Update 2006: Magen- und Ösophaguskarzinom

Priv.-Doz. Dr. Peter Reichardt

Berlin

CHARITÉ CAMPUS BUCH

CHARITÉ CAMPUS VIRCHOW-KLINIKUM

Ösophaguskarzinom

Ösophagus – neoadjuvant – Radiochemo +OP vs OP alleine
Tepper, Baltimore, abstr 4012

CALGB 9781 (aktiviert Juli 1998):

Statistik: 475 Pat um Steigerung 5yrOS von 20% auf 32% festzustellen

Chemo: Cisplatin 100mg/m^2, 5-FU 1g/m^2 d1-4, d1+d29

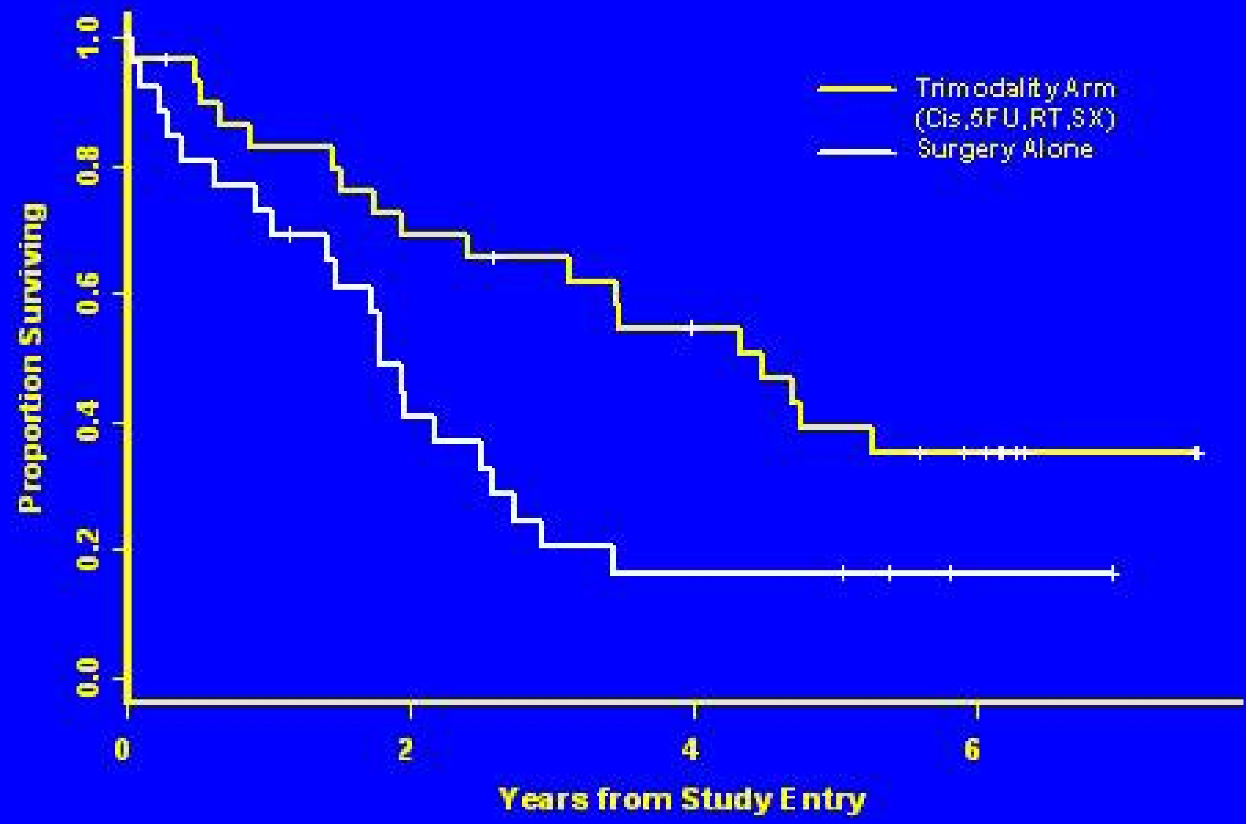
Radiatio: 50,4 Gy, Boost 5,4 Gy

Ergebnisse:

vorzeitig beendet

n= 56, 42 Adeno, 14 Plattenepithel-Ca

Ösophagus – neoadjuvant – Radiochemo +OP vs OP alleine
Tepper, Baltimore, abstr 4012



Ösophagus – neoadjuvant – Radiochemo +OP vs OP alleine

Diskussion

Randomisierte Studien mit neoadjuvanter Radiochemo (Cis/FU-basiert)

Studie	Histo	Behandlg	n	path CR %	3 yr OS
Urba	Adeno +	OP	50		16%
	Plattenep	+präop Chemo + 45 Gy	50	28	30%
Walsh	Adeno	OP	55		6%
		+präop Chemo +40 Gy	58	25	32% sign

Ösophagus – neoadjuvant – Radiochemo +OP vs OP alleine

Diskussion

A.Forastiere

Conclusion

- An adequately powered randomized trial with a surgery control arm will not be undertaken again in the US
  - Overall survival benefit is likely on the order of 10-15%

Ösophagus – resektabel Radiatio vs Chirurgie
Yu et al, China., abstr 4013

Moderne Radiatio: „late course accelerated hyperfractionation,

3D CRT & IMRT“

45 Gy konventionelle Radiatio,

gefolgt von 24 Gy hyperfraktionierter Radiatio

(=68 Gy Gesamtdosis)

Plattenepithel-Ca, resektabel, keine palpablen LK-Metastasen

n=269 Pat.

Ösophagus – resektabel Radiatio vs Chirurgie
Yu et al, China., abstr 4013

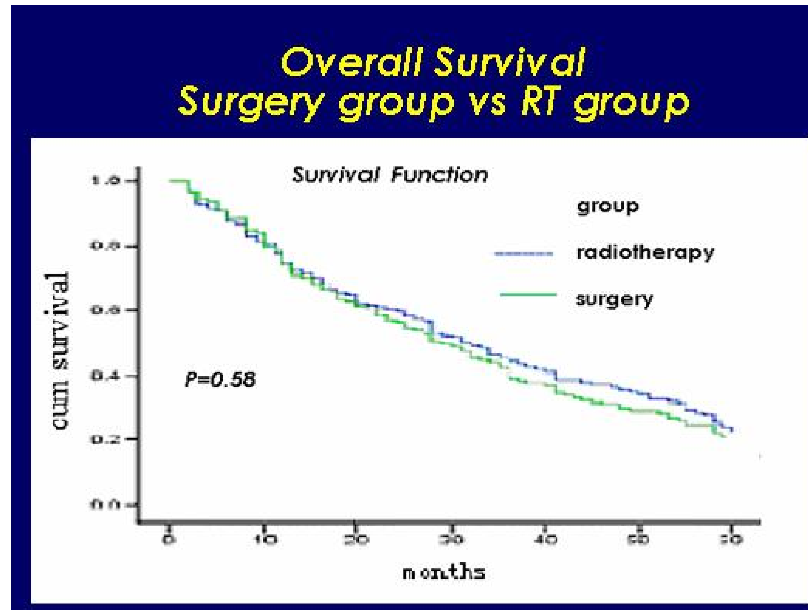
Ergebnisse:

gleiches Gesamtüberleben

gleiche PFS

Radiatio signifikant mehr Lokalrezidive

Chirurgie signifikant mehr lokale LK-Metastasen



Ösophagus – resektabel Radiatio vs Chirurgie
Yu et al., abstract 4013

Diskussion

A.Forastiere

- Radiochemo ist Radiatio überlegen (5yrOS 26% vs 0%) [Herskovic, NEJM 1992]
- Aktuelle Studie überprüft Stellenwert moderner Radiatio
- Radiochemotherapie ist der Standard bei Verzicht auf OP
- Vergleich Radiochemo versus OP logischer nächster Schritt

2 randomisierte Studien Radiochemo +OP vs alleinige Radiochemo

Stahl JCO 2005

Bedenne ASCO 2002:

- therapiebedingte Todesfälle höher bei OP
- Lokale Kontrolle besser bei OP
- OS gleich

Ösophagus – resektabel - Therapieempfehlung

Neoadjuvante Therapie + Operation bleibt Standard (ab Stadium IIb)

Neoadjuvant:

Plattenepithel-CA: Radiochemo Cisplatin/5-FU + 45-52Gy + OP (USA)

Urba JCO 2001, Walsh NEJM 1996

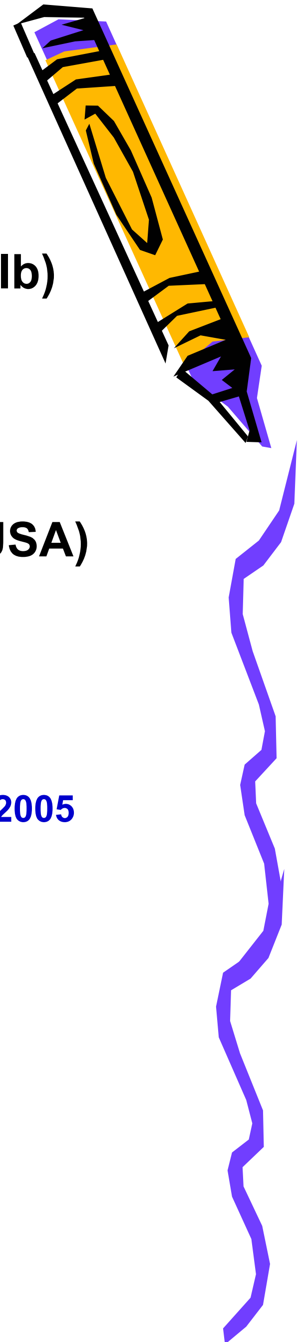
Adeno-Ca: Chemo ECF + OP + ECF (UK)

MRC, Lancet 2002, Cunningham ASCO 2005

Insbesondere bei Plattenepithel-CA:

alleinige Radiochemo kann erwogen werden

Stahl, JCO 2005, Bedenne ASCO 2002



Magenkarzinom

Magen – adjuvant – OP + ELFE vs OP

De Vita, Neapel, abstr. 4014

Chirurgie + ELFE vs Chirurgie

n=228, Stadium IB-IIIB, D1-Resektion

Etoposid, Leukovorin, 5-FU, Epirubicin

Ergebnis:	**5yrOS**	**48% vs 43,5%**	**(p=0,610)**
	5yr DFS	**44% vs 39%**	**(p=0,305)**
	Trend bei positiven LK		**(p=0,068)**

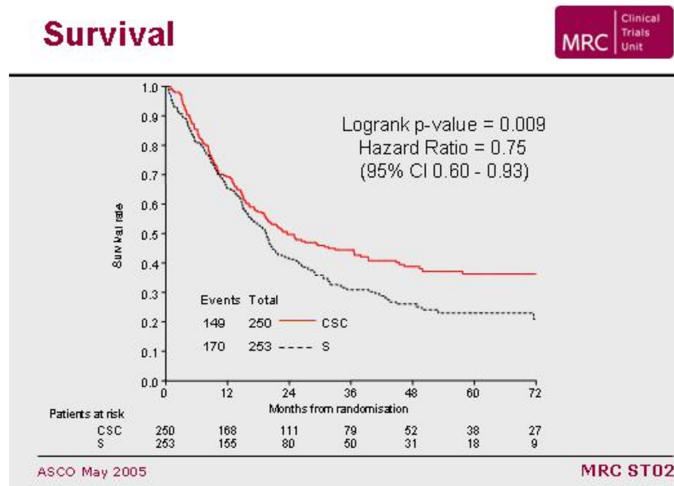
Fazit: **Keine Verbesserung des Überlebens**

Magen – adjuvant - Therapieempfehlung:

USA (ab Stadium IB): adjuvante Radiochemotherapie

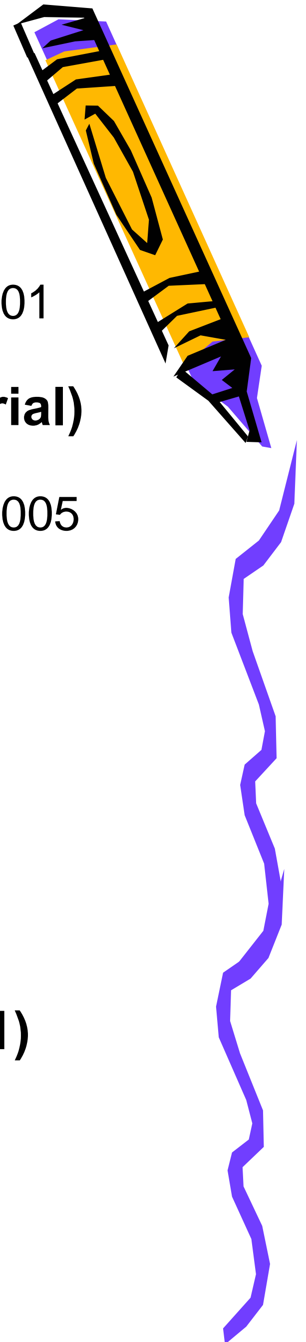
Macdonald NEJM 2001

Europa (ab Stadium II): 3x ECF → OP → 3x ECF (MAGIC-Trial)



Cunningham ASCO 2005

Europa: bei ausgedehnt LK-resizierten Pat (mindestens D1) ist adjuvante Therapie kein Standard



REAL 2: 2 x 2 randomisation

	ECF		ECX
E	Epirubicin 50 mg/m^2 iv	E	Epirubicin 50 mg/m^2 iv
C	Cisplatin 60 mg/m^2 iv	C	Cisplatin 60 mg/m^2 iv
F	PVI 5-FU 200 mg/m^2/d*	X	Capecitabine 625 mg/m^2/bd
	q 3 weeks		q 3 weeks

	EOF		EOX
E	Epirubicin 50 mg/m^2 iv	E	Epirubicin 50 mg/m^2 iv
O	Oxaliplatin 130 mg/m^2 iv	O	Oxaliplatin 130 mg/m^2 iv
F	PVI 5-FU 200 mg/m^2/d*	X	Capecitabine 625 mg/m^2/bd
	q 3 weeks		q 3 weeks

Planned treatment duration 24 weeks (8 cycles)

CT scan baseline, 12 weeks and 24 weeks

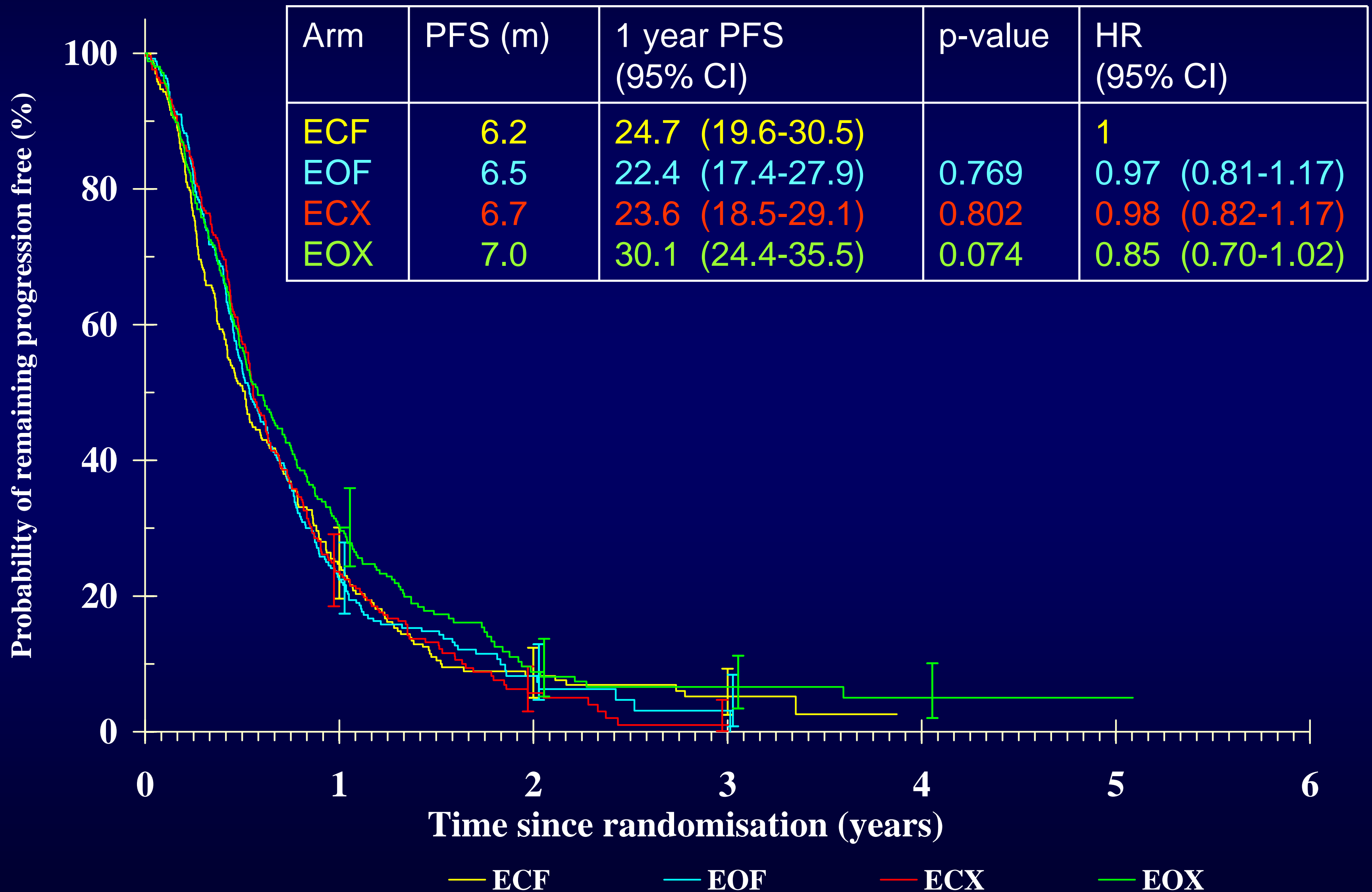
* PVI 5FU delivered by central venous access catheter

Cunningham et al., ASCO 2006, LBA4017

Best overall Response

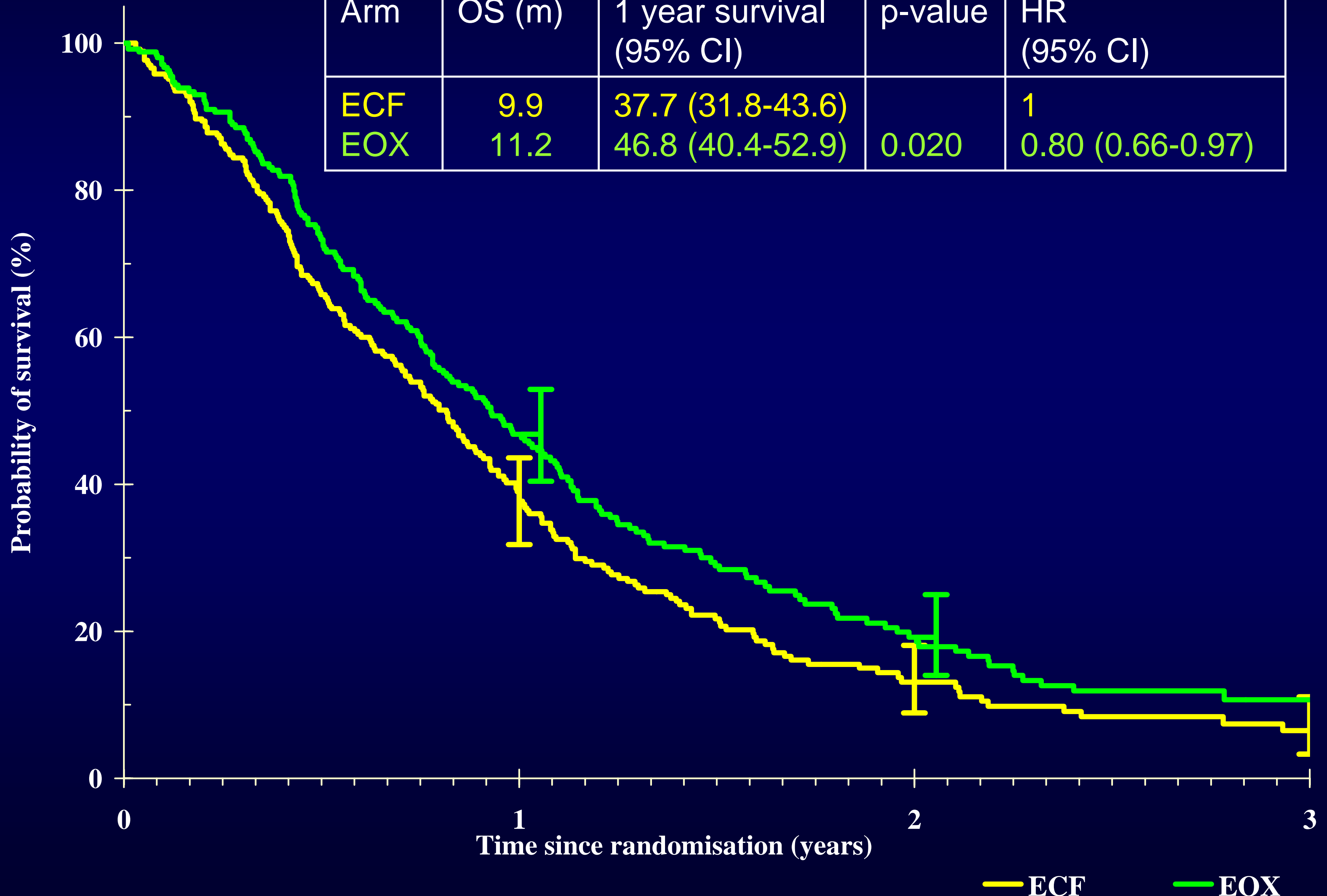
Response (%)	ECF n=249	ECX n=241	EOF n=235	EOX n=239
Evaluable	246	237	231	234
CR PR	4.1% 36.6%	4.2% 42.2%	2.6% 39.8%	3.9% 44.0%
CR + PR 95% CI p-value vs ECF	**40.7%** (34.5-46.8)	**46.4%** (40.0-52.8) 0.202	**42.4%** (36.1-48.8) 0.694	**47.9%** (41.5-54.3) 0.112
SD	31.3%	32.1	15.2%	27.8%
PD or died	28.0%	21.5%	24.7%	24.4%

Progression-free survival (ITT)



Arm	PFS (m)	1 year PFS (95% CI)	p-value	HR (95% CI)
ECF	6.2	24.7 (19.6-30.5)		1
EOF	6.5	22.4 (17.4-27.9)	0.769	0.97 (0.81-1.17)
ECX	6.7	23.6 (18.5-29.1)	0.802	0.98 (0.82-1.17)
EOX	7.0	30.1 (24.4-35.5)	0.074	0.85 (0.70-1.02)

Survival by Regimen ECF vs EOX (ITT)



Arm	OS (m)	1 year survival (95% CI)	p-value	HR (95% CI)
ECF	9.9	37.7 (31.8-43.6)		1
EOX	11.2	46.8 (40.4-52.9)	0.020	0.80 (0.66-0.97)

Study Design

Measurable metastatic or locally advanced gastric or EGJ adenocarcinoma
Age ≥ 18 years old
ECOG PS ≤ 2
Adequate hematological and biochemical parameters
Signed written informed consent

RANDOMIZE

FLO
Oxaliplatin(85mg/m²) +
FA (200mg/m²) +
5-FU (2600mg/m²) 24h
d1,15,29,43; qd57

Pharmacogenomics / tumor infiltrating T-cells/ EGFR

FLP
Cisplatin (50 mg/m²) d 1, 15, 29; +
FA (200mg/m²) 2h +
5-FU (2000mg/m²) d 1, 8,15, 22, 29, 36;
qd50

- Tumor assessments planned every 6 weeks in both arms
- Cycles repeated until progression or limiting toxicity

Al-Batran et al., ASCO 2006, LBA4016

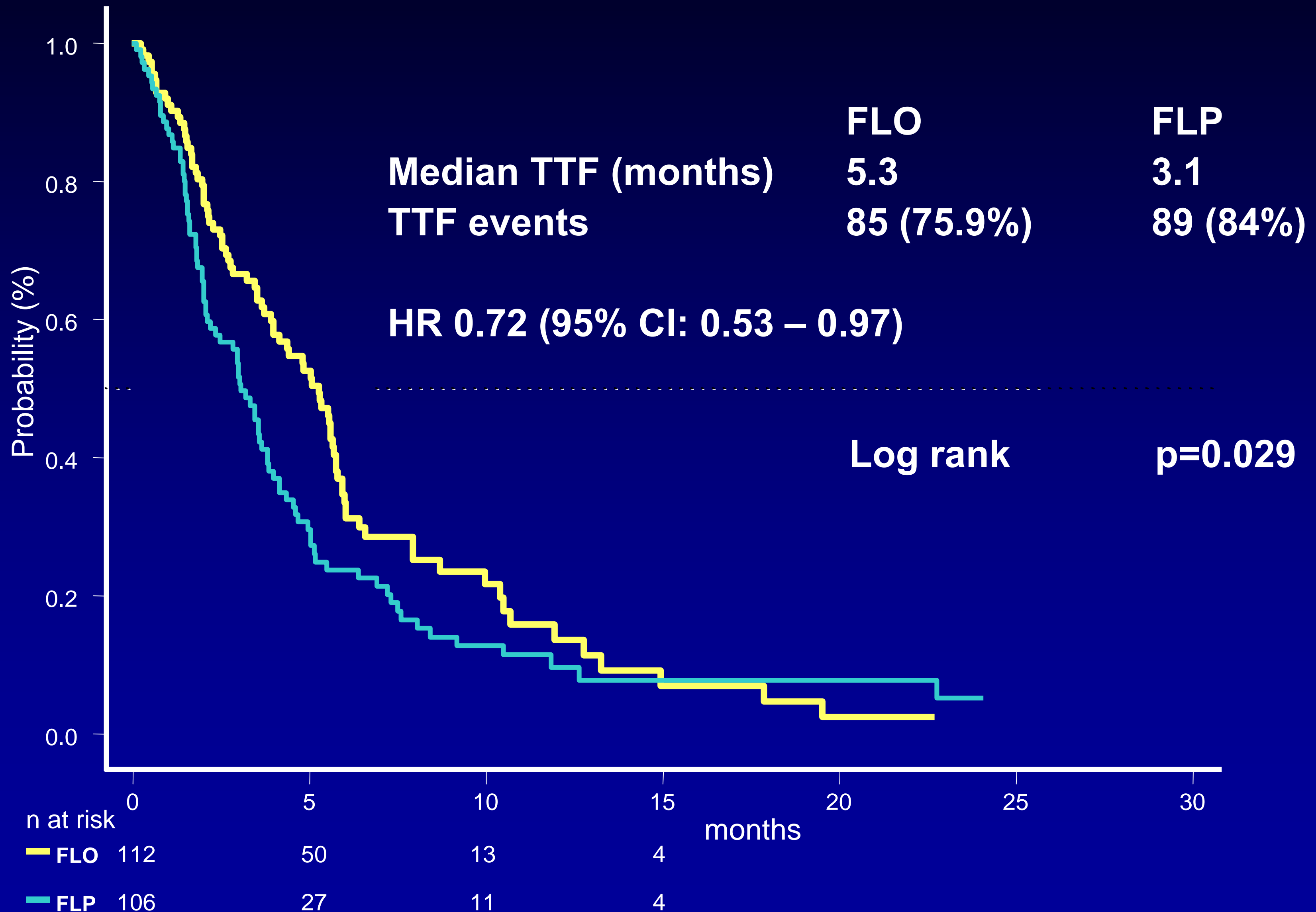
Best Overall Response (ITT)

	FLO n=112	FLP n=106
CR	4 (4%)	-
PR	34 (30%)	27 (25%)
RR	38 (34%)	27 (25%)
95% CI	[25 – 43%]	[18 – 35%]
SD	46 (41%)	33 (31%)
PD	17 (15%)	32 (30%)
NE	11 (10%)	14 (13%)

NE, non-evaluable

p=0.0072 (chi-square for trend)

Time to Treatment Failure (ITT)



XP vs. FP in advanced gastric cancer: trial design

KPS ≥70%

18–75 years

Advanced and/or metastatic gastric cancer (AGC)

≥1 measurable lesion

No prior treatment for AGC

RANDOMIZATION

FP

Cisplatin

80 mg/m² 3-hour i.v. infusion

5-FU c.i.

800 mg/m²/day; d1–5 q3w

XP

Cisplatin

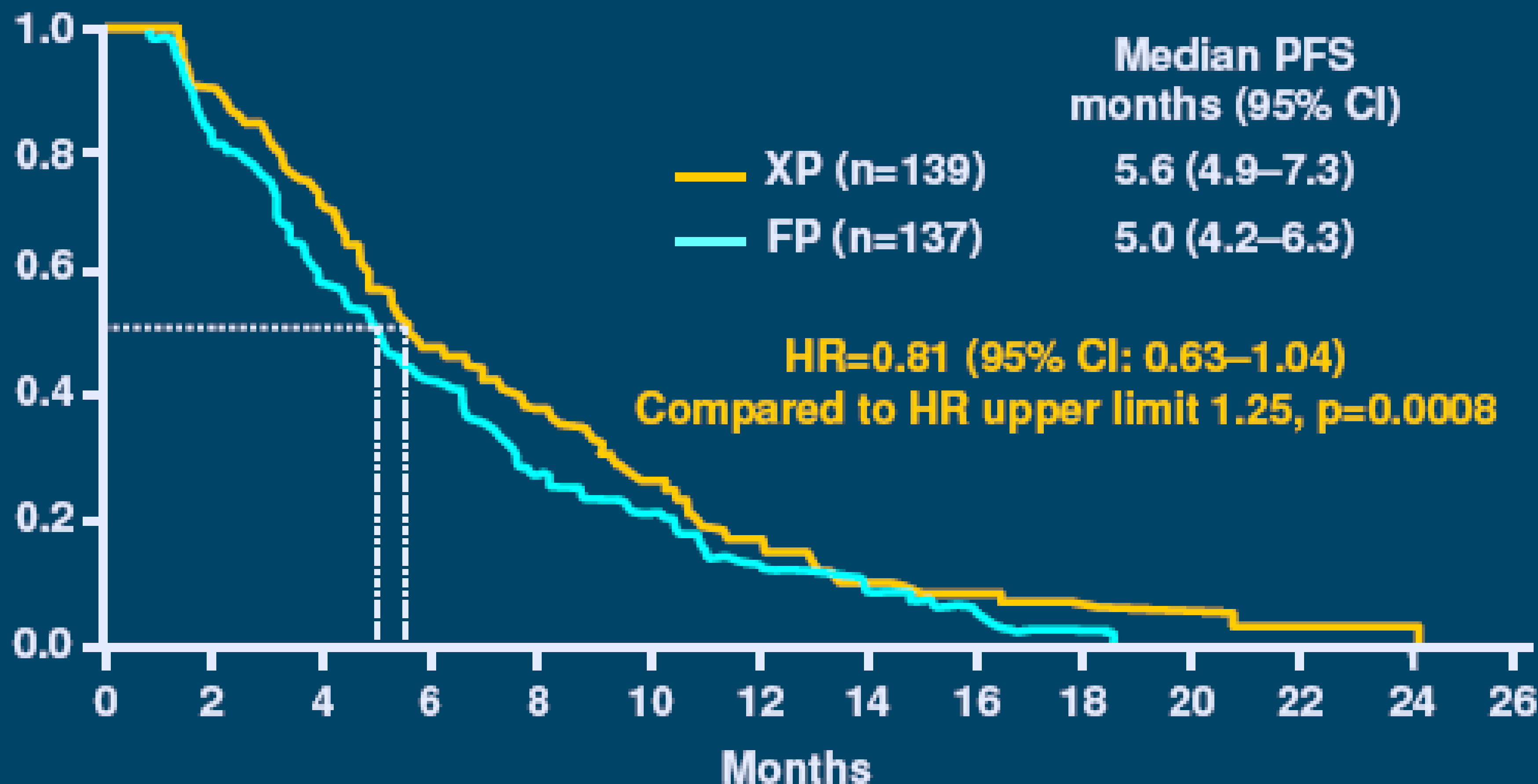
80 mg/m² 3-hour i.v. infusion

Capecitabine

1000 mg/m² twice daily; d1–14 q3w

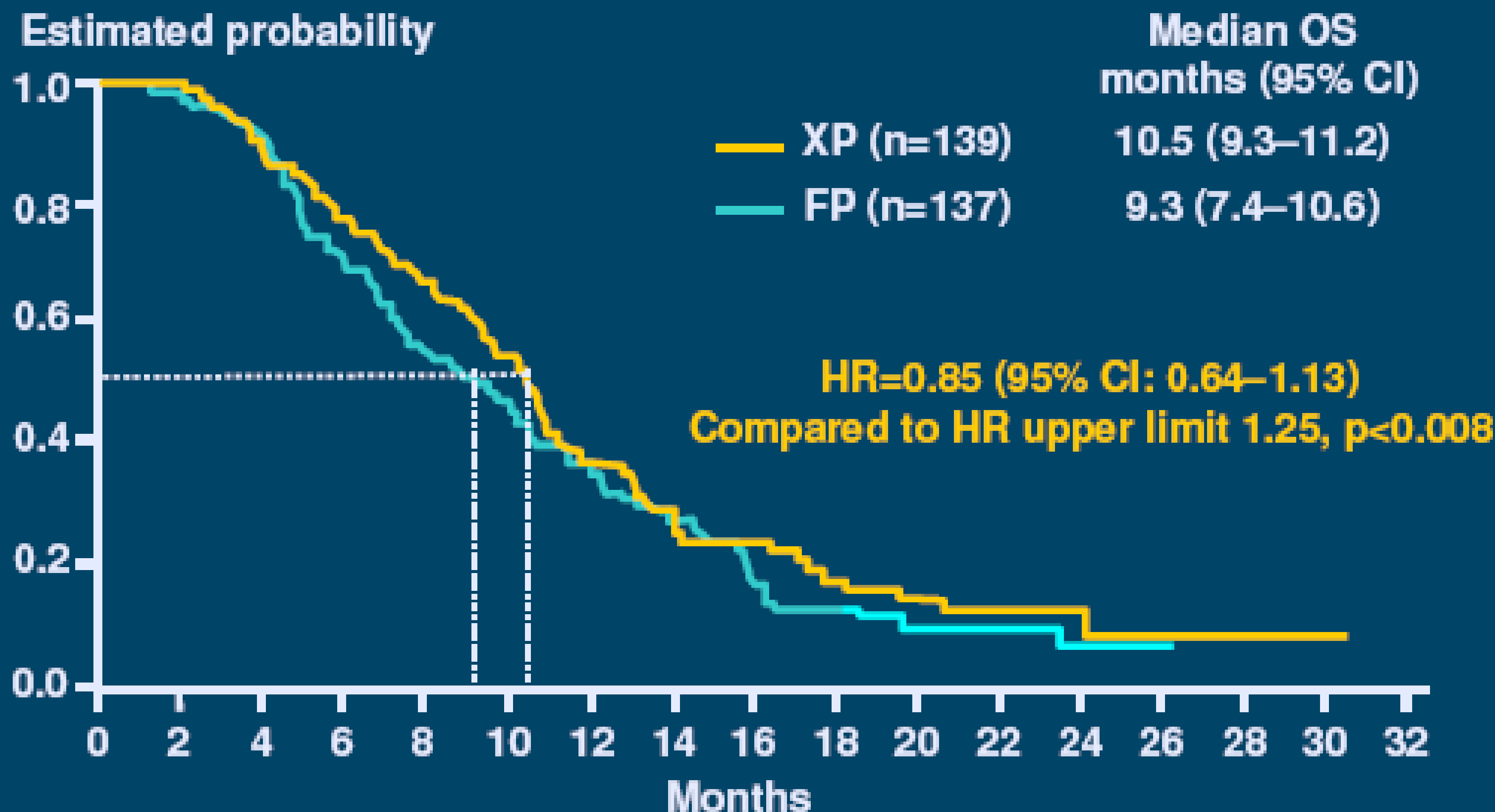
Kang et al., ASCO 2006, LBA4018

Primary endpoint met: progression-free survival HR 0.81



Per protocol analysis

Overall survival HR 0.85



Per protocol analysis

Superior response rate with XP vs. FP

RECIST confirmed response % (95% CI)	XP (n=160)	FP (n=156)	p-value
Overall response	41 (33–49)	29 (22–37)	0.030
Complete response	2	3	0.668
Partial response	39	26	0.019
Progressive disease	10	18	0.041

Magen – palliativ – Capecitabin / Oxaliplatin

Diskussion

- Applikationsmodus von Capecitabin ist vorteilhaft
- anderes Toxizitätsprofil hilft Therapie zu individualisieren (z.B. Nieren-Tox)
- Effektivität ist vielversprechend:

    CapeP sign besseres Ansprechen als FP

    EOX sign besseres Überleben als ECF

- Capecitabin und Oxaliplatin kein neuer Standard aber
- definitive Bereicherung der Therapie
- Zulassung für Capecitabin eventuell 1/07 (?)

palliative Therapie – Capecitabin und Docetaxel

Phase II Studien

Möhler, Mainz, abstr. 4032: Irino/cape vs Cis/Cape

RR 39% vs 42%; beide Regime gut durchführbar

Tebbutt, Australien, abstr. 4067:

DCF wöchentlich vs Doce/Cape wöchentlich:

wDCF besseres Ansprechen aber toxischer

Thuss-Patience et al, abstr 4068: CapDoc q3w

Part I: (2000mg/m²d1-14/ 75mg/m²) :RR 55,3%

Part II (1600mg/m² d1-14/ 60mg/m²):

noch bessere Verträglichkeit bei gleicher Effektivität?

Final Results of a Randomized Controlled Phase III Trial (TAX 325) Comparing Docetaxel (T) Combined with Cisplatin (C) and 5-fluorouracil (F) to CF in Patients with Metastatic and Locally Recurrent Gastric Cancer

V. M. Moiseyenko, J. A. Ajani, S. A. Tjulandin, A. Majlis, M. Constenla, C. Boni, A. Anelli, A. J. Yver, E. Van Cutsem, on behalf of the TAX 325 Study Group

ASCO 2005

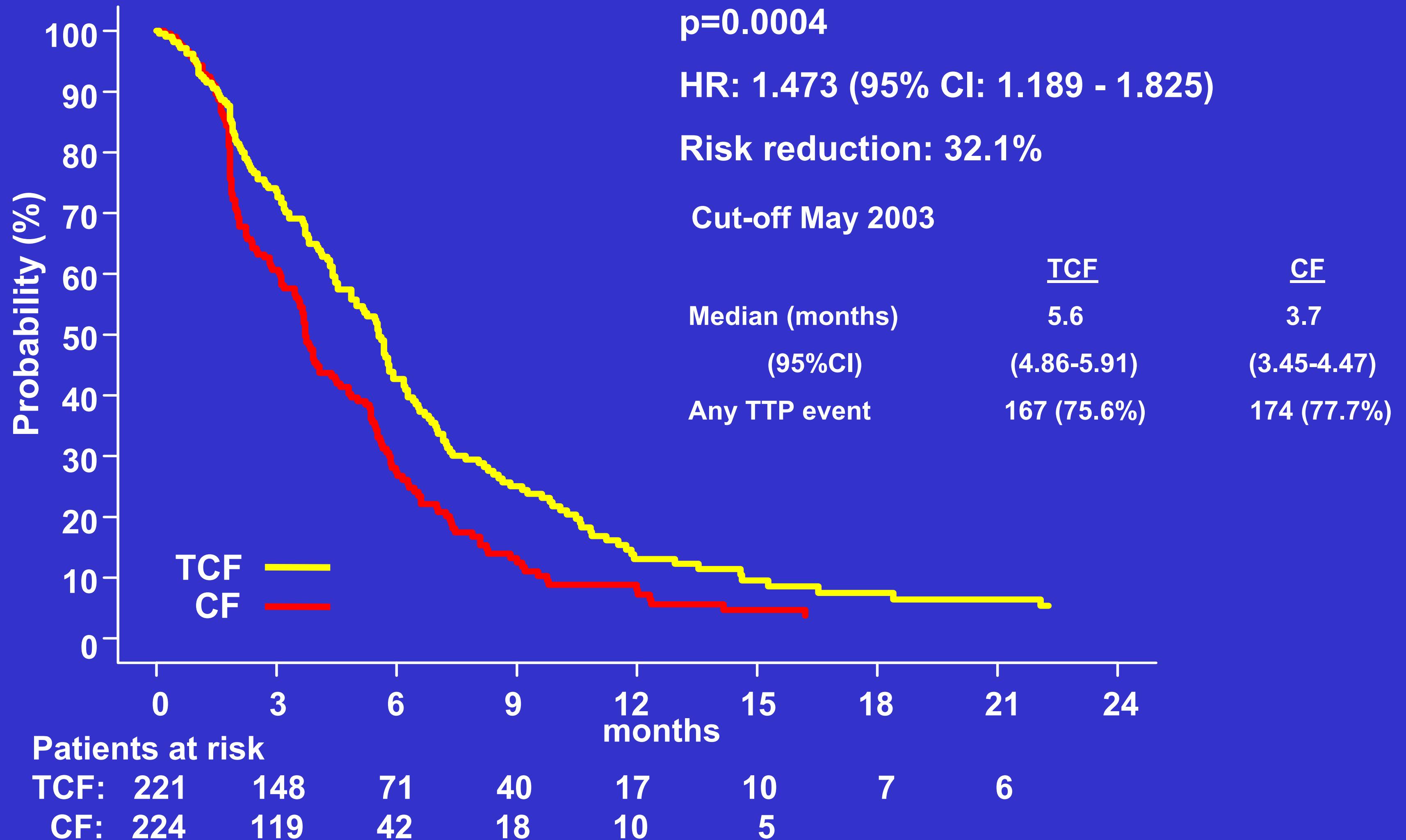
Best Overall Response (FAP)

	Number (%) of patients		
	TCF N=221	**CF** N=224	*p*-value
Overall RR (CR+PR)	81 (36.7)	57 (25.4)	χ^2 0.0106
95% CI	(30.3 - 43.4)	(19.9 - 31.7)	
Complete response (CR)	4 (1.8)	3 (1.3)	
Progressive disease (PD)	37 (16.7)	58 (25.9)	
Duration of response from onset of PR/CR			
Median, months (95% CI)	6.1 (5.0-8.3)	5.6 (4.2-6.4)	*Logrank 0.3175*
Number (%) among responders with response duration > 9 months	21/81 (25.9%)	8/57 (14.0%)	

All tumor responses were determined by ERRC, except for 8 patients

All partial or complete responses were confirmed at least 4 weeks after the occurrence of response

TTP – Final Analysis (FAP)

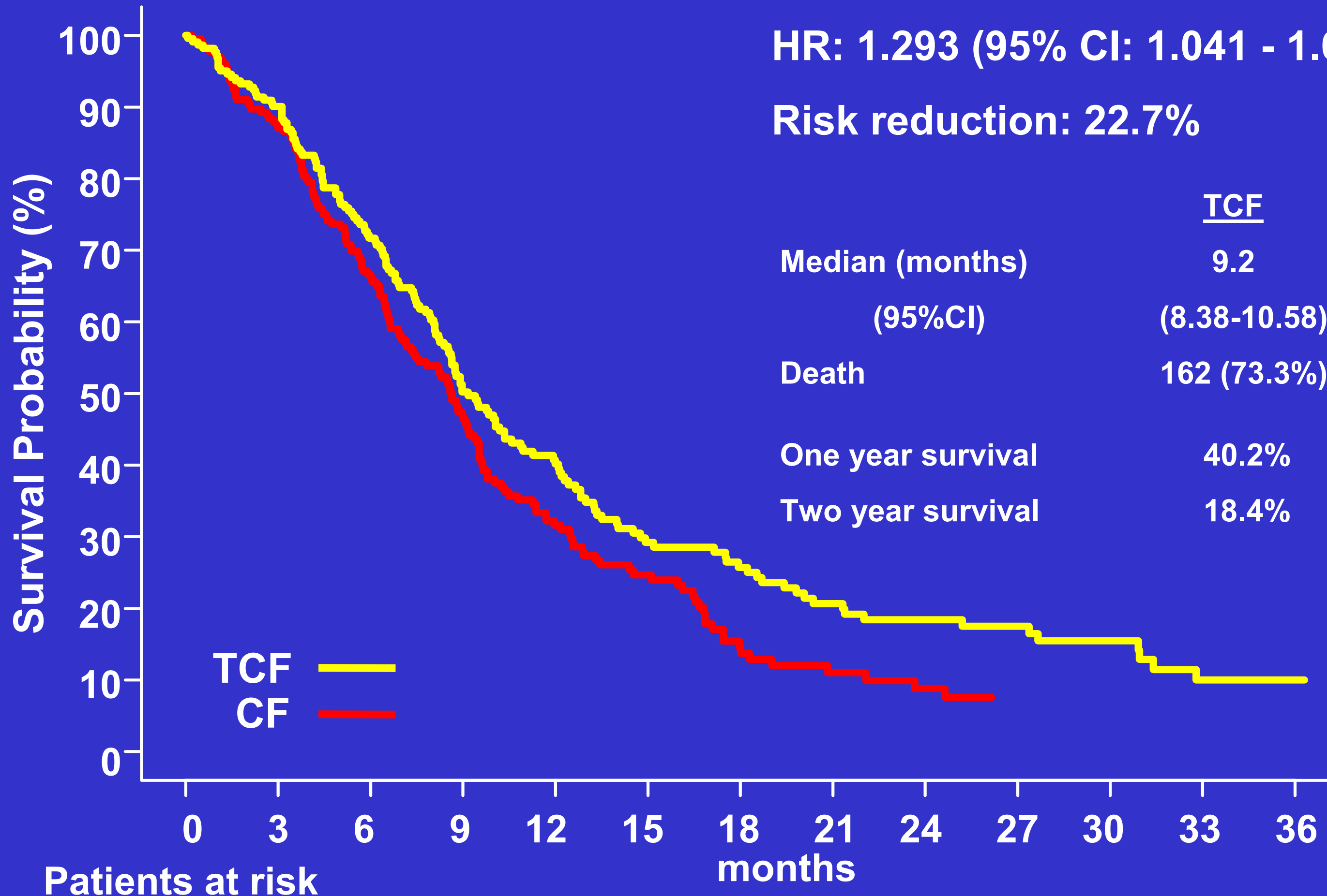


Overall Survival – Final Analysis (FAP)

p=0.0201

HR: 1.293 (95% CI: 1.041 - 1.606)

Risk reduction: 22.7%

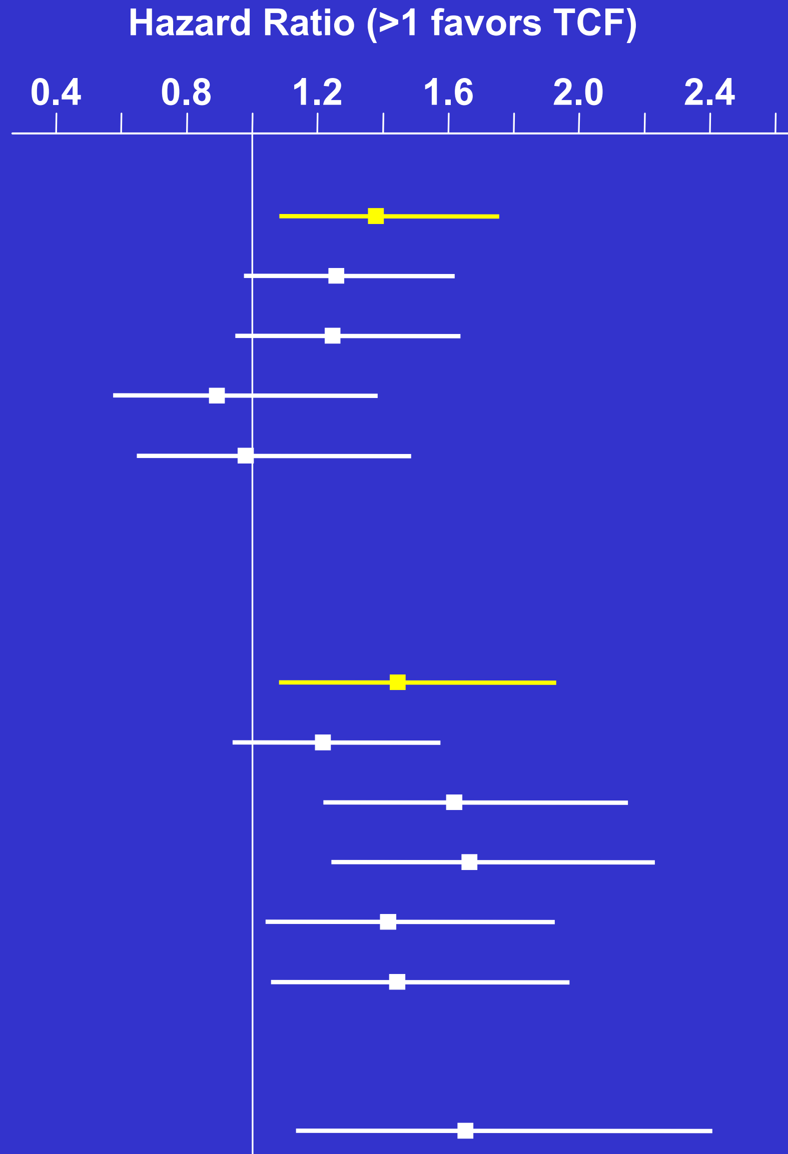


Patients at risk

TCF:	221	199	149	93	68	45	36	28	22	17	12	7	5
CF:	224	195	136	87	54	35	17	11	8				

	TCF	CF
Median (months)	9.2	8.6
(95%CI)	(8.38-10.58)	(7.16-9.46)
Death	162 (73.3%)	172 (76.8%)
One year survival	40.2%	31.6%
Two year survival	18.4%	8.8%

Clinical Benefit and QoL



Clinical Benefit

Time to definitive worsening KPS (n=444)

Time to definitive 5% weight loss (n=444)

Time to definitive worsening appetite (n=425)

Pain-Free Survival (n=200)

Time to 1st cancer-pain related opioid (n=355)

EORTC QLQ-C30

(time to 5% definitive worsening)

Global Health Status (n=384)

Physical Functioning (n=389)

Social Functioning (n=387)

Nausea and Vomiting (n=390)

Pain (n=391)

Appetite Loss (n=388)

EQ-5D

Thermometer (n=223)