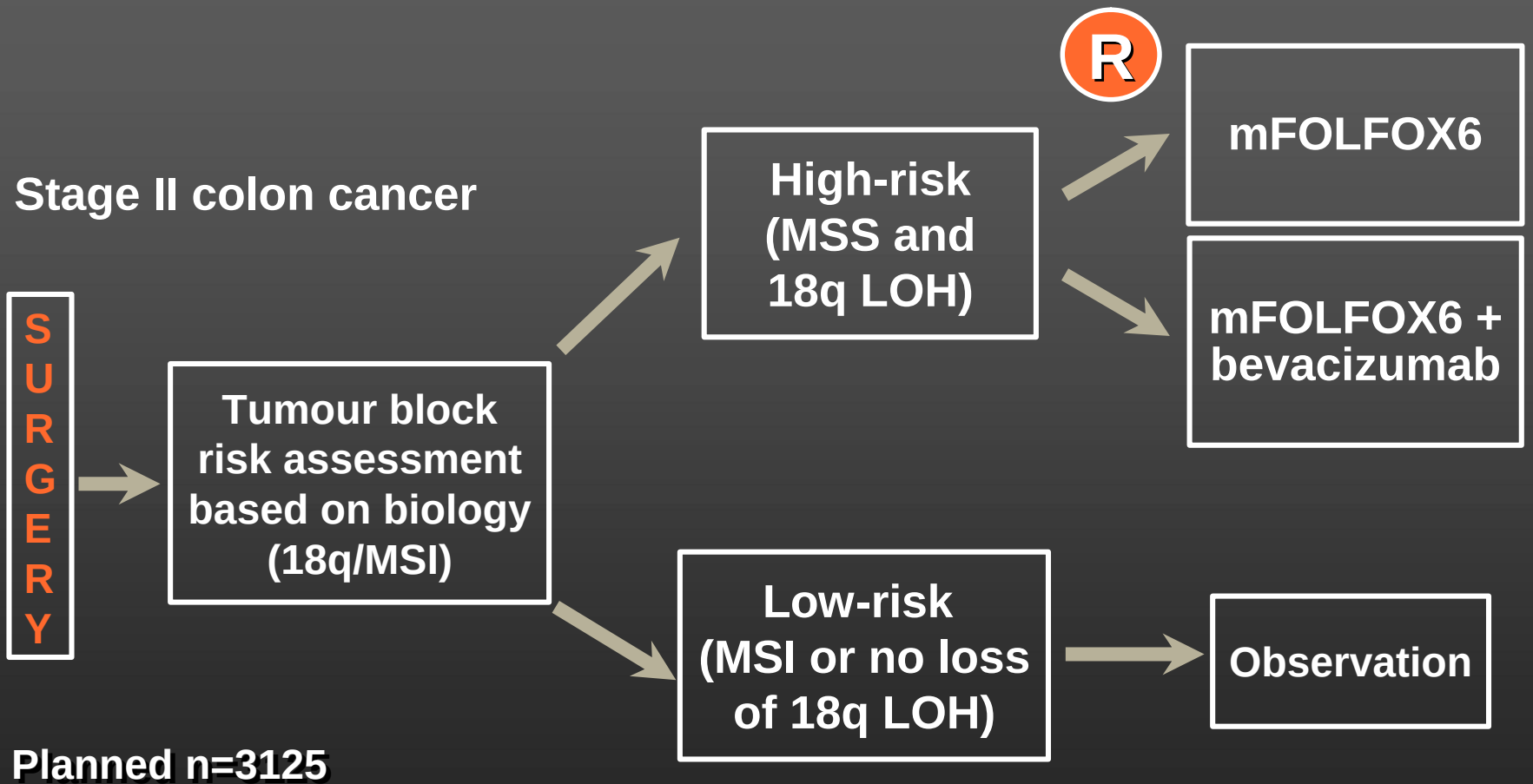
- T1, N0, M0 and T2, N0, M0 (stage I)
  - No chemotherapy
- T3, M0, N0 (stage II, no high-risk features)
  - Consider single-agent fluoropyrimidine or 5-FU/LV + oxaliplatin
  - **Deutscher Konsensus: keine Behandlung (im Einzelfall überlegen)**
- N0 high risk

  FOLFOX (XELOX)

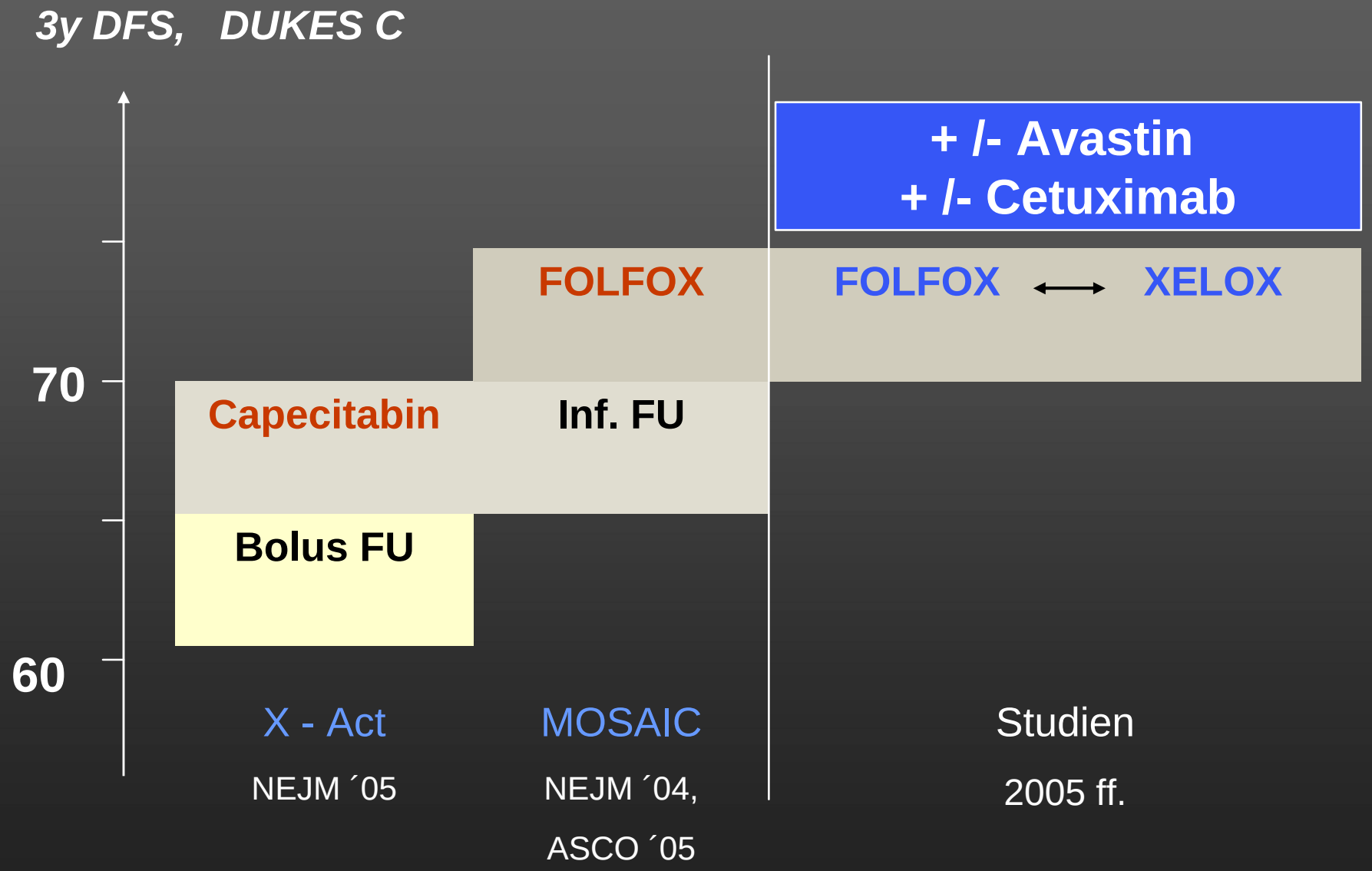
  Deutscher Konsensus: im Einzelfall entscheiden
  FOLFOX 6 Monate

NCCN Clinical Practice Guidelines in Oncology v2.2006.

Future directions: E5202

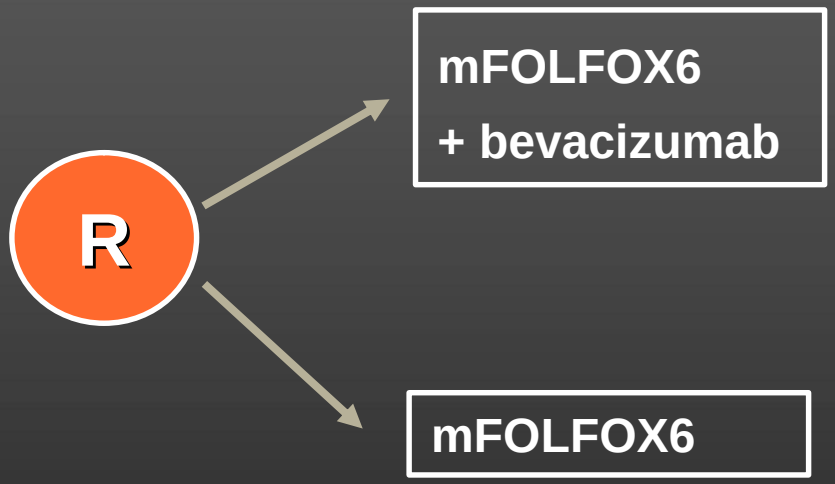


Adjuvante Therapie des Kolon-Ca.: Studienfragen



Future directions: NSABP C-08

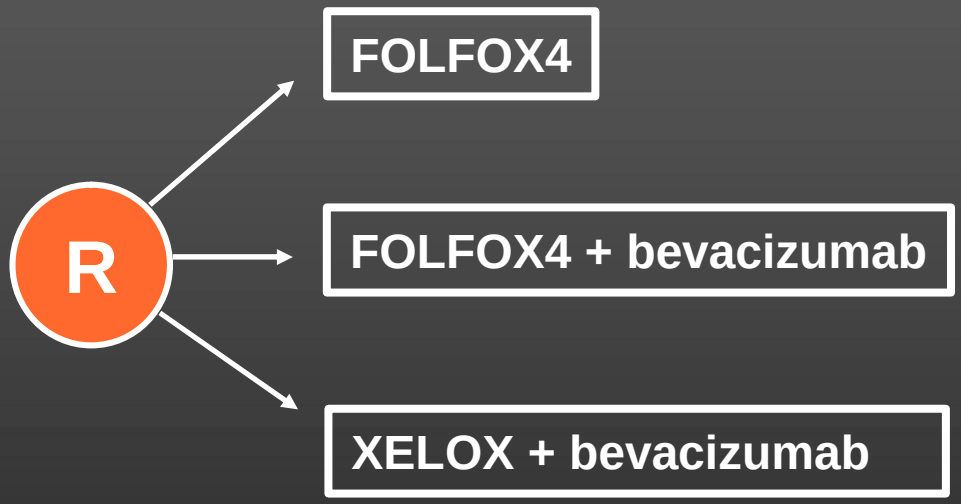
Stage II and III
colon cancer
n=2500



Primary endpoint: DFS

AVANT: oxaliplatin-based chemotherapy + bevacizumab for stage II/III colon cancer

Stage II and III colon cancer n=3450 patients



Primary endpoint: DFS

Future directions: NO147

Before ASCO 2005:

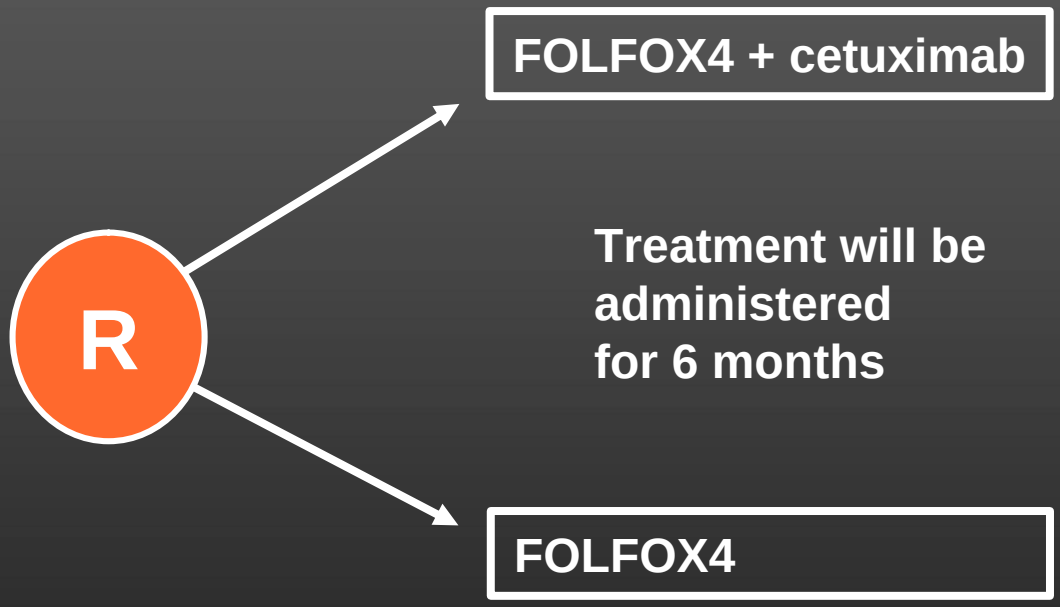
Modification in June 2005:

Future directions: PETACC-8

Phase III trial

Fully resected stage III colon cancer

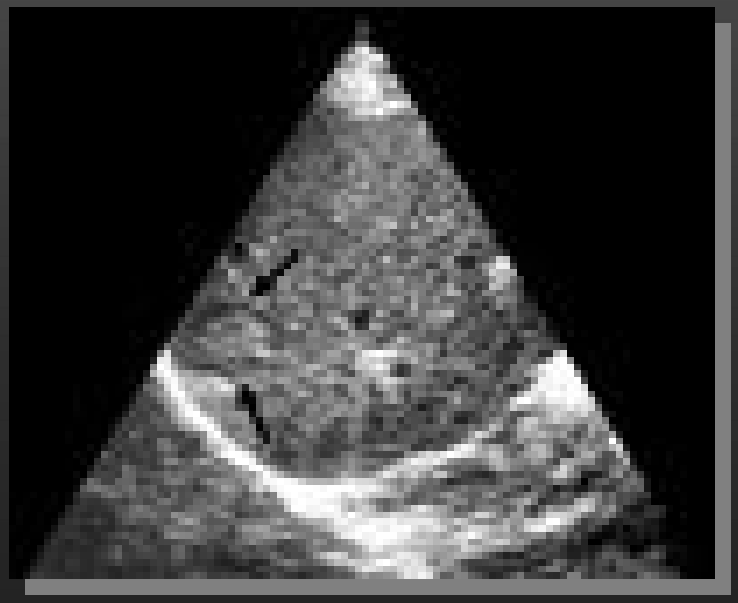
Planned n=2000

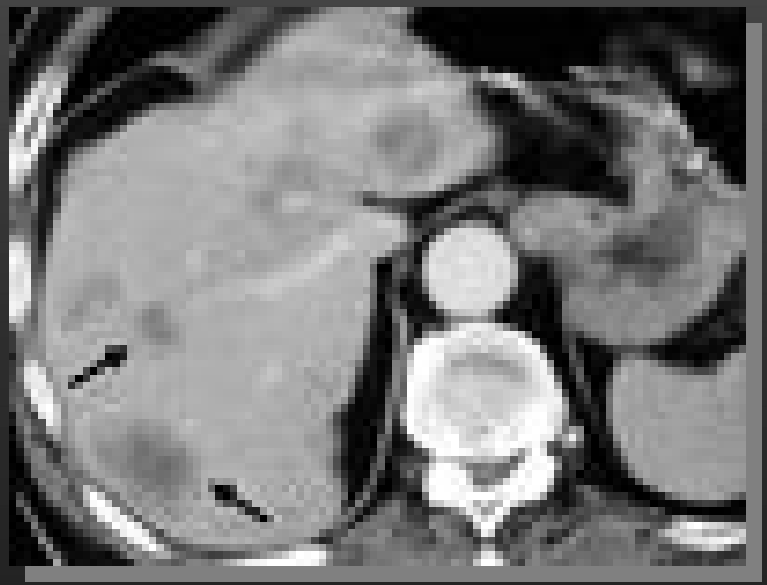


Primary endpoint: DFS

Liver metastases in ACRC

In 33%-35%: liver metastases only!





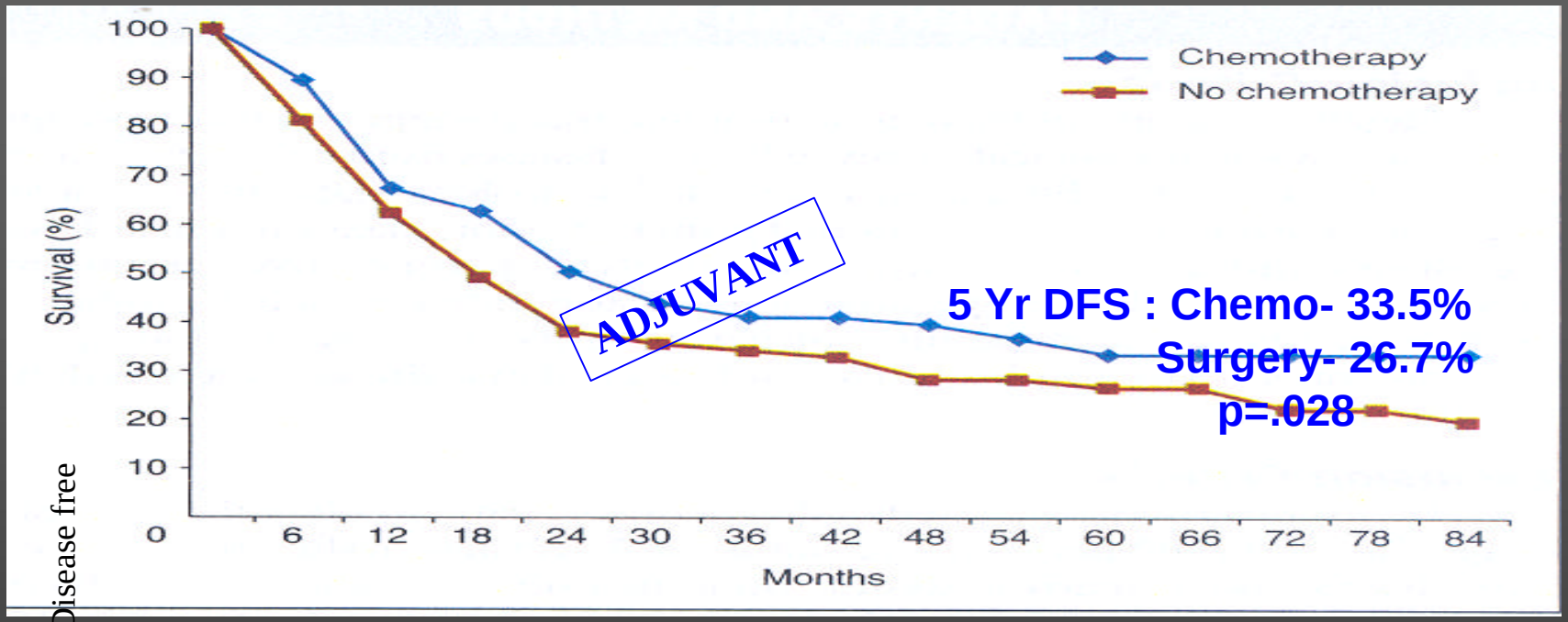
Prognosis after nach resection: Fong-Score

Table CLINICAL RISK SCORE FOR TUMOR RECURRENCE

	Survival (%)					
Score	1-yr	2-yr	3-yr	4-yr	5-yr	Median (mo)
0	93	79	72	60	60	74
1	91	76	66	54	44	51
2	89	73	60	51	40	47
3	86	67	42	25	20	33
4	70	45	38	29	25	20
5	71	45	27	14	14	22

Each risk factor is one point: node-positive primary, disease-free interval <12 months, >1 tumor, Size >5 cm, CEA >200 ng/ml.

Fong et al, 2003



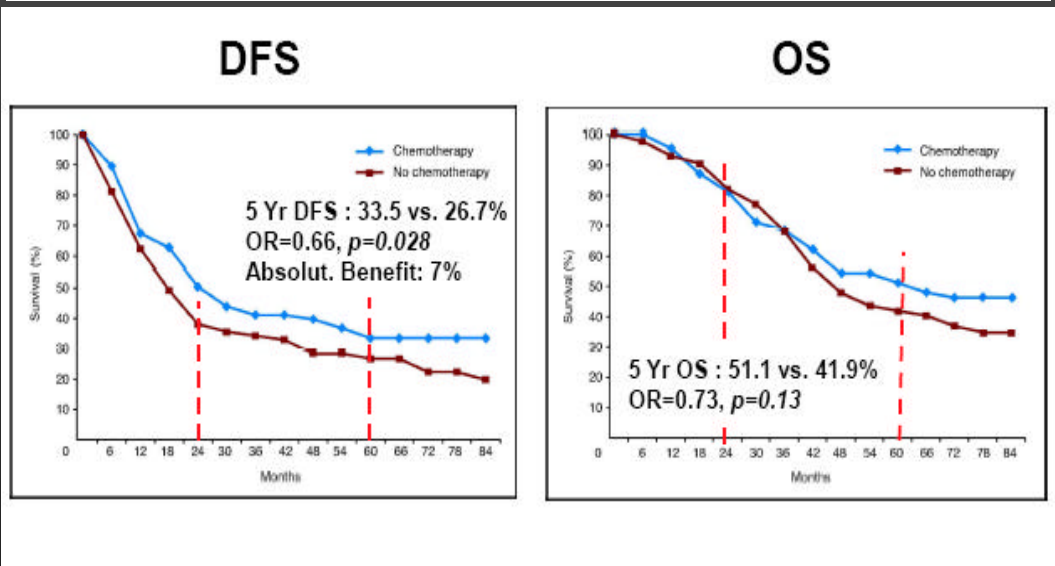
Portier et al, Multicenter Randomized Trial of Adjuvant Fluorouracil & Folinic Acid Compared with Surgery Alone After Resection of Colorectal Liver Metastases: FFCD ACHBTH AURC 9002 Trial, J Clin Oncol 24; 4976-4981, 2006

Enrolled 173 Pts of planned 200 Pts over 10 yrs. Slow accrual /trial stopped.

Adjuvant CTX after resection of liver mets: really beneficial?

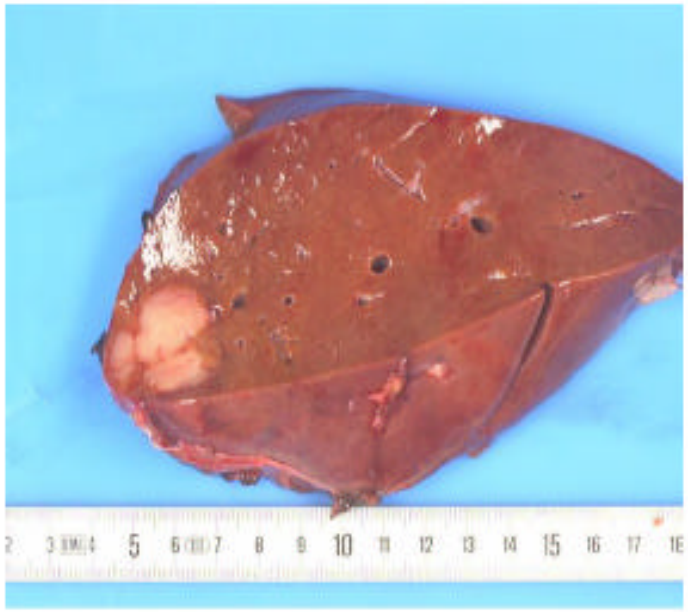
	Autor	Design	n	DFS/OS
	Langer 2002	5-FU/FS Bolus x6 M1 (1-4, Leber/Lunge)	129 (-22) (Ziel: 478)	HR: 1.28/1.30 *n.s.*
+	Portier 2002	5-FU/FS Bolus x6 M1 (Leber)	167 (-5) (Ziel: 200)	Diff: +9%/+7% *n.a.*
=	Mitry 2006	Metaanalyse	278	HR: 1.33/1.30 *p=0.059 (PFS)*

„Meta analysis“,
Mitry et al., ASCO 2006

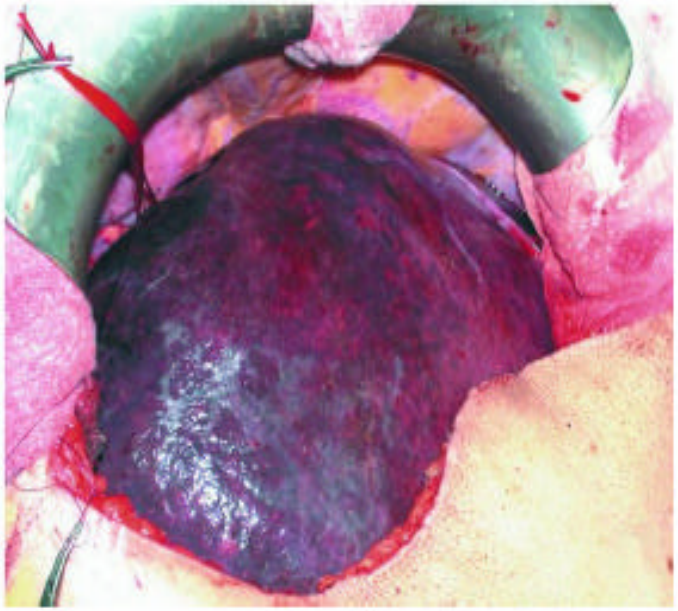


Portier et al.,
J Clin Oncol 2006

***Pre*operative chemotherapy: Liver damage**



CASH
V.a. Irinotecan



„Blue Liver“
V.a. Oxaliplatin

Vauthey et al, J Clin Oncol 2006

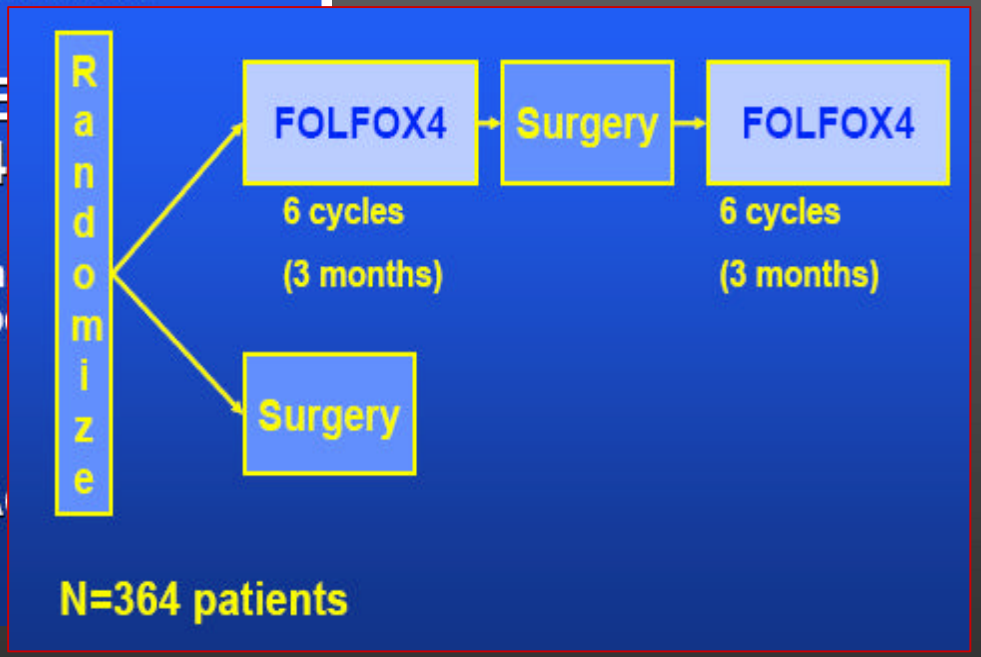
Peri-operative FOLFOX4 chemotherapy and surgery for resectable liver metastases from colorectal cancer

Final efficacy results of the E Intergroup phase III study 4

B. Nordlinger, H. Sorbye, B. Glimelius, G.J. Poston
P. Rougier, W.O. Bechstein, J. Primrose, E.T. Walp
T. Gruenberger

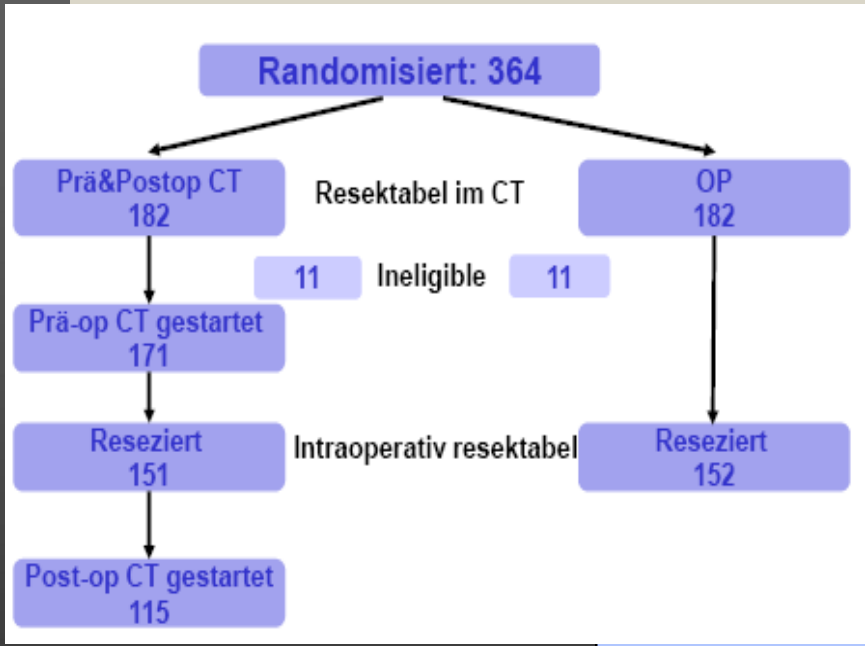
Statistical analysis L. Collette

For the EORTC GI Group, CR UK, ALMCAO, A
FFCD



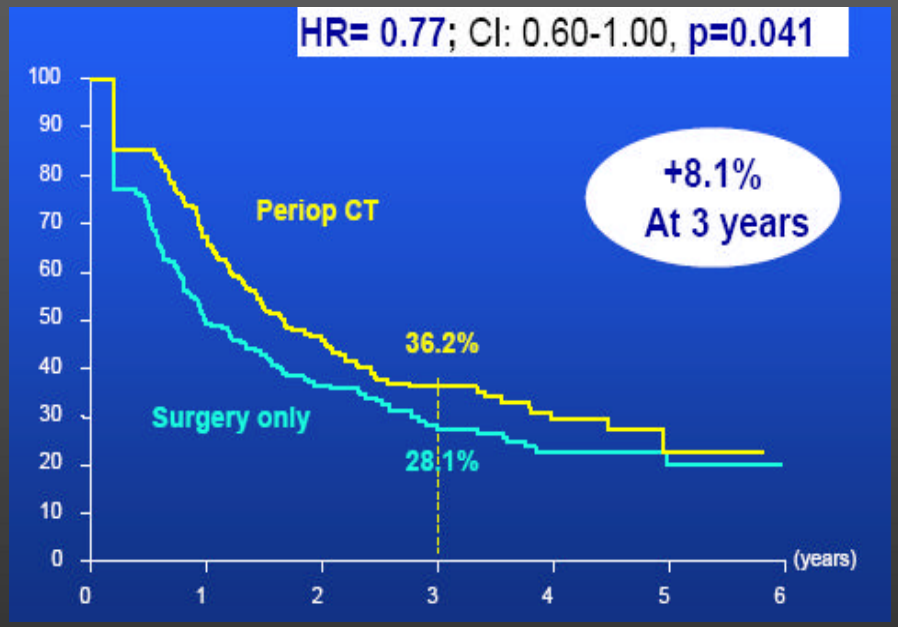
- Definition of progression
  - Recurrent or progressive disease
  - Metastases not resectable at surgery
  - Death of any cause if prior to progression
- Objective: to demonstrate a 40% increase in median PFS (HR=0.71) with 80% power and 2-sided significance level 5%
- Sample size: 330 patients (for 278 events)
- 364 patients (182 x 2) recruited from September '00 to July '04

EORTC 40983: PFS

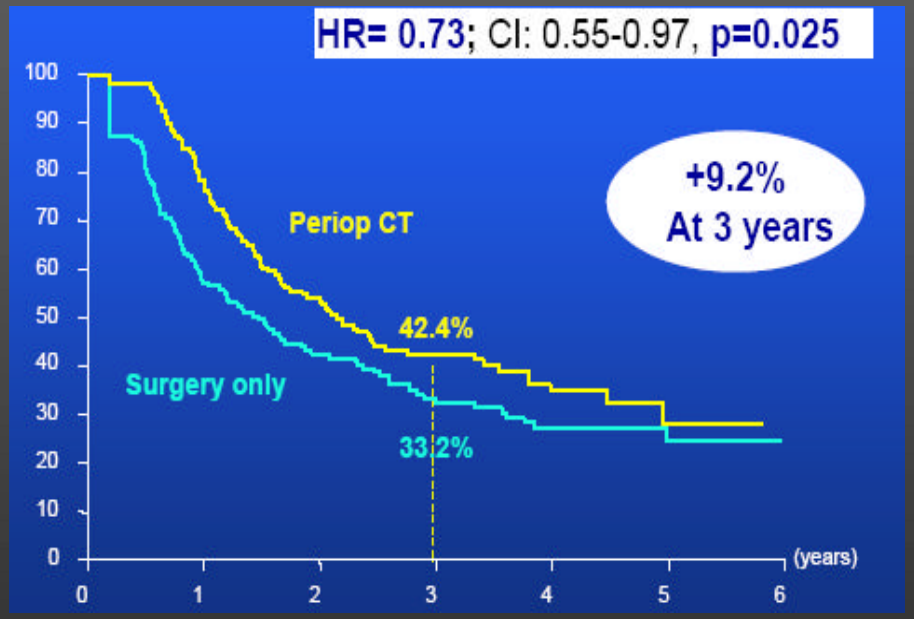


	N pts Surgery	% absolute difference in 3-year PFS	Hazard Ratio (Confidence Interval)	P-value
All patients	182	+7.2% **(28.1%/ 35.4%)**	0.79 **(0.62-1.02)**	P=0.058
All eligible Patients	171	+8.1% **(28.1% / 36.2%)**	0.77 **(0.60-1.00)**	P=0.041
All resected Patients	151	+9.2% **(33.2% / 42.4%)**	0.73 **(0.55-0.97)**	P=0.025

EORTC 40983: Results and Conclusion

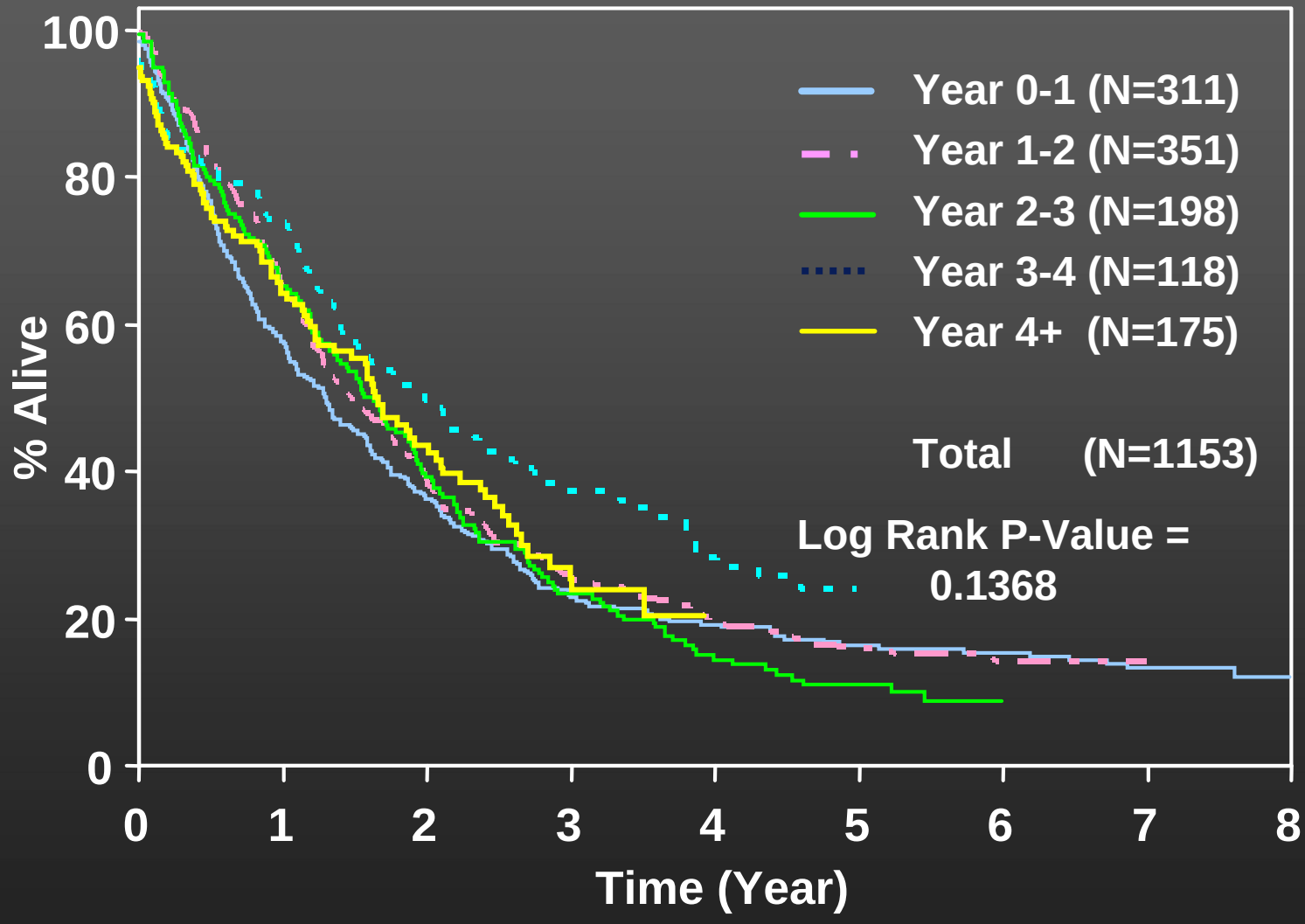


Eligible pts.



Resected pts.

Time from Recurrence to Death by Year of Recurrence for Stage II Patients



Rectal Cancer

Possible role of chemotherapy in rectal cancer

In addition to perioperative radiotherapy:

enhance efficacy of radiation

Þ improve local control

enable resection and sphincter preservation

Adjuvant systemic therapy - after perioperative (chemo)radiation

eradicate micrometastasis

Þ reduce rate of distant relapse

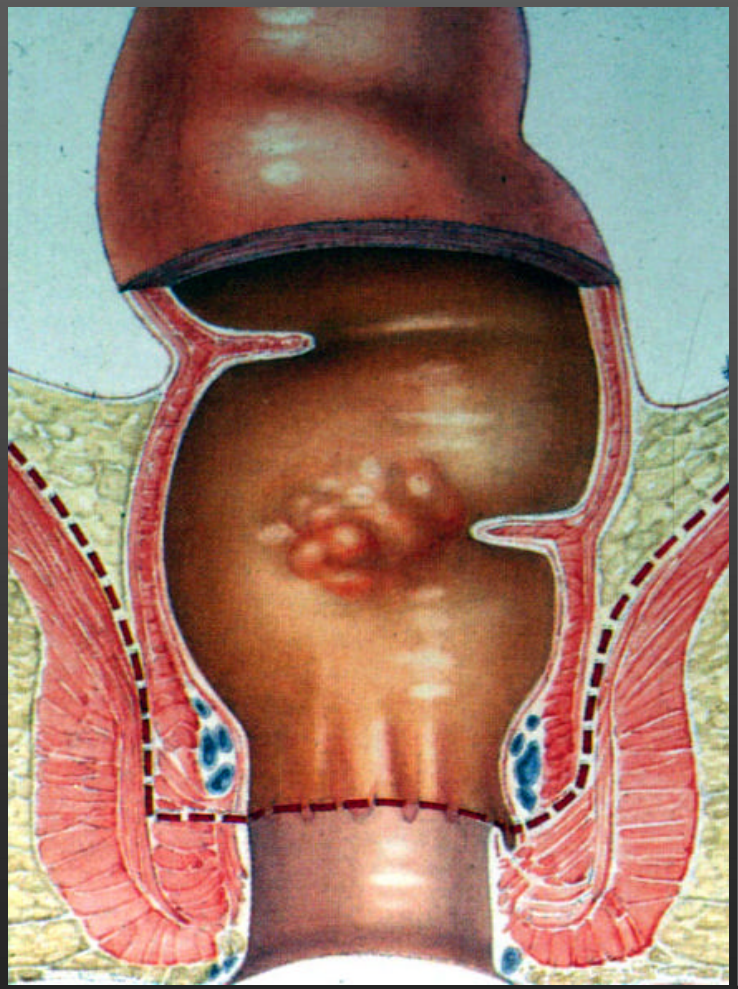
Before perioperative chemoradiation

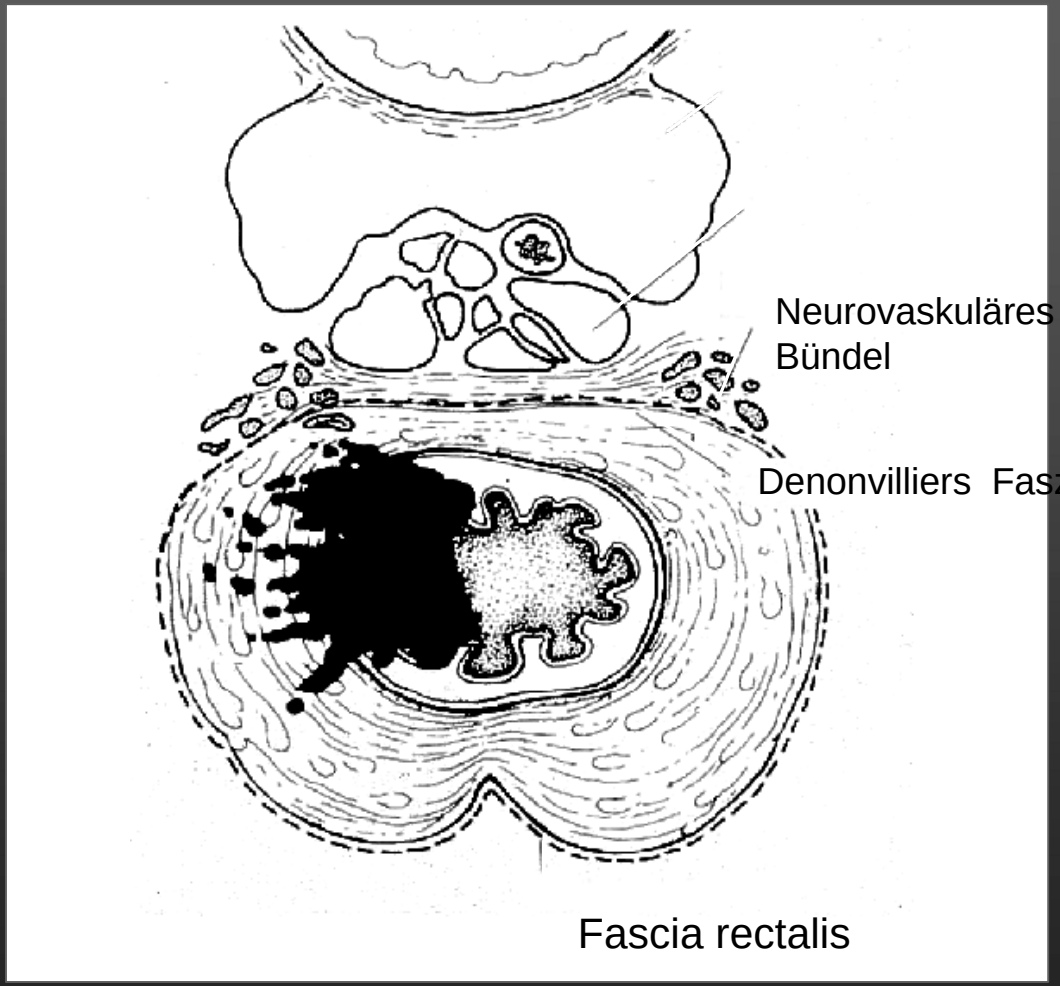
reduce local tumor size and eradicate micrometastases

Who cures rectal cancer?

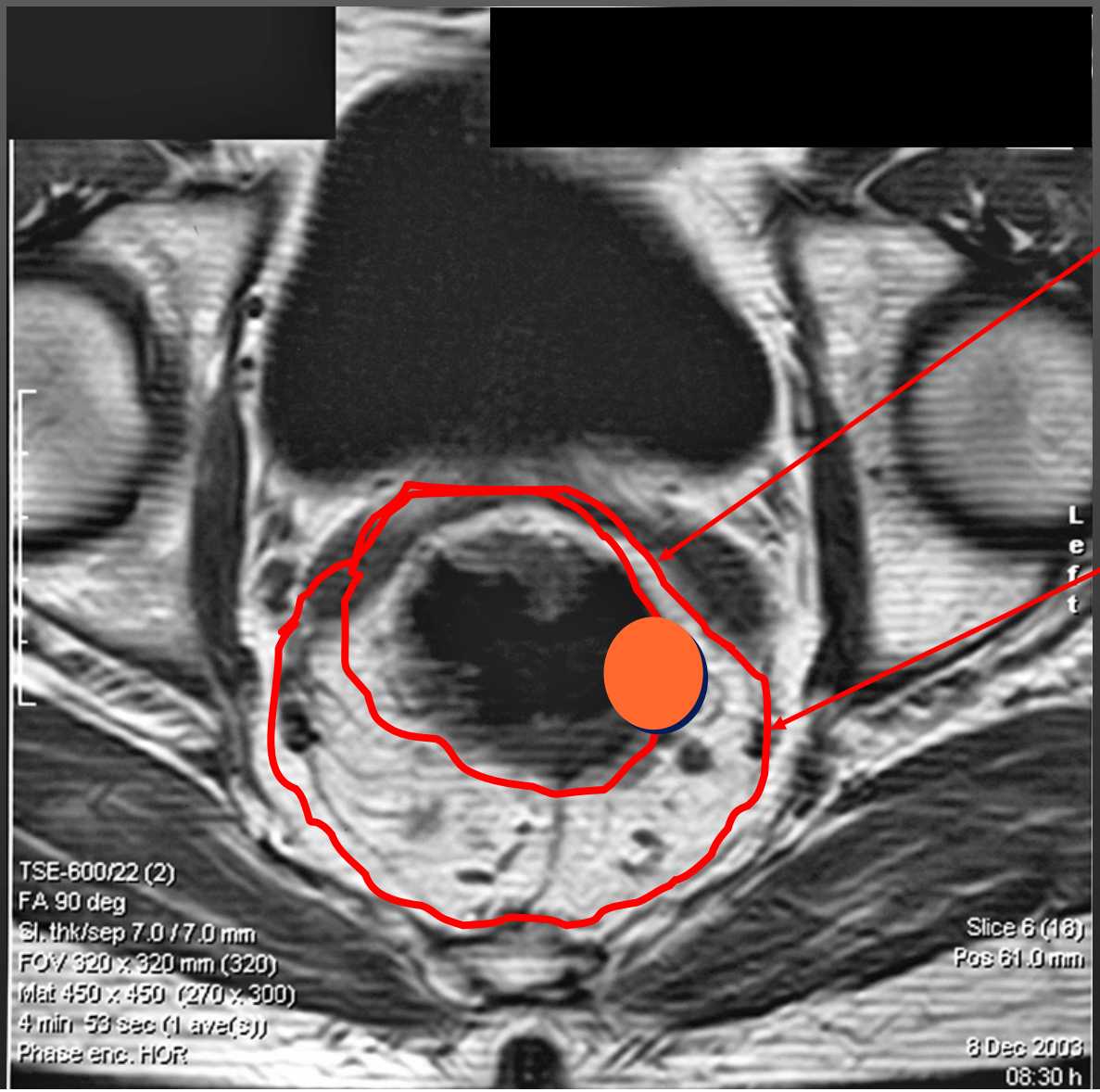
Surgeons:	optimal = radical surgery (TME)
	is most important for cure
Radiotherapists:	high dose radiation +/-
	chemotherapy is most
	important for cure
Medical Oncologists:	systemic chemotherapy only
	may effectively eradicate micrometastes
	- locoregional
	- systemic spread

Rectal Cancer: „Mesorectum“





From conventional surgery to TME



Conventional excision of the tumor.

TME: Sharp excission at mesorectal fascia (MRF).

PreOP trials: Patterns of failure

		local failure		distant mets.		5y OS	
		vs.		vs.		vs.	
FFCD ASCO 2005	RT vs. RChT	16%	8%	36%	38%	66%	67%
EORTC ASCO 2005	RT vs. RChT	17%	9%	32%	35%	65%	65%
AIO/CAO/ARO NEJM 2004	Pre vs. post	13%	6%	36%	38%	74%	76%*
Marijnen ASCO GI 2005	5x5	11%	6%	n.a.		63%	64%

Despite significant reduction of local relapse,
no influence on distant mets. and survival observed

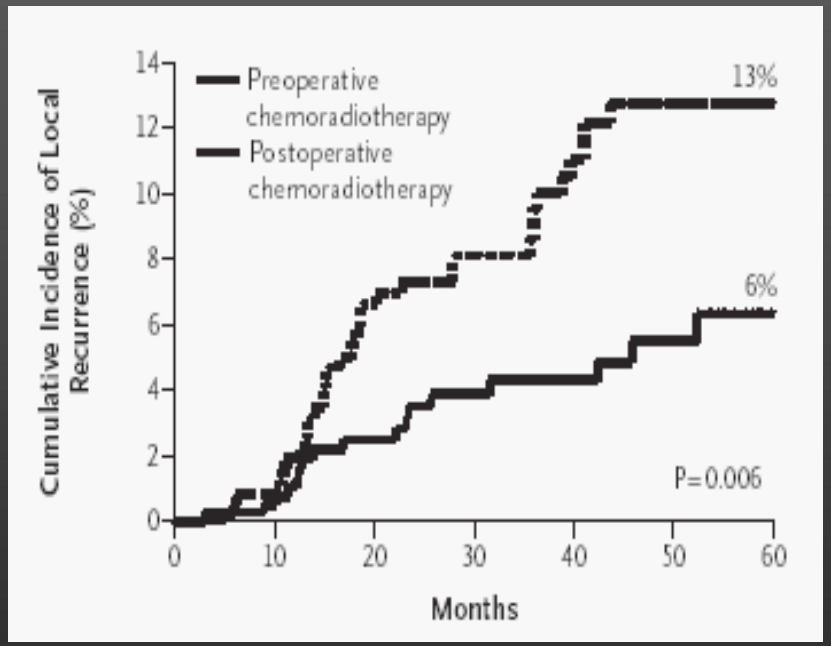
Local Relapse Rates: Significantly Reduced

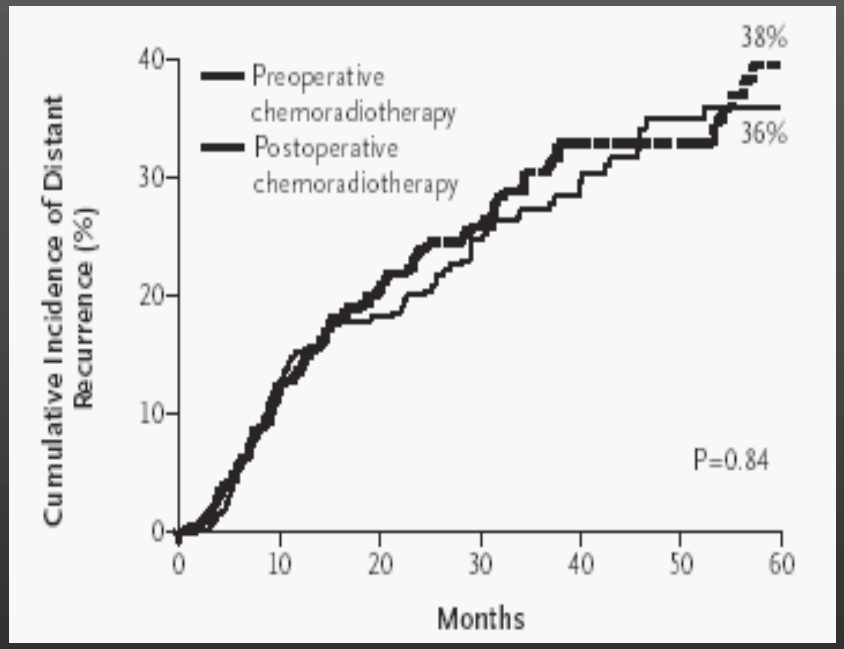
	Preop Chemo radiatio n	Preop radiation	Postop Chemo radiatio n		p
FFCD (%)	8	16.5			**.003**
EORTC (%)	9	17			**.002**
AIO/CAO/ARO* (%)	6		13		**.006**
Polish Trial	14	9 (5x5)			**n.s.**

Bosset et al. NEJM 2006; Gerard et al. ECCO 2005
Sauer et al., NEJM 2004; Bujko et al., Br J Surg 2006

Local vs. distant relapse and survival

AIO/ARO/CAO-94 trial





Does the addition of chemotherapy influence the outcome?

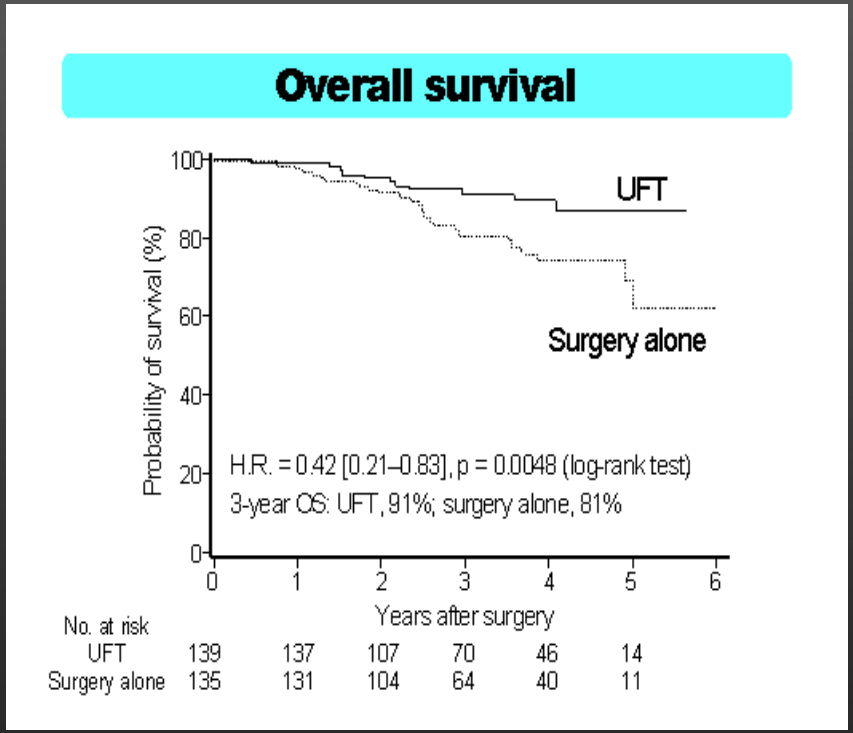
			Local failure	OS
GITSG (1985)	N= 227	Res Res + RT Res (+/- RT) + CTx	+	=
NSABP R01, 1988	N= 574	Res + RTx Res + CTx	=	+
NCCTG/Mayo, 1985	N= 204	Res + RT Res + RT + CTx	+	+
Tveit, 1997,	N= 144	Res + RT Res + RT + CTx	+	trend
QUASAR (2004)	N= 948	Res (+/- RT) Res (+/- RT) + CTx		+
EORTC (2005)	N=1011	RT → Res RT → Res + CTx	+	trend
Japan (2006)	N= 276	Res Res + CTx	trend	(RFS:) +

Adjuvant UFT/FA after TME (no XRT!)

Japanese NSAS-01 Trial

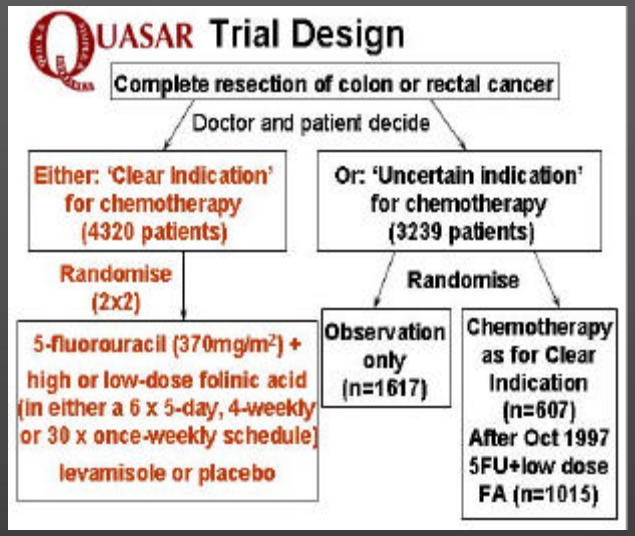
276 Pts., all Stage III; >80% pT3/4; 60% upper 1/3

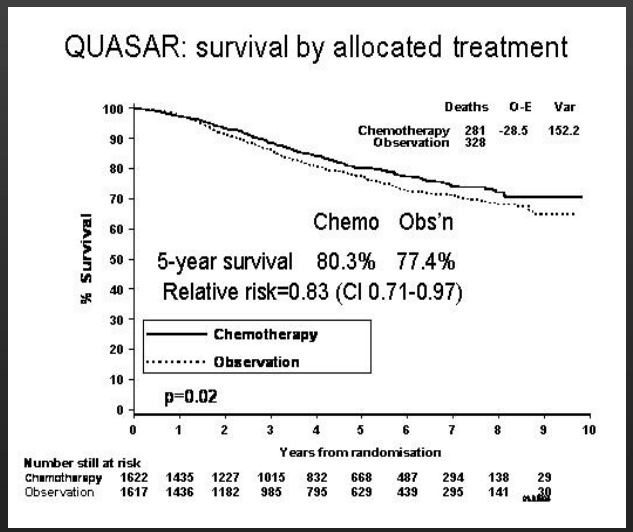
	TME	TME UFT/ LV	
Local failure	10%	6%	n.s.
RFS @ 3 yrs.	60%	78%	0.001

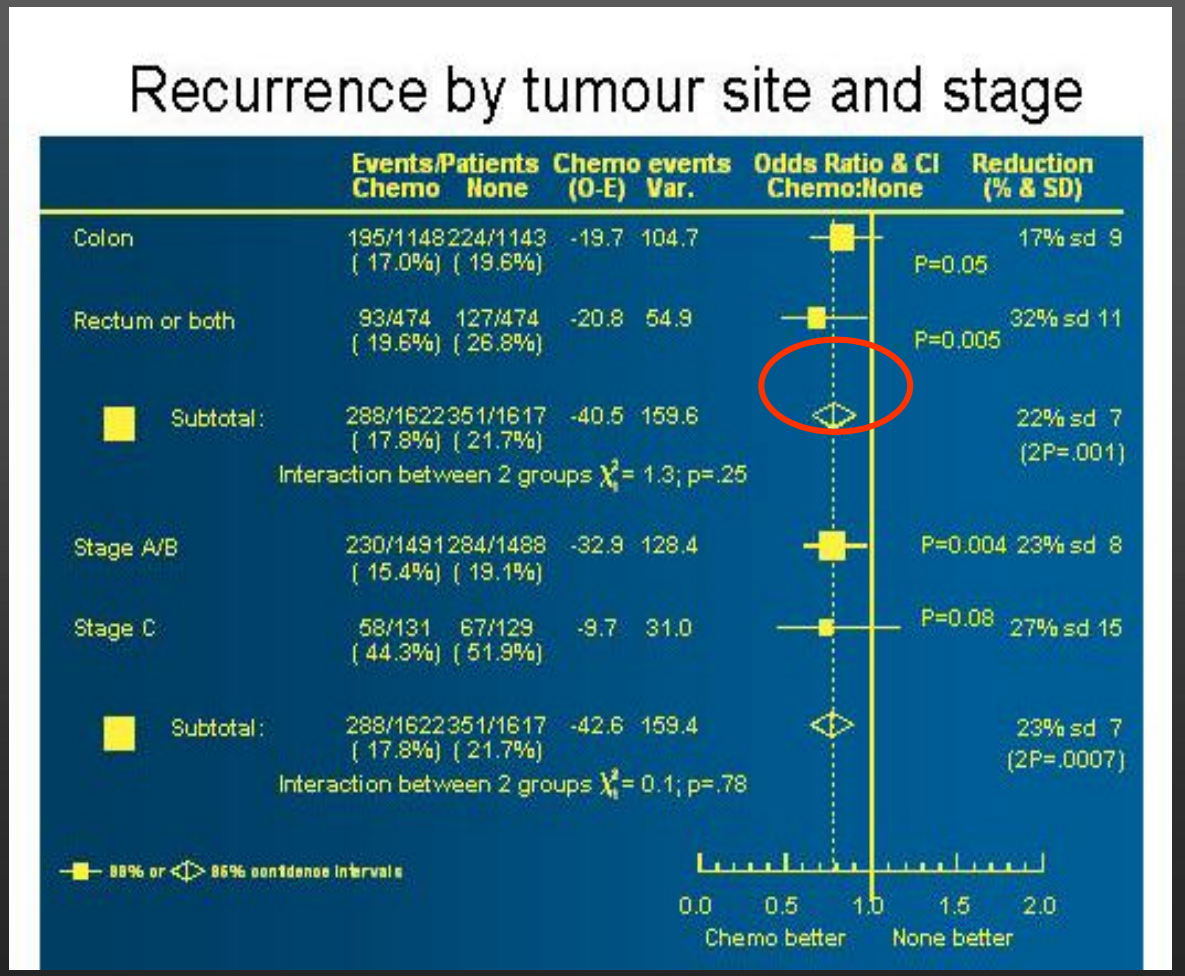


Akasu et al., J Clin Oncol 2006

QUASAR trial; n=948 rectal cancer pts.





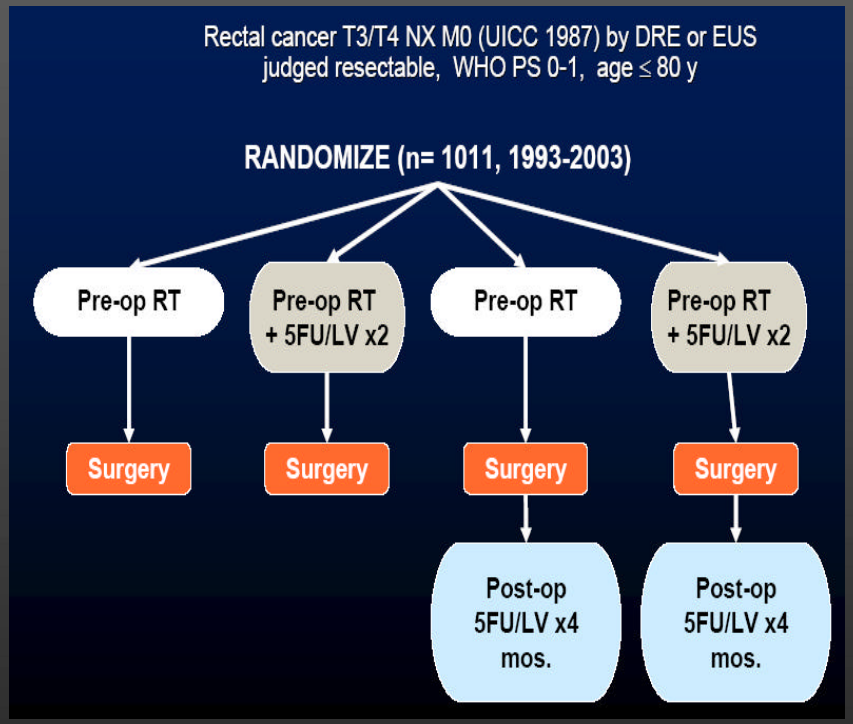


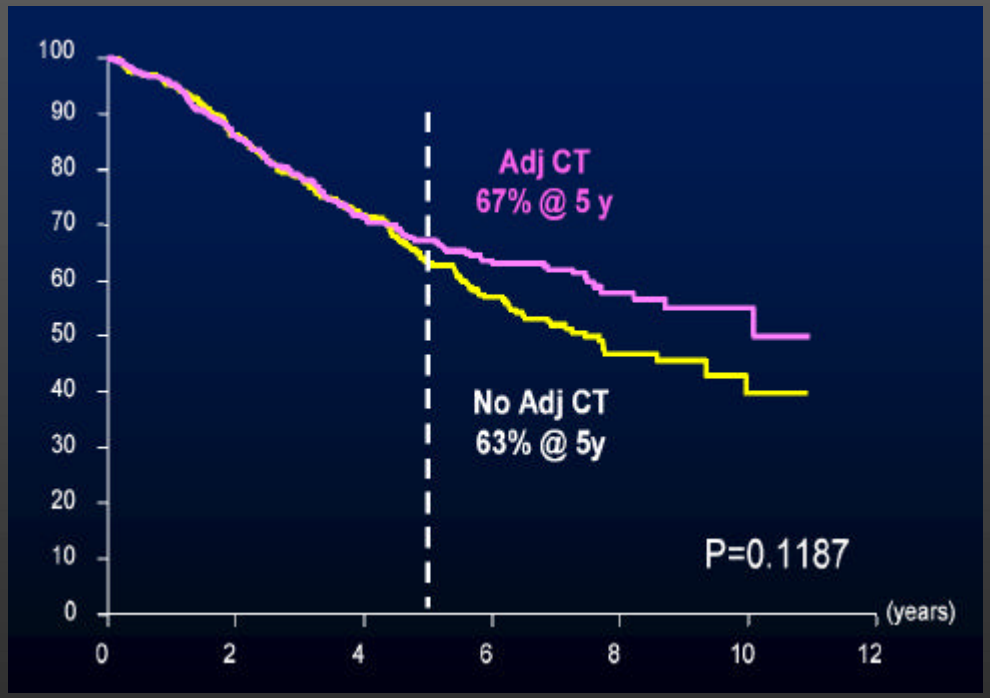
Post OP systemic chemotherapy

	year	N pts	pre OP	post OP
EORTC 22921	2005	1011	RT vs. RChT	+/- 5-FU/FA bolus
FFCD 9203	2005	733	RT vs. RChT	no chemo
AIO/CAO/ARO	2004	815	pre vs. post	5-FU bolus (all pts.)
Polish Trial	2005	311	RChT vs. 5x5	optional FU/FA

Bosset et al. NEJM 2006 & Colette et al. JCO 2007; Gerard et al. JCO 2006
Sauer et al., NEJM 2004; Bujko et al., Br J Surg 2006

EORTC Trial

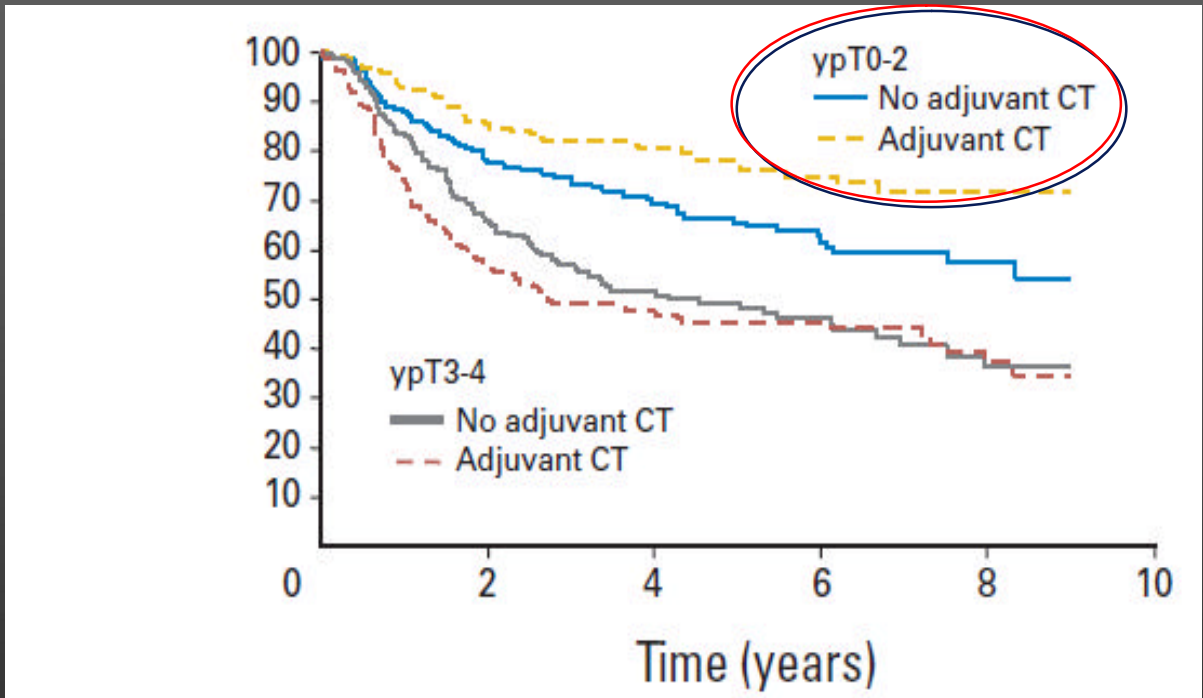




Overall survival @ 5 yrs.

Bosset et al., NEJM 2006

EORTC trial: Stage dependent DFS by adjuvant chemotherapy



ypT0-2	O	N	No. of patients at risk			
No adjuvant CT	77	225	157	101	57	22
Adjuvant CT	45	196	150	111	59	16
ypT3-4						
No adjuvant CT	92	176	107	63	42	15
Adjuvant CT	100	183	94	62	42	17

Collette et al., JCO 2007 (Oct 1st)

Univariate analysis: Benefit from chemotherapy: Histopathology

Histopathology										
Tumor length, mm										
≤ 30	244	60.5	238	62.3						
> 30	143	35.5	132	34.6	.474	0.85	0.53 to 1.34	.780	0.92	0.53 to 1.60
Missing	16	4.0	12	3.1						
WHO differentiation										
Well	174	43.2	153	40.1						
Poor/moderate	213	52.9	205	53.7	.419	0.83	0.52 to 1.31	.778	0.92	0.53 to 1.60
Missing	16	4.0	24	6.3						
Histology										
Mucinous	23	5.7	18	4.7		Not tested			Not tested	
Other	380	94.3	363	95.0						
Missing	0	0.0	1	0.3						
Pathologic tumor stage										
ypT0-2	225	55.8	198	51.8						
ypT3-4	176	43.7	183	47.9	.008	1.87	1.18 to 2.98	.024	1.89	1.09 to 3.27
Missing	2	0.5	1	0.3						
No. of examined lymph nodes										
< 8	188	46.7	167	43.7						
≥ 8	206	51.1	207	54.2	.714	0.92	0.59 to 1.44	.895	0.96	0.56 to 1.66
Missing	9	2.2	8	2.1						
Pathologi nodal status										
ypN0	278	69.0	281	73.6						
ypN+	119	29.5	97	25.4	.818	1.06	0.67 to 1.66	.903	1.04	0.59 to 1.80
Missing	6	1.5	4	1.0						
Venous, perineural, or lymphatic invasion										
No	310	76.9	294	77.0	.568	1.15	0.71 to 1.88	.423	1.28	0.70 to 2.32
Yes	82	20.3	80	20.9						
Missing	11	2.7	8	2.1						

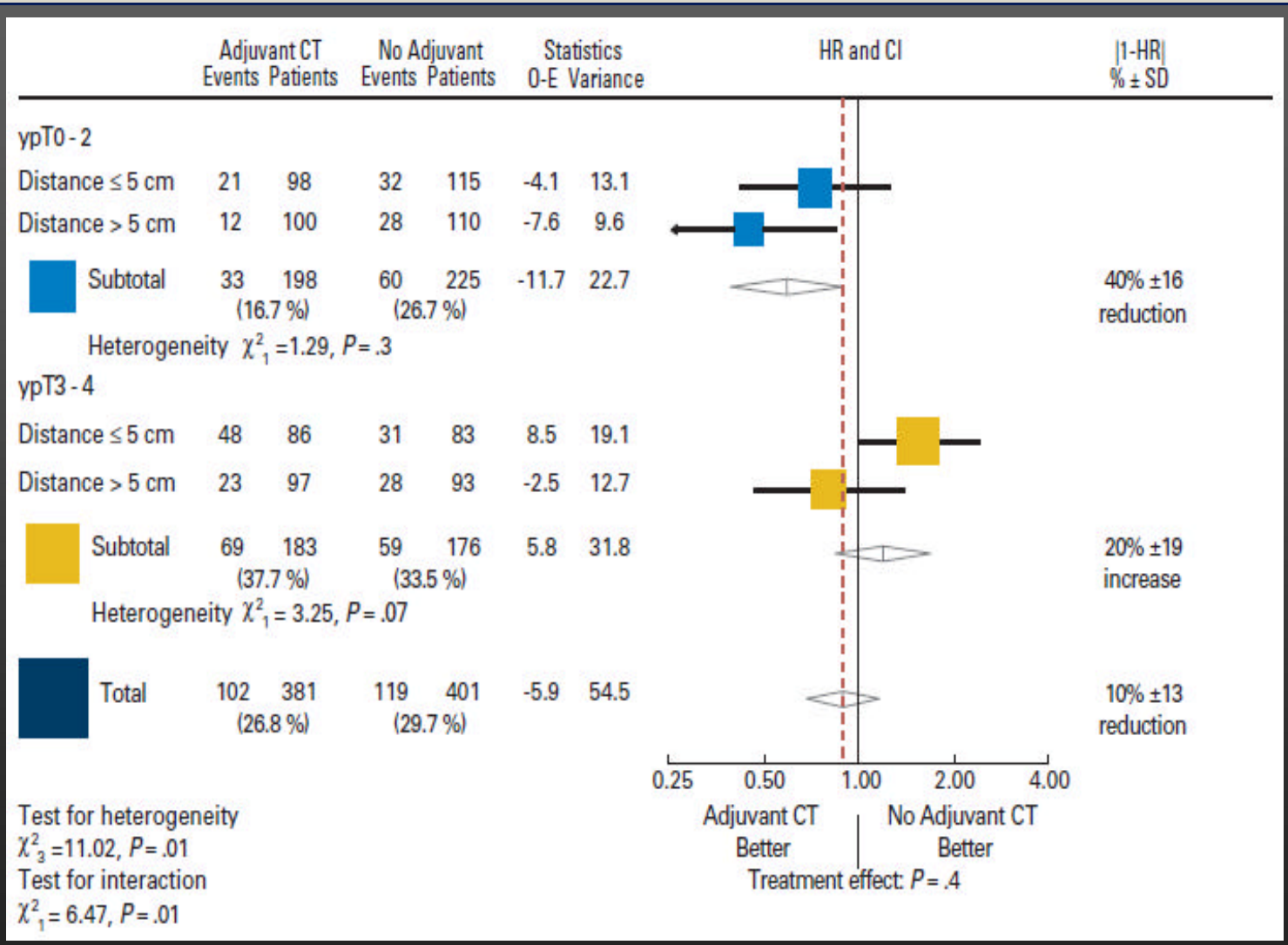
Collette et al., JCO 2007

Other factors: also no difference in benefit

Patient and disease characteristics at study entry										
Age, years										
Median	62.5		63.2							
Range	23.3-79.6		22.0-78.6							
≤ 60	175	43.4	161	42.1						
> 60	228	56.6	221	57.9	.983	1.01	0.64 to 1.58	.969	1.00	0.58 to 1.72
Sex										
Male	295	73.2	285	74.6						
Female	108	26.8	97	25.4	.588	1.16	0.68 to 1.97	.965	1.01	0.52 to 1.98
Distance between tumor and anal verge, cm										
0-5	198	49.1	185	48.4						
> 5	205	50.9	197	51.6	.202	0.75	0.48 to 1.17	.026	0.54	0.31 to 0.93
Clinical T category[3]										
T3	368	91.3	345	90.3						
T4	35	8.7	37	9.7	.757	0.90	0.44 to 1.81	.962	1.02	0.48 to 2.18
Preoperative treatment										
RT	199	49.4	190	49.7						
RT-CT	204	50.6	192	50.3	.763*	1.07	0.69 to 1.67	.482*	1.21	0.71 to 2.06
Worst WHO grade toxicity during preoperative treatment										
0-1	212	52.6	197	51.6						
≥ 2	178	44.2	176	46.1	.764	0.93	0.59 to 1.47	.879	0.96	0.56 to 1.67
Missing	13	3.2	9	2.4						
Surgery										
WHO performance status prior to surgery										
0	294	73.0	242	63.4						
> 0	101	25.1	123	32.2	.984	1.01	0.62 to 1.63	.398	0.78	0.43 to 1.39
Missing	8	2.0	17	4.5						
Time from end of the preoperative treatment to surgery, weeks										
≤ 6	271	67.2	262	68.6						
> 6	132	32.8	120	31.4	.398	0.81	0.50 to 1.32	.283	0.72	0.39 to 1.31
Surgical procedure										
APR	163	40.4	149	39.0						
AR or other	240	59.6	233	61.0	.146	0.72	0.46 to 1.12	.023	0.54	0.32 to 0.92

Collette et al., JCO 2007

EORTC trial: Effect of adjuvant chemotherapy on overall survival



Collette et al., JCO 2007

- “Good prognosis” patients may be retrospectively identified as being those who achieved down-staging by pre-operative treatment

- ypT0-2 (“good prognosis”) patients significantly benefit from post-operative chemotherapy

- Patients with no down-staging (“poor prognosis”) did not benefit of adjuvant CT

- Should these pts. be excluded from chemotherapy ?

- - or should these pts. receive more active chemotherapy ?

Adjuvant chemotherapy: Open questions

Should patients with no downstaging be *excluded* from chemotherapy?

- or should these patients receive *more active* therapy?

What could be regarded as a *standard* in stage II/III rectal cancer after preOP Rtx.?

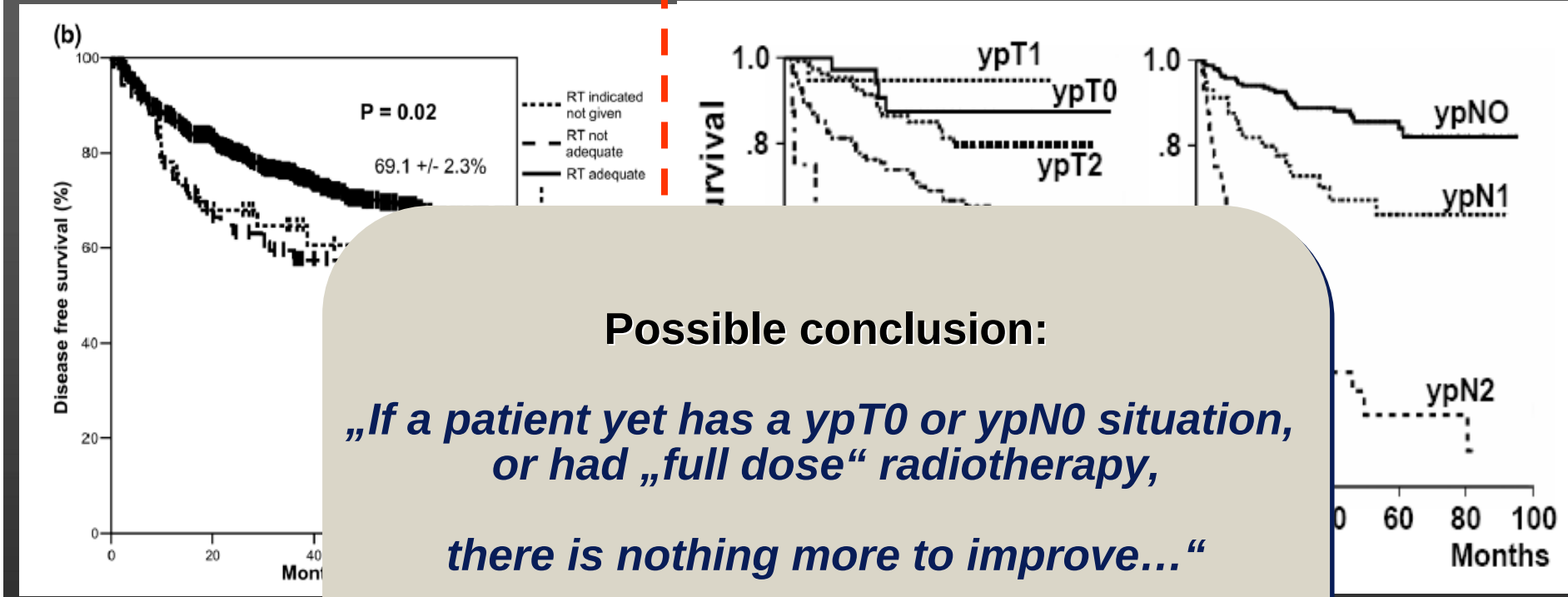
Is rectal cancer *different from colon cancer*?

New questions

- Do all patients need postoperative chemotherapy?

- Do they need „5-FU-only“ chemotherapy
- or more intensive regimen ?

If adjuvant chemotherapy: Are all patients in need of it?



Possible conclusion:

„If a patient yet has a ypT0 or ypN0 situation, or had „full dose“ radiotherapy,

there is nothing more to improve…“

But: most of these patients *had* chemotherapy !

RT Inter

Fietkau et al
Int J Radiol
2006

Rectal Cancer different from Colon Cancer?

- **specific anatomical location:**
- yes, but only a risk for local relapse, not for survival
- **metastatic behavior different:**
- no data demonstrating real difference
- **different sensitivity to chemotherapy:**
- rectal vs colon primary tumor: no sign. difference
- **different biology/gene signature:**
- probably, but not related to clinical behavior,
- chemosensitivity etc.

Which treatment should be administered?

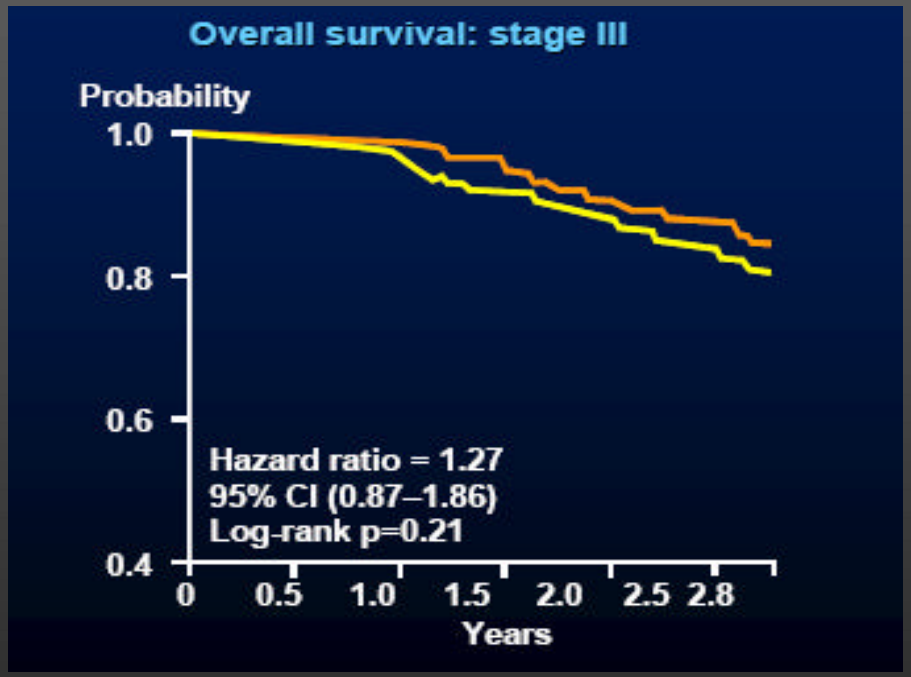
5-FU

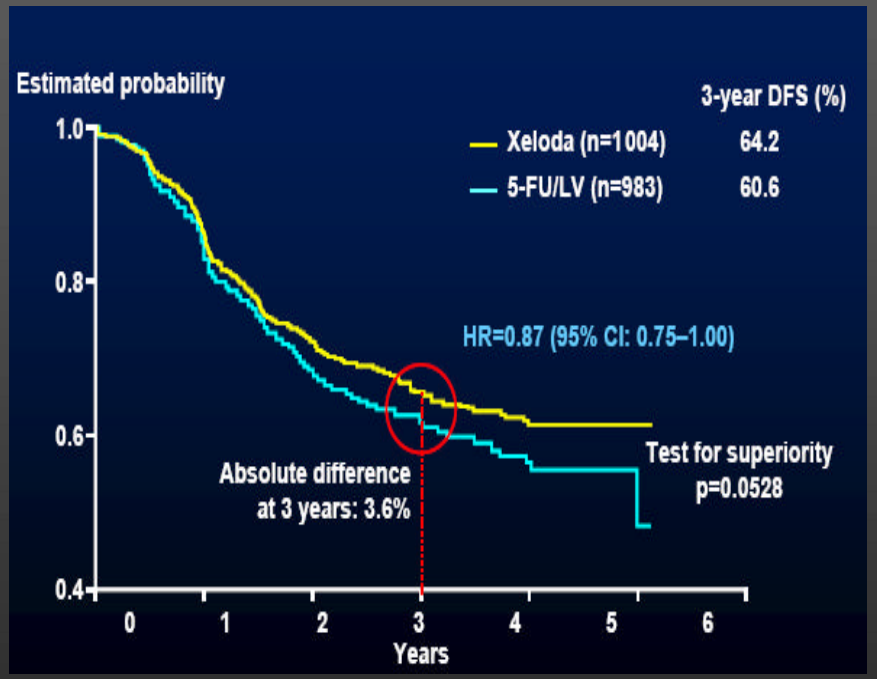
bolus FU/(FA): Standard in post-OP trials

Positive trials: EORTC (trend), Quasar, Japan (with UFT)

Capecitabine may be substitute (-> colon cancer experience)

No Bolus 5-FU in adjuvant therapy of stage III colon cancer anymore





5FU inf / FA

André et al., J Clin Oncol 2003

Capecitabin

Twelves et al., NEJM 2005

Which treatment should be administered?

5-FU

bolus FU/(FA): Standard in post-OP trials

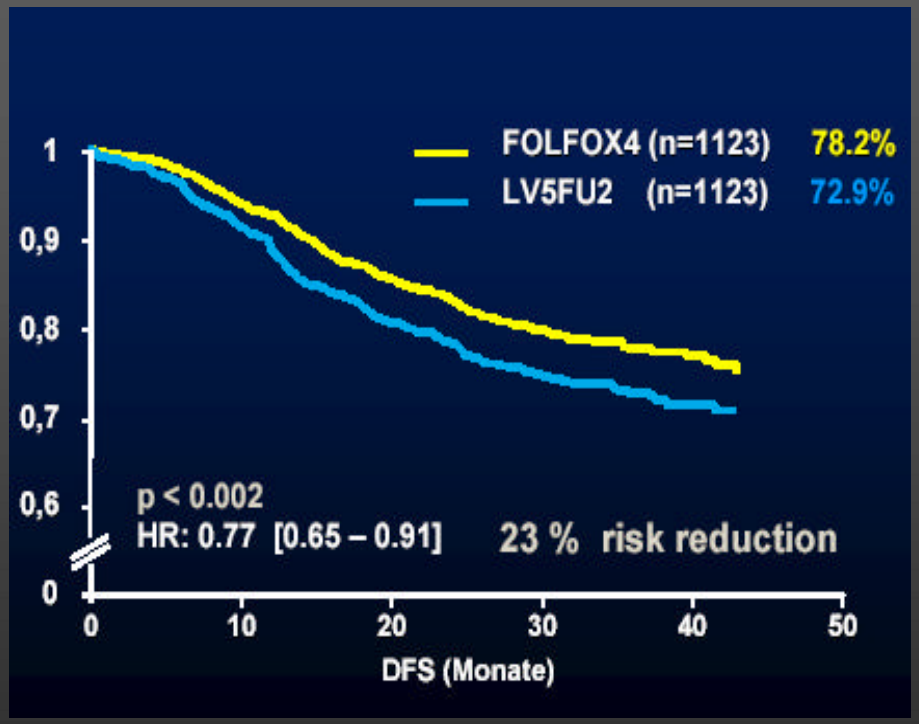
Positive trials: EORTC (trend), Quasar, Japan (with UFT)

Capecitabine may be substitute (-> colon cancer exp.)

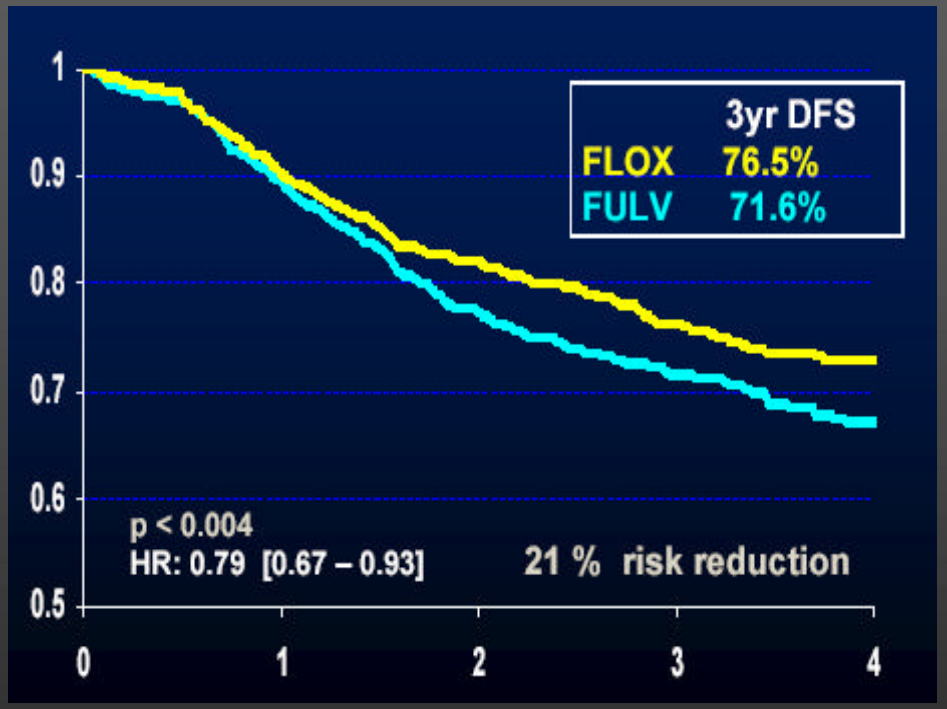
5-FU/ Oxaliplatin

Standard in colon cancer stage III/(II)

Colon cancer stage II/III:
Oxaliplatin combinations > FU/FA



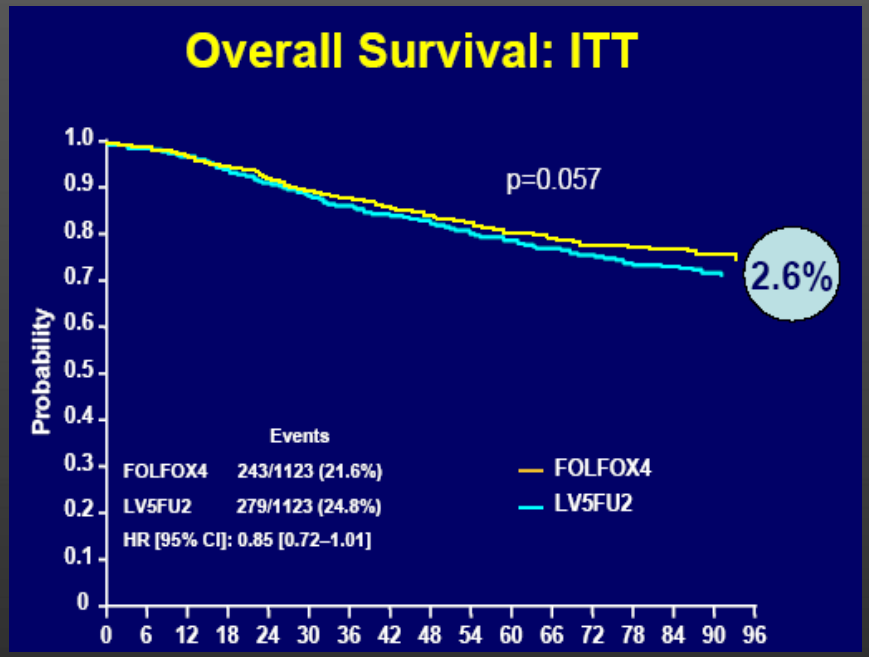
MOSAIC

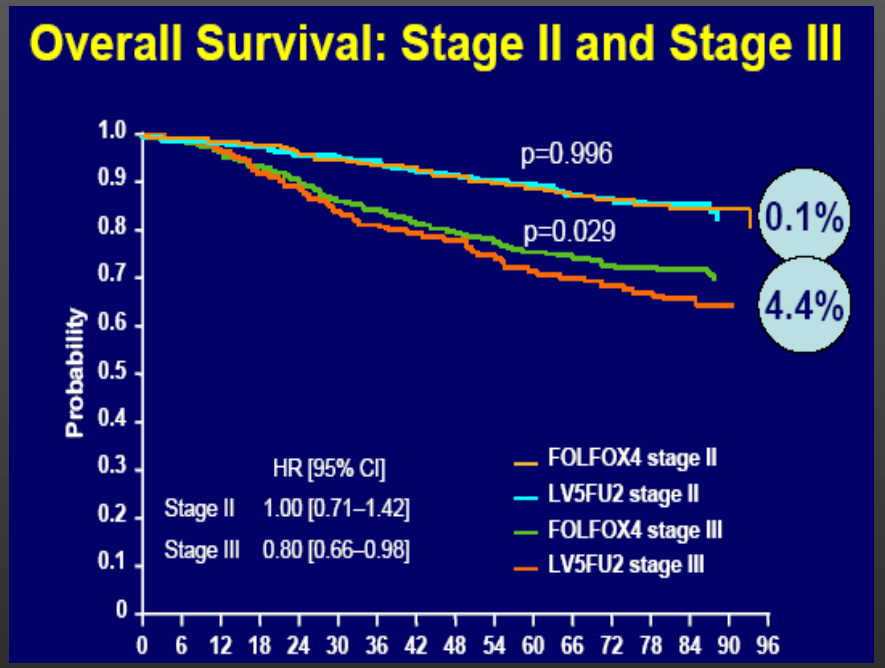


NSABP C07

André T et al., NEJM, 2004; Wolmark N et al., ASCO 2005

Recent Overall Survival Data: Supporting Oxaliplatin Combinations





De Gramont et al., ASCO 2007

Which treatment should be administered?

5-FU

bolus FU/(FA): Standard in post-OP trials

Positive trials: EORTC (trend), Quasar, Japan (with UFT)

Capecitabine may be substitute (-> colon cancer exp.)

5-FU/ Oxaliplatin

Standard in colon cancer stage III/(II)

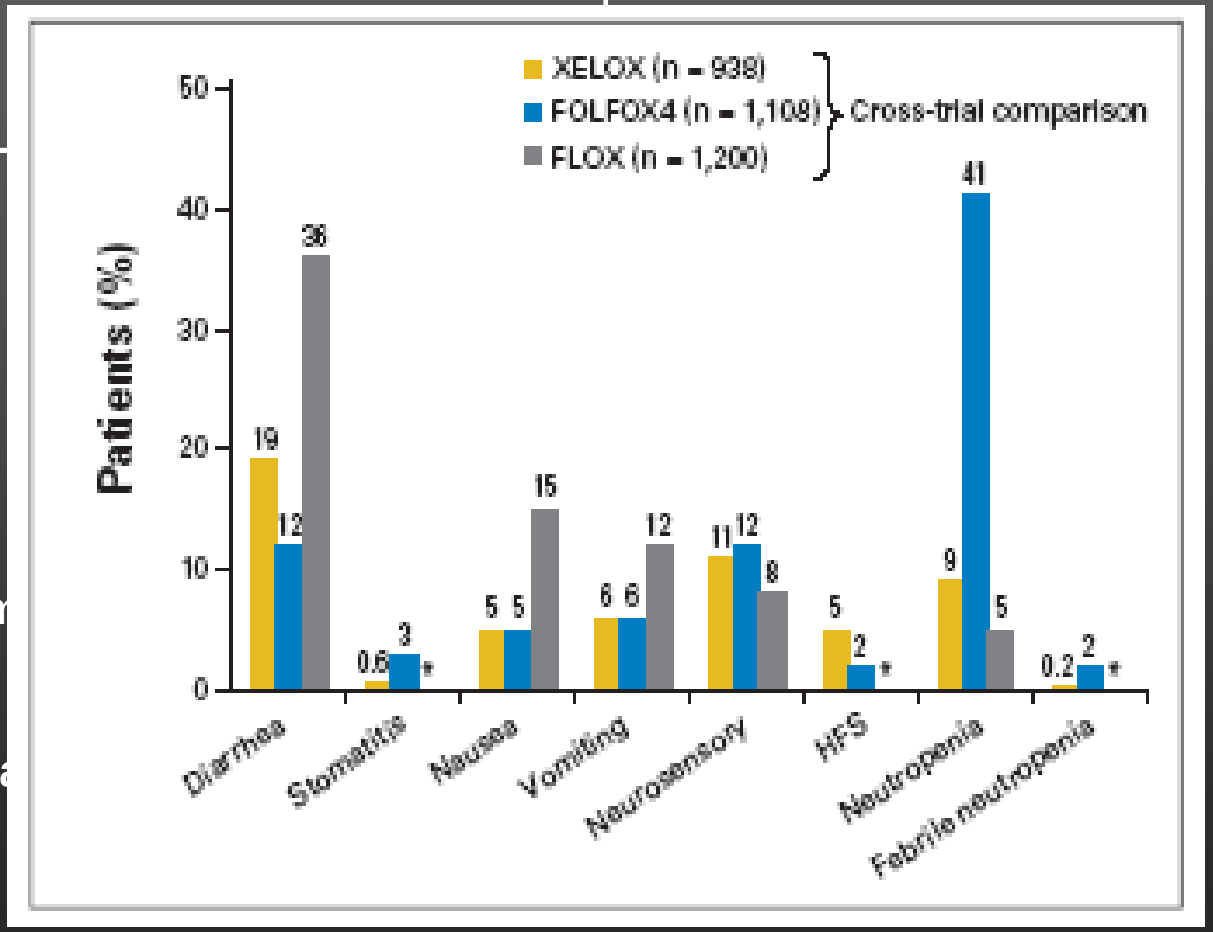
Capecitabine / Oxaliplatin

well tolerated, effective

experience in colon (XELOX) and rectum (CORE, German)

Grade 3/4 AEs: XELOX vs bolus 5-FU/LV (total, Mayo and RP regimens)

% of patients with grade 3/4 AE*
Diarrhoea
Stomatitis
Nausea
Vomiting
Neurosensory**
Hand-foot syndrom
Neutropenia
Febrile neutropenia



Schmoll et al., JCO 2007

Pre- and post-OP chemotherapy with XELOX

- AIO/ARO/CAO trial (n=110, J Clin Oncol 2007)
- CORE trial (n= 93, ASCO 2006)

  - Post-operative combination with capecitabine and oxaliplatin is feasible
  - No increased perioperative complications when started after 4 weeks postoperatively or later

Rutten ASCO 2006; Rödel, Arnold et al., J Clin Oncol 2007

XELOX pre- and postoperatively in rectal cancer: Phase II trial

	preOP chemorad		postOP adjuvant	
	Grade 1,2	Grade 3,4	Grade 1,2	Grade 3,4
Leukopenia	50	4	67	1
Diarrhea	55	12	33	12
Nausea	48	6	67	7
Stomatitis	7	1	7	0
Hand-Foot-syndrome	8	1	34	1
Infection	6	3	7	2

Rödel, Arnold et al., J Clin Oncol 2007

Which treatment should be administered?

5-FU

bolus FU/(FA): Standard in post-OP trials

Positive trials: EORTC (trend), Quasar, Japan (with UFT)

Capecitabine may be substitute (-> colon cancer exp.)

5-FU/ Oxaliplatin

Standard in colon cancer stage III/(II)

Capecitabine / Oxaliplatin

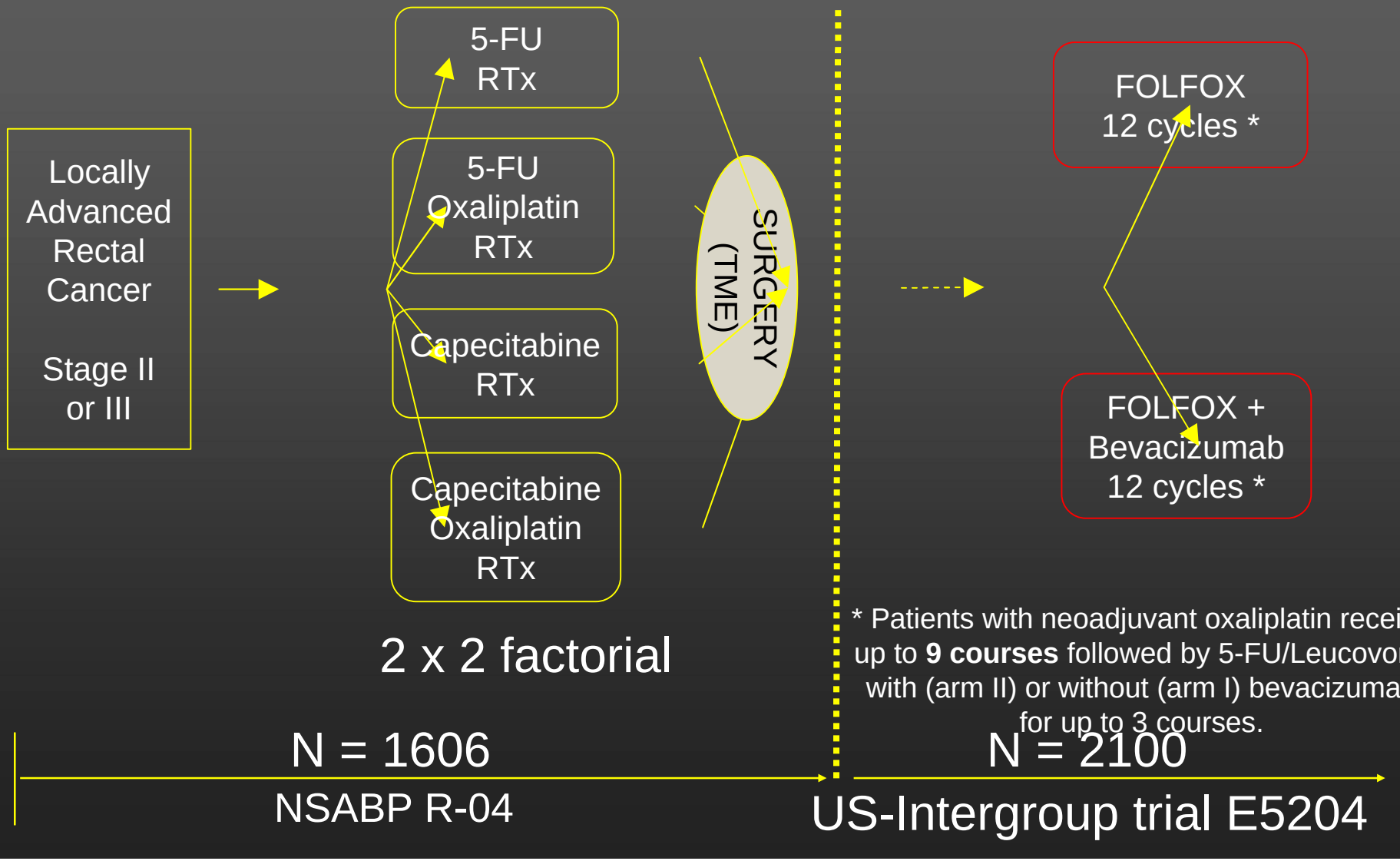
well tolerated, effective

experience in colon (XELOX) and rectum (CORE, German)

„Targeted drug“ combinations

FOLFOX or XELOX with bevacizumab or cetuximab feasible

NSABP US-Intergroup Trial - Rectal Cancer



More data in favour of chemotherapy!

5-FU

bolus FU/(FA): Standard in post-OP trials

Positive trials: Quasar, Japan (with UFT), EORTC (subgr.)

Capecitabine may be substitute (-> colon cancer exp.)

5-FU/ Oxaliplatin

Standard in colon cancer stage III/(II)

Capecitabine / Oxaliplatin

well tolerated, effective

experience in colon (XELOX) and rectum (CORE, German)

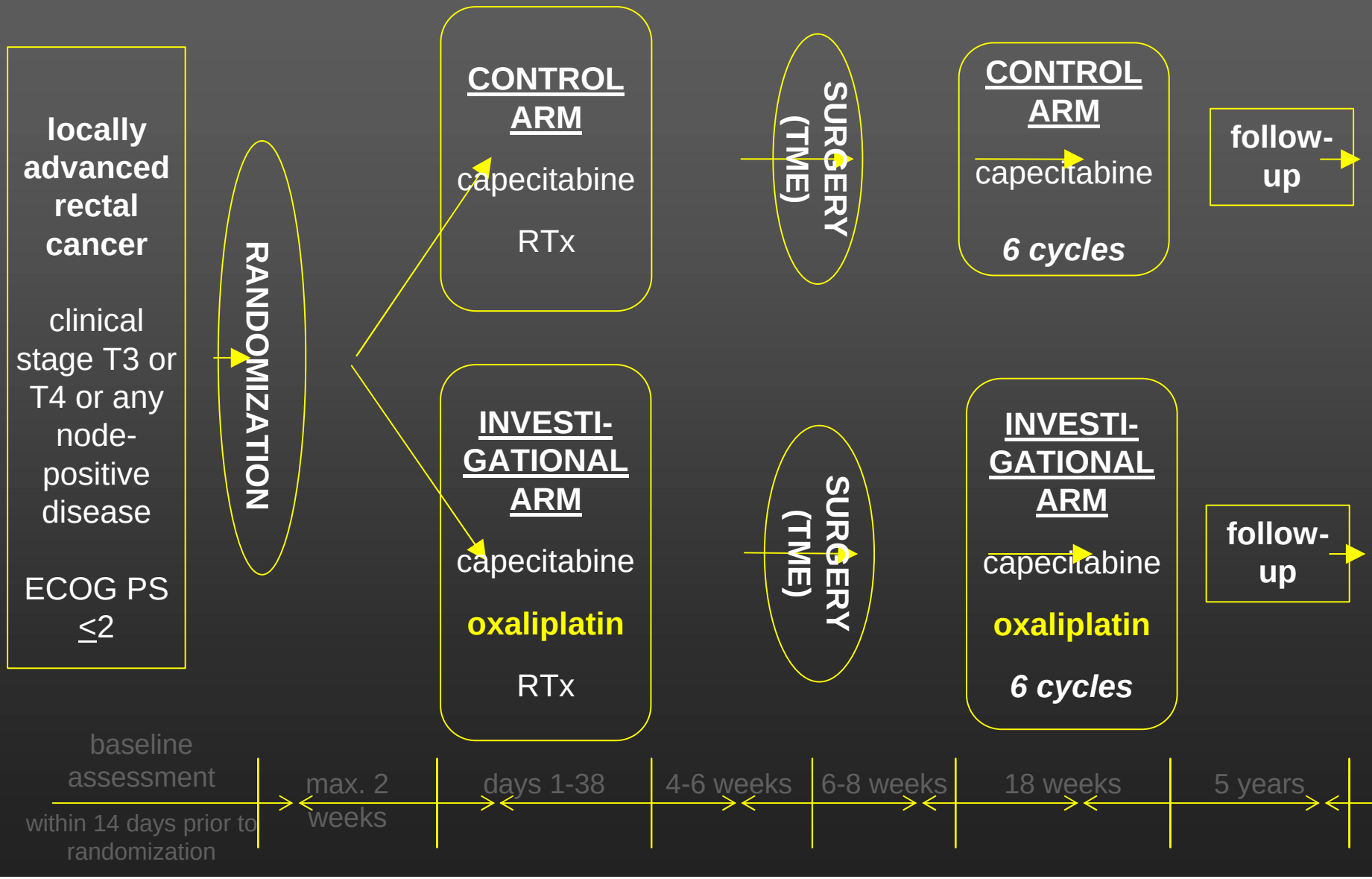
„Targeted drug“ combinations

FOLFOX or XELOX with bevacizumab or cetuximab feasible

PETACC-6
EORTC 40054-22062

Preoperative chemoradiotherapy and postoperative chemotherapy
with capecitabine and oxaliplatin
vs. capecitabine alone
in locally advanced rectal cancer

Treatment Arms in PETACC-6



Endpoints

Primary:

Disease-free survival (+7% at 3 years), defined as the interval from randomization to loco-regional failure, metastatic recurrence, the appearance of a secondary colorectal cancer or death, whichever occurs first. Loco-regional failure is defined as local or regional recurrence, inoperable disease, R1 or R2 resection.

Secondary:

Overall survival

Pathological downstaging (ypT0-T2N0) rate

Pathological complete remission rate

Histopathological R0 resection rate

Tumor regression grading

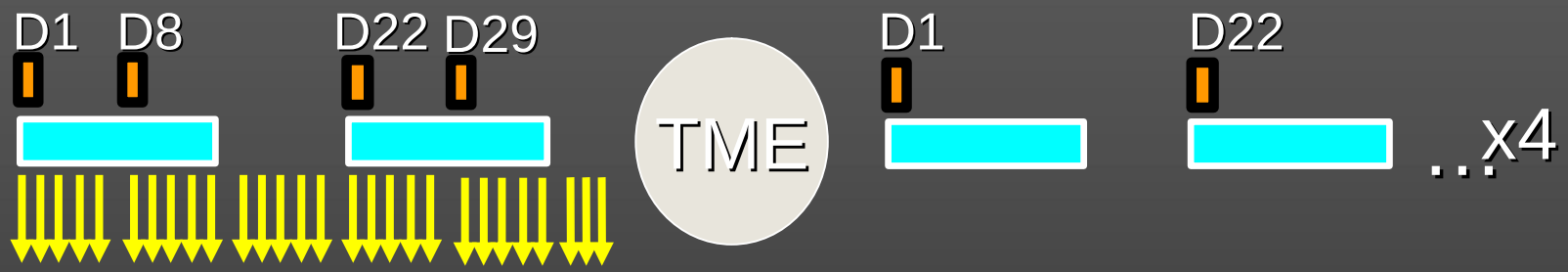
Sphincter preservation rate

Perioperative surgical complication rate

Toxicity

Loco-regional failure rate

German Multicenter Phase-II Study



Oxaliplatin: 50 mg/m²

Capecitabine: 1650 mg/m²/d

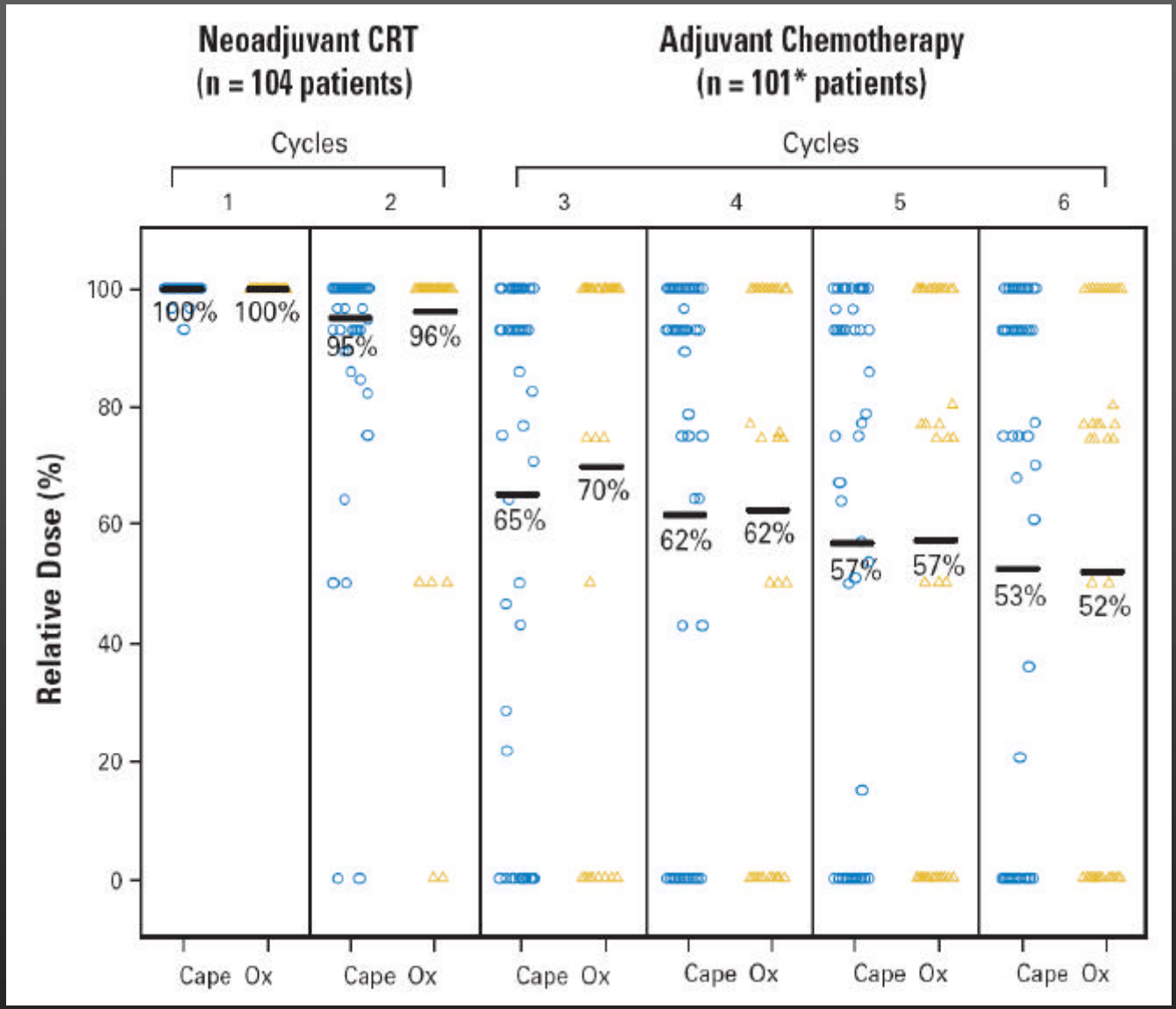
RT: 1.8 Gy to 50.4 Gy

Oxaliplatin: 130 mg/m²

Capecitabine: 2000 mg/m²/d

Rödel et al. JCO 2007

Mean relative dose-intensities



Rödel et al. JCO 2007

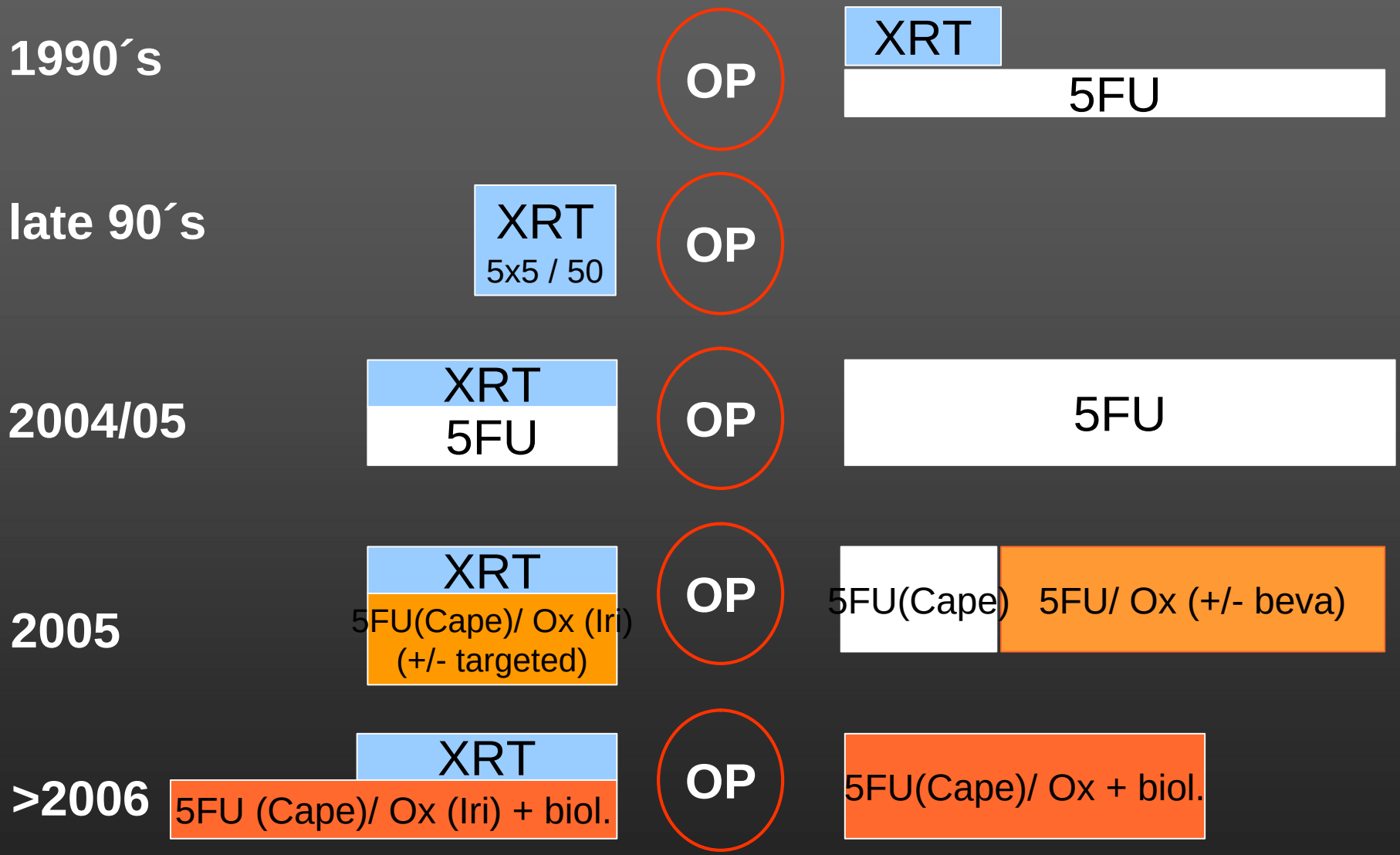
Main eligibility criteria

- Histologically proven adenocarcinoma of the rectum
- (tumour = 12 cm from the anal verge)
- cT3/4 or N+
- No evidence of metastatic disease
- No prior radiotherapy to the pelvis, for any reason
- The disease must be considered either resectable at the time of entry or thought to become resectable after preoperative chemoradiation
- ECOG Performance Status = 2
- No peripheral neuropathy = grade 2

Organisation

- Sponsor/Database: EORTC
- Leading group is the EORTC GI Group
- Investigator fee of approximately 500€ per patient
- Capecitabine and oxaliplatin will be supplied free of charge
- Telefone Monitoring

Evolution of rectal cancer approaches



Preoperative Regimens

	Control arm	Investigational arm
Capecitabine	825 mg/m^2 PO BID on days 1-33 w/o weekends	825 mg/m^2 PO BID on days 1-33 w/o weekends
Oxaliplatin		50 mg/m^2 IV on days 1, 8, 15, 22 & 29
Radiation	45 Gy, 1.8 Gy on days 1-33 w/o weekends **Optional:** 5.4 Gy day 36-38 with capecitabine 825 mg/m^2 PO BID *	45 Gy, 1.8 Gy on days 1-33 w/o weekends **Optional:** 5.4 Gy day 36-38 with capecitabine 825 mg/m^2 PO BID *

* Centres have to choose one option and adopt it for both arms for the entire study.

Postoperative Regimens

Control arm	Investigational arm
6 cycles of: Capecitabine 1000 mg/m^2 PO BID on days 1 to 14	**6 cycles of:** Capecitabine 1000 mg/m^2 PO BID on days 1 to 14 Oxaliplatin 130 mg/m^2 IV on day 1
Start next cycle on day 22 !	***Start next cycle on day 22 !***

Translational Research

- **GENEPI-2 – participation as a trial with a central storage of blood and tissue**
- **Pharmacogenomics studies related to capecitabine, or oxaliplatin.**
- **Immunohistochemical expression relevant biological markers in tumour tissue and gene expression arrays**
- **Proteomic analyses**
- **Blood/Tissue collection for further research.**

Organisation

- **Sponsor/Database: EORTC**
- **Leading group is the EORTC GI Group**
- **Investigator fee of 458€ per patient**
- **Capecitabine and oxaliplatin will be supplied free of charge**

Potential interests

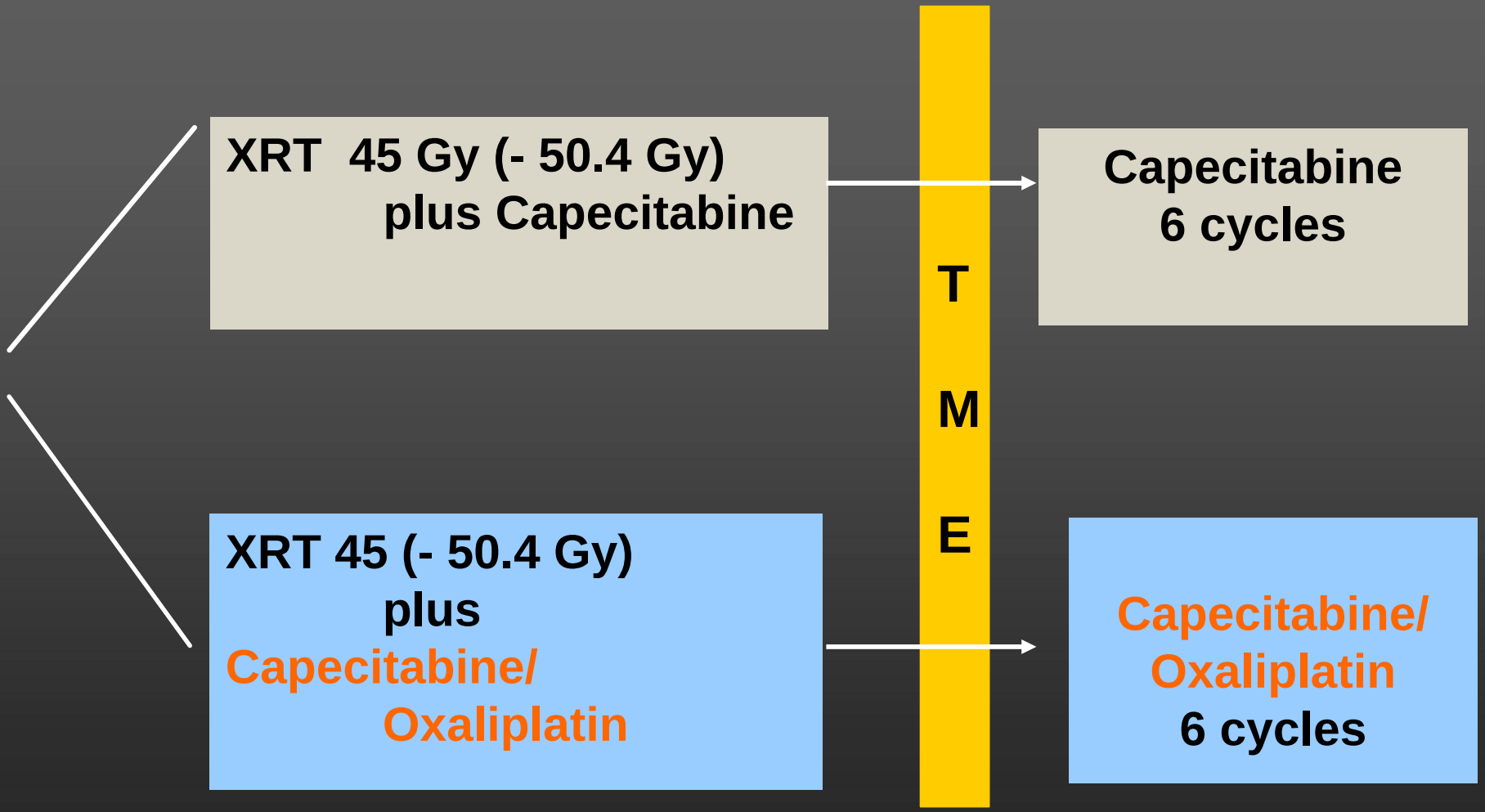
Country / group	annual pts.
Australia	50-100
Austria	70
Belgium	80-100
Canada	100
Egypt	30-50
France FFCD/GERCOR	100-200?
Germany	1037-1220
Hungary	30-50
Israel	35
Italy	10

Country / group	annual pts.
Netherlands	<20?
Poland	50-100
Serbia and Montenegro	60
Slovenia	15
Sweden	30-50
Switzerland	17
Turkey	8
UK	150-200
total	**1872-2285**
EORTC GI (overlapping)	**368**

Study Coordinators

- Chemotherapy: Hans-Joachim Schmoll
  (Chair Steering Committee)
- Radiotherapy: Karin Haustermans
- Surgery: Christophe Penna

PETACC-6 trial: T3,4 or N+ (N=1120)



Endpoint: Disease free survival after 3 years (6%)

Possible role of chemotherapy in rectal cancer

In addition to perioperative radiotherapy:

enhance efficacy of radiation

Þ improve local control

enable resection and sphincter preservation

Adjuvant systemic therapy - after perioperative (chemo)radiation

eradicate micrometastasis

Þ reduce rate of distant relapse

Before perioperative chemoradiation

reduce local tumor size and eradicate micrometastases

Neoadjuvant chemotherapy as first modality

Spanish trial

FOLFOX	RT: UFT/FA	OP	

Chau, Cunningham et al. (poor risk, JCO 2006)

XELOX	RT: FU	OP	XELOX

UK trial

FOLFOX - Cetux	RT: FU - Cetux	OP	

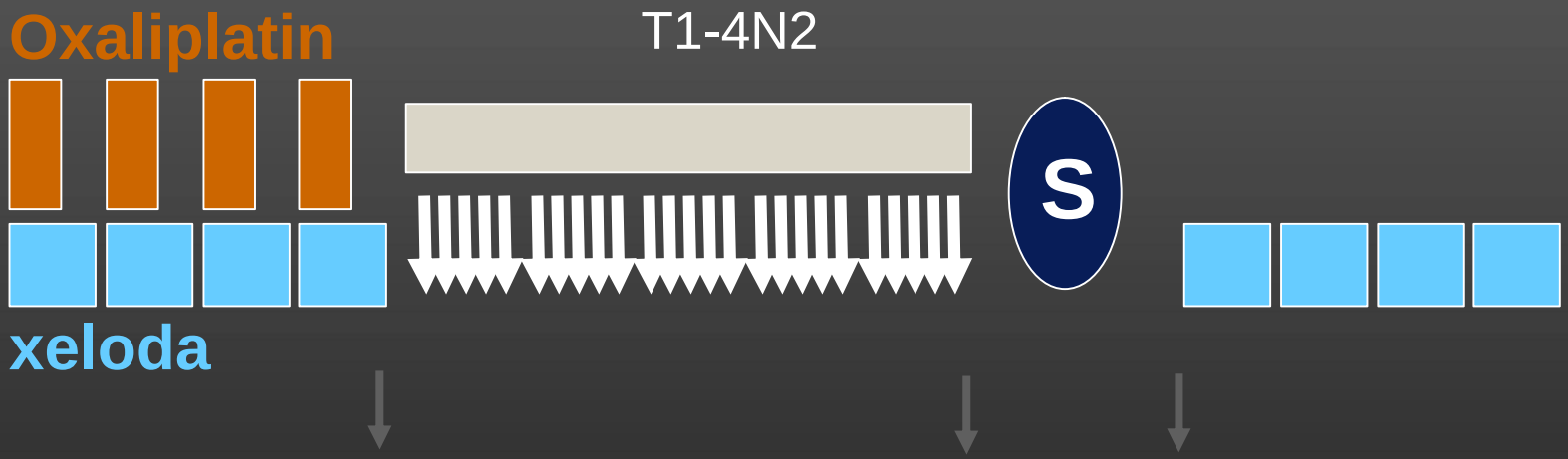
US ACSOG

→	RT: CapOx	OP	→ CapOx
CapOx →	RT: CapOx	OP	

Neadjuvant XELOX followed by Chemoradiation
in MRI-defined Poor-Risk Rectal Cancer

Poor Risk: = 5mm into perirectal fat
or = 1mm to mesorectal fascia

T3 at or below levators
T1-4N2



n=77 **CR+PR: 88%** **CR+PR: 97%** **pCR: 24%**

Chau et al. J Clin Oncol 2006