Erstlinientherapie des metastasierten kolorektalen Karzinoms

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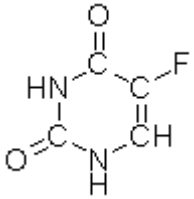
Nationales Centrum für Tumorerkrankungen, Heidelberg

Medizinische Onkologie

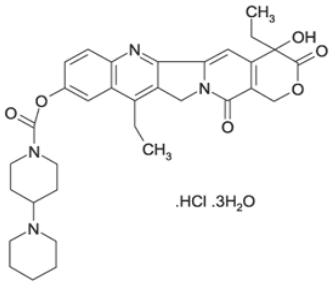
NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

Aktive Medikamente bei Kolorektalkarzinom

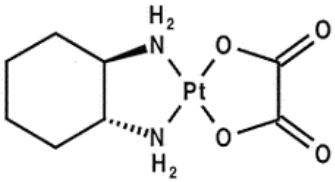
1957 **5-Fluorouracil**



1998 **Irinotecan**

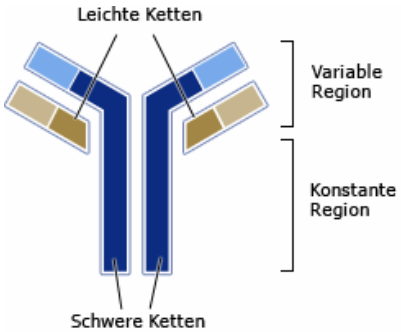


1998 **Oxaliplatin**

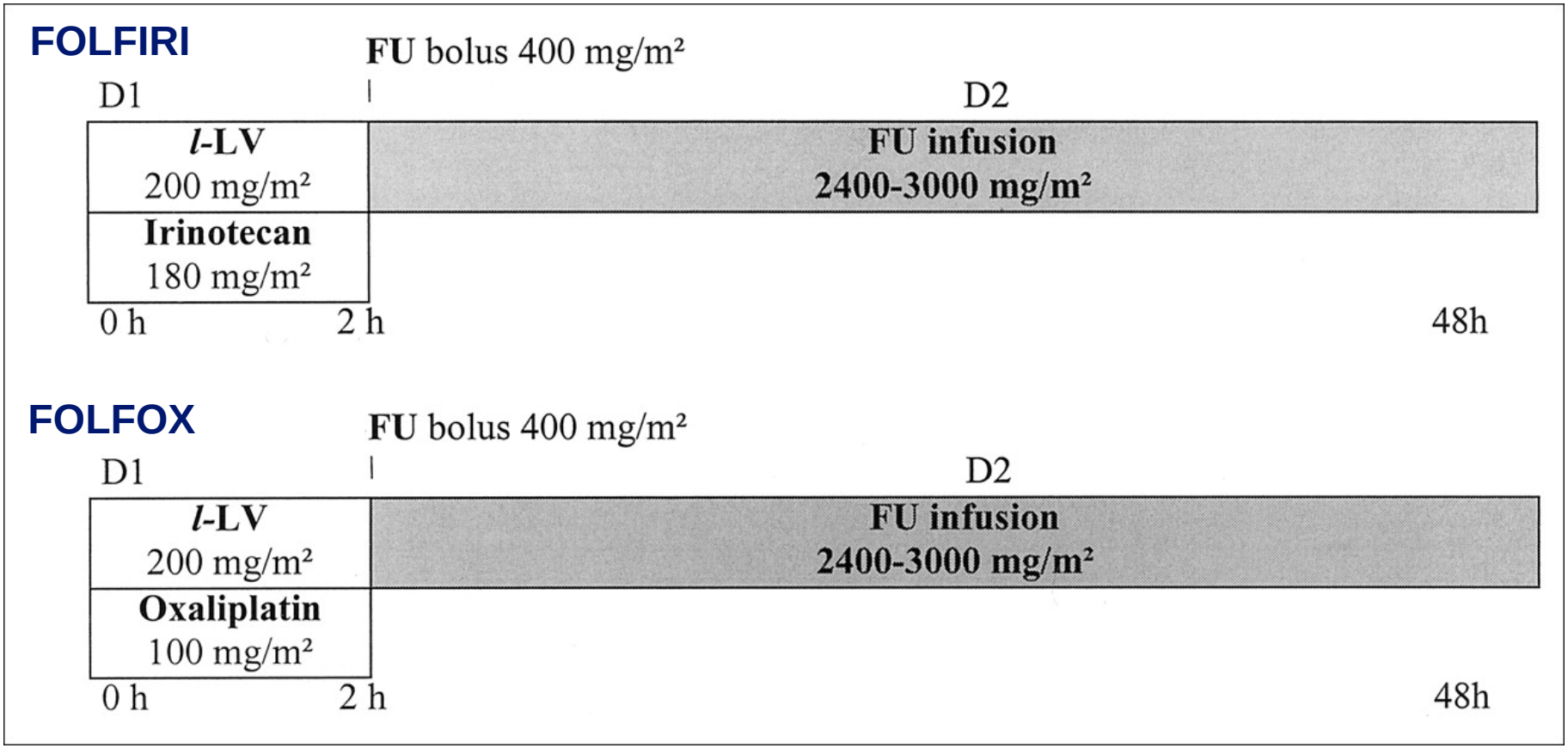


2004 **Cetuximab (Erbitux)**

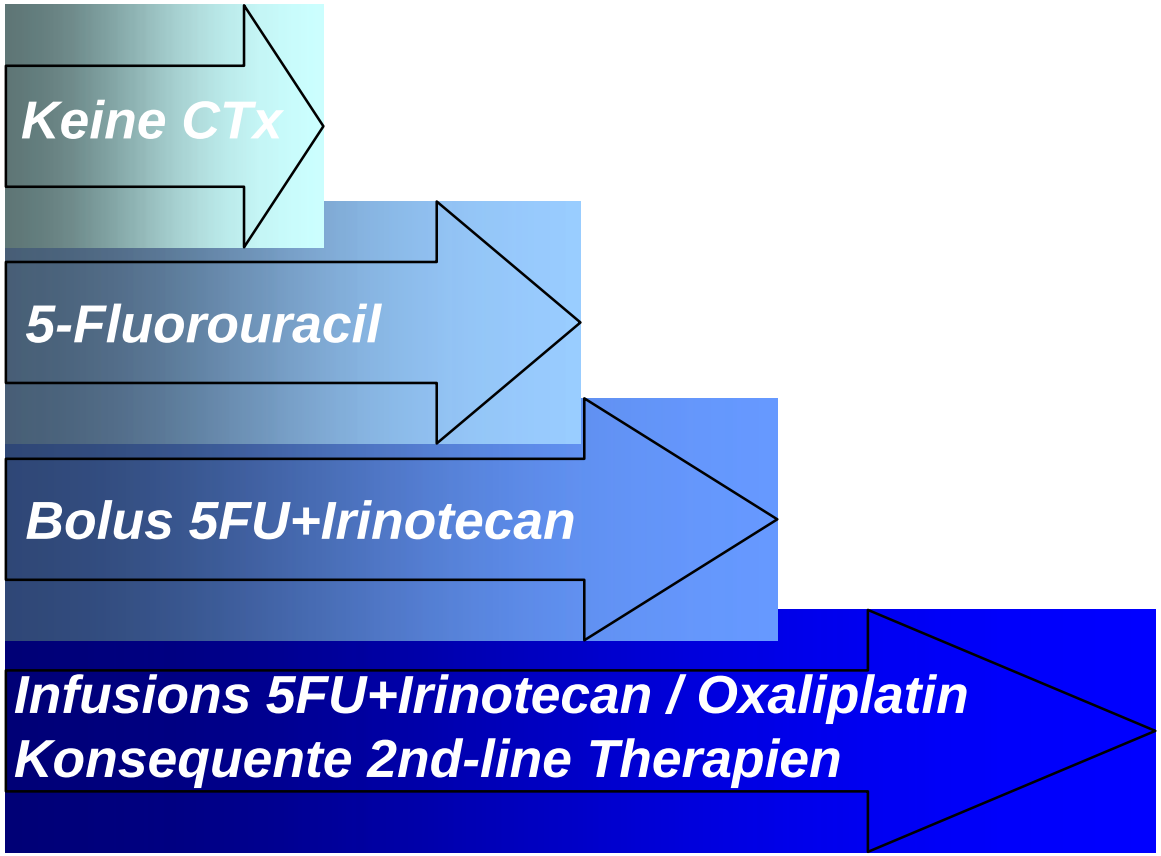
2006 **Bevacizumab (Avastin)**



Aktive CTx-Schemata bei Kolorektalkarzinom



Überleben CRC Stadium IV

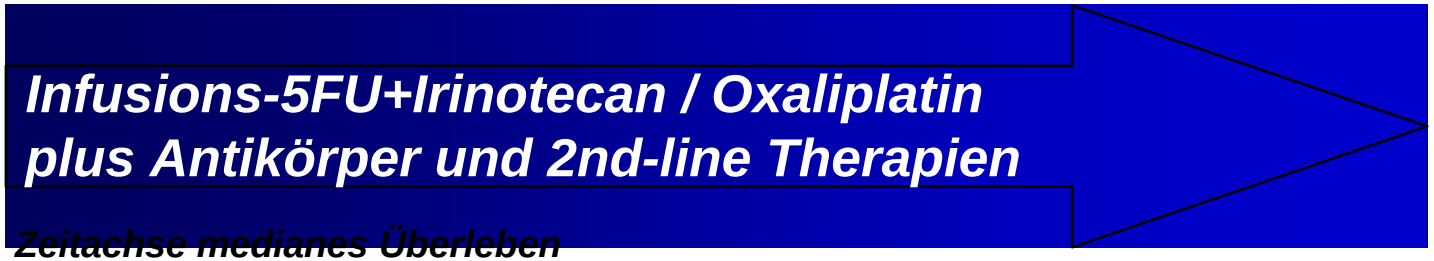


4-6 Monate

12 Monate

15 Monate

21 Monate



> 21 Monate
?

Zeitachse medianes Überleben

Erstlinientherapie – aktuelle Fragen

- Mono-Chemotherapie oder Kombinationen?
- Welche Zytostatika first-line?
- Therapiedauer?
- Stellenwert von Bevacizumab?
- Stellenwert von Cetuximab?

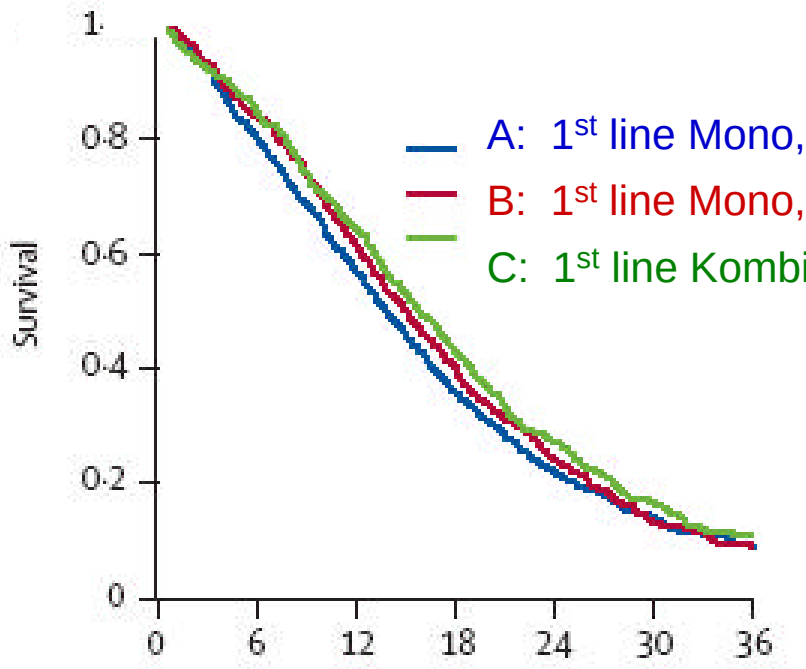
CTx-Monotherapie (5-FU/LV) vs Kombination

Studie		PFS	p-Wert
Saltz 2000 (n=683)	Mayo IFL	7,0 Monate 4,3 Monate	0,004
Douillard 2000 (n=387)	LV5FU2 FOLFIRI	6,7 Monate 4,4 Monate	<0,001
De Gramont 2000 (n=420)	LV5FU2 FOLFOX-4	9,0 Monate 6,2 Monate	0,0003
Grothey 2002 (n=242)	Mayo FUFOX	7,9 Monate 5,3 Monate	<0,0001
Köhne 2005 (n=430)	5FU-AIO Iri-5FU-AIO	8,5 Monate 6,4 Monate	<0,0001

CTx-Monotherapie (5-FU/LV) vs Kombination

Studie		PFS	p-Wert	Überleben	p-Wert
Saltz 2000 (n=683)	Mayo IFL	7,0 Monate 4,3 Monate	0,004	12,4 Monate 14,8 Monate	0,04
Douillard 2000 (n=387)	LV5FU2 FOLFIRI	6,7 Monate 4,4 Monate	<0,001	14,1 Monate 17,4 Monate	0,034
De Gramont 2000 (n=420)	LV5FU2 FOLFOX-4	9,0 Monate 6,2 Monate	0,0003	14,7 Monate 16,2 Monate	0,17
Grothey 2002 (n=242)	Mayo FUFOX	7,9 Monate 5,3 Monate	<0,0001	16,1 Monate 21,4 Monate	0,15
Köhne 2005 (n=430)	5FU-AIO Iri-5FU-AIO	8,5 Monate 6,4 Monate	<0,0001	16,9 Monate 20,1 Monate	0,28

FOCUS: CTx-Monotherapie vs Kombinationen



A: 1st line Mono, 2nd line Mono, 3rd line Kombination

B: 1st line Mono, 2nd line Kombination

C: 1st line Kombination

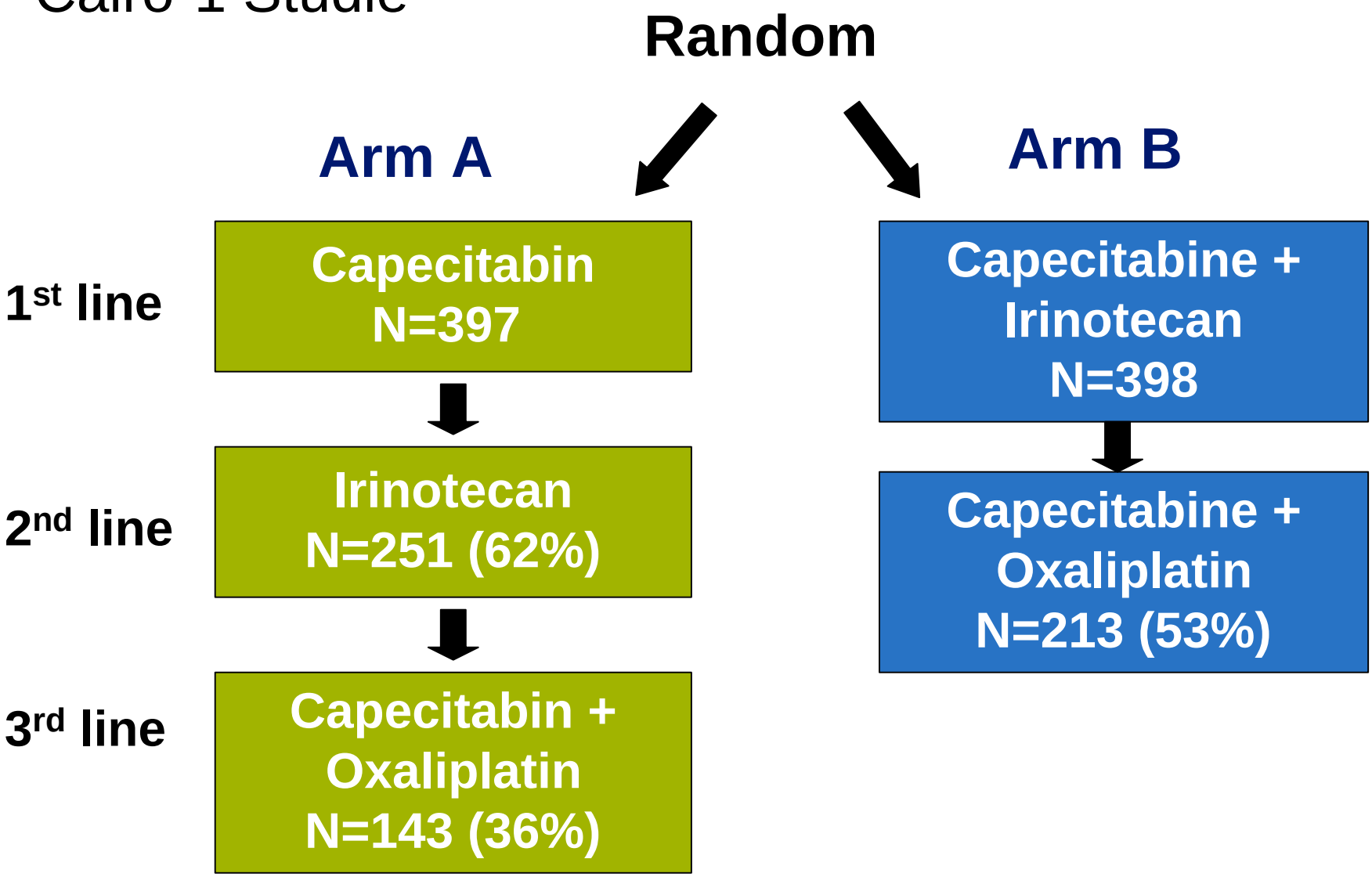
Patients at risk							
Strategy A	710	562	397	247	139	73	40
Strategy B	712	594	425	270	153	72	38
Strategy C	713	598	448	294	174	84	42

(A) 1st- 2nd-line Mono, 3rd Kombination
(C) vs. 1st-line Kombination

13,9 vs. 15,8 Monate Überleben
p=0,02

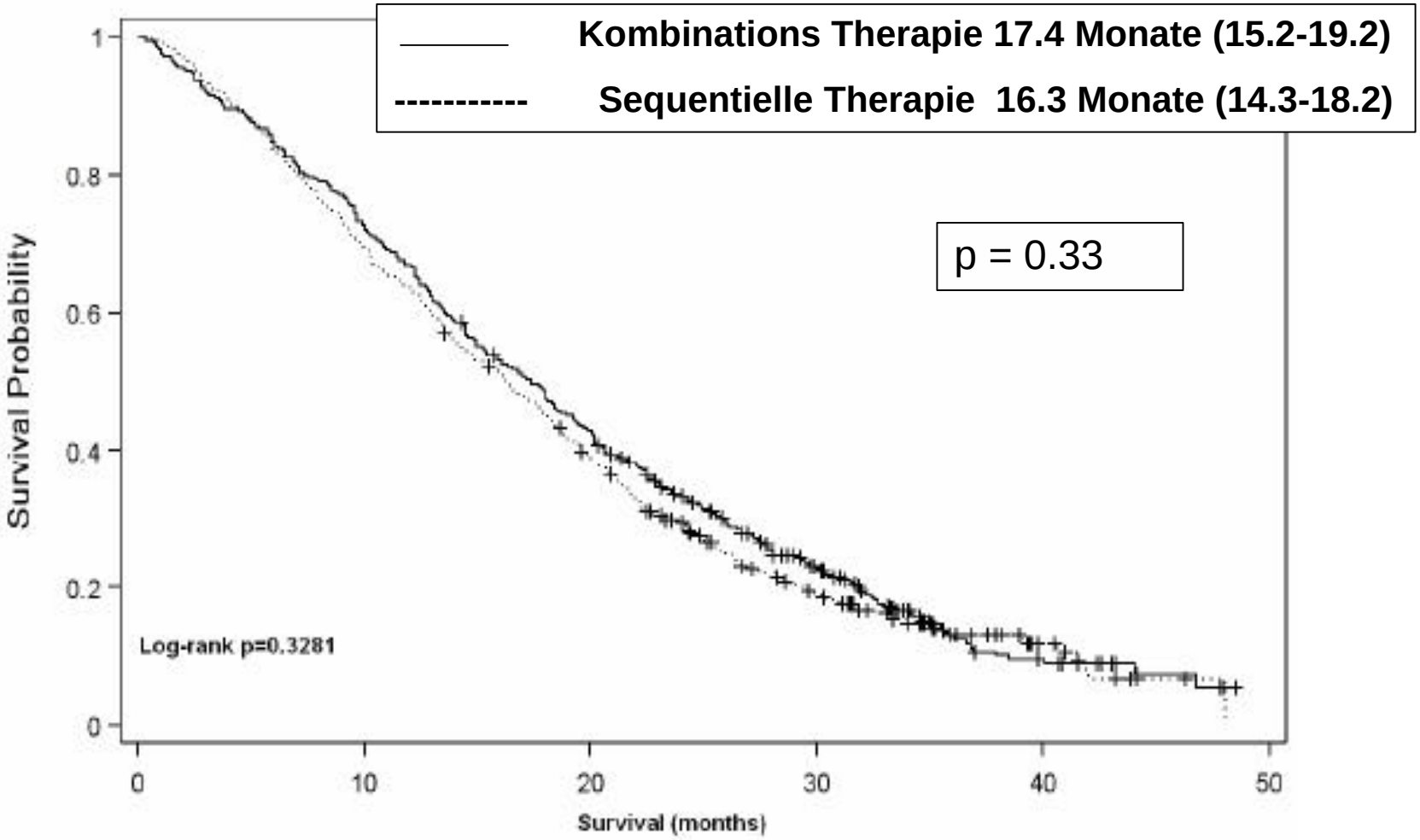
Seymour MT et al. *Lancet* 2007; 370: 143-152

Cairo-1 Studie



Koopman M et al. *Lancet* 2007; 370: 135-42

Cairo-1 Studie



Koopman M et al. *Lancet* 2007; 370: 135-42

1st-line Monotherapie versus Kombination

- **Wer benötigt unbedingt eine Erstlinien-Kombinationstherapie?**
  - **Patienten mit potenziell resektabler Tumorerkrankung**

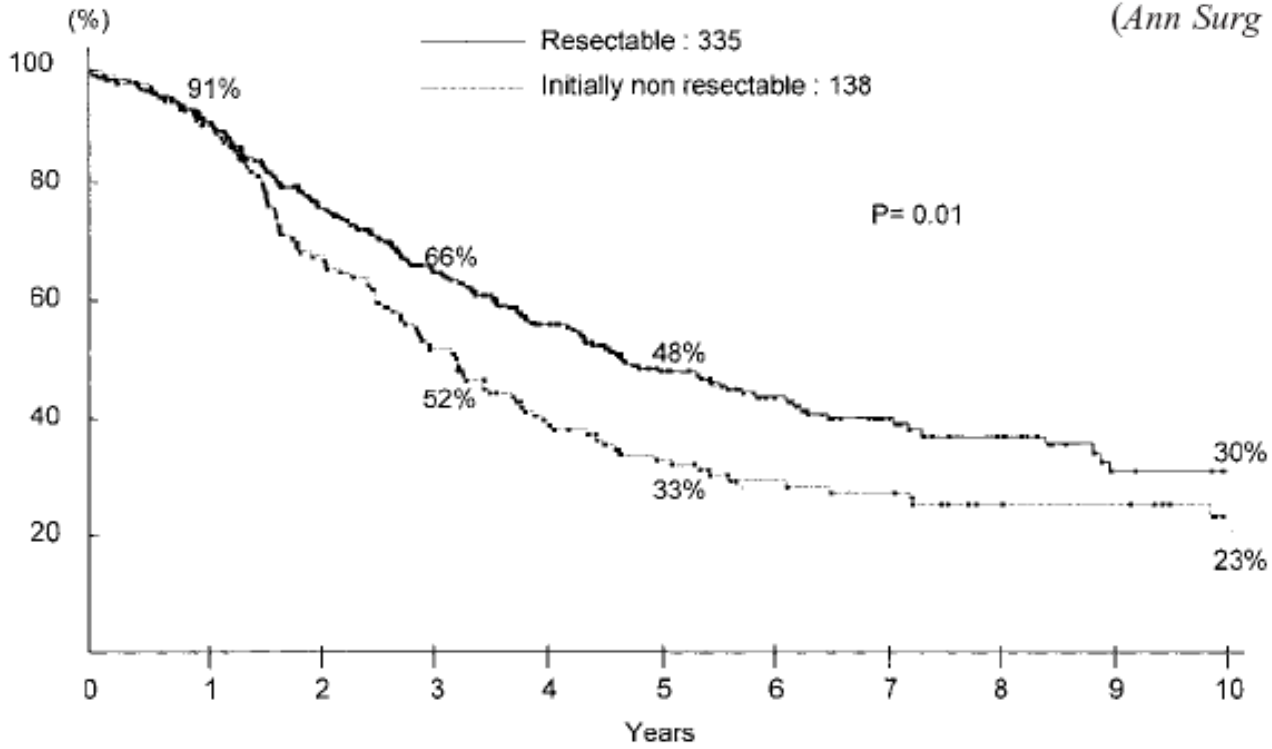
Rescue Surgery for Unresectable Colorectal Liver Metastases Downstaged by Chemotherapy

A Model to Predict Long-term Survival

René Adam, MD, PhD, Valérie Delvart, Gérard Pascal, MD, Adrian Valeanu, MD, Denis Castaing, MD, Daniel Azoulay, MD, PhD, Sylvie Giacchetti, MD, Bernard Paule, MD, PhD, Francis Kunstlinger, MD, Odile Ghémard, MD, Francis Levi, MD, PhD, and Henri Bismuth, MD, FACS Hon

NCT

(*Ann Surg* 2004;240: 644–658)



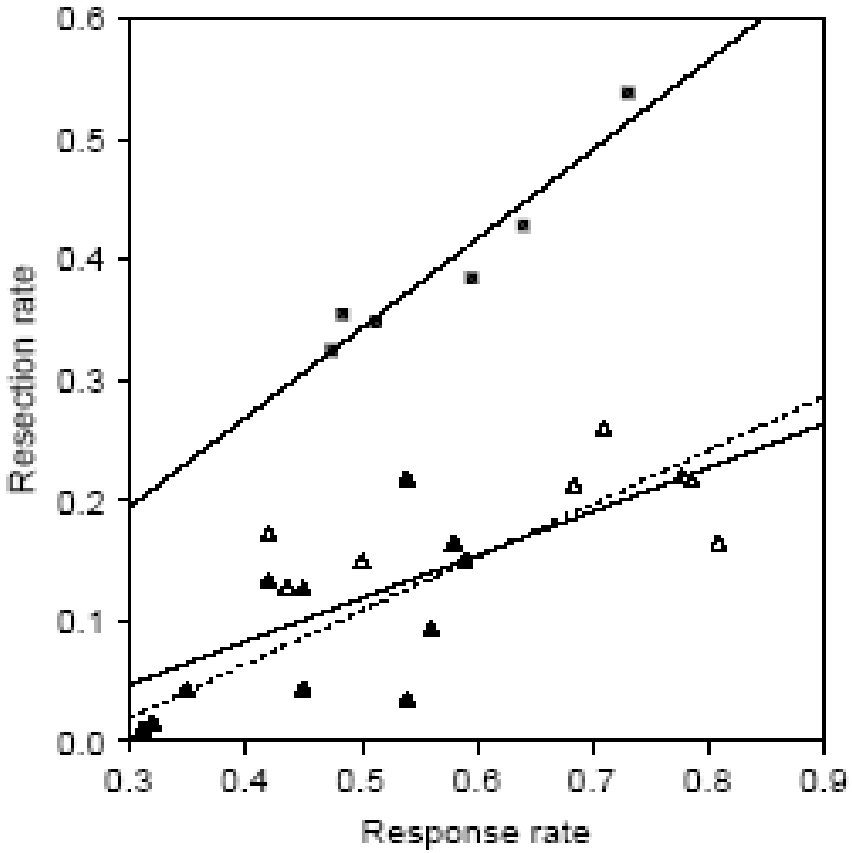
No Pts at risk	0 Yr	1 Yr	3 Yrs	5 Yrs	8 Yrs	10 Yrs
Non resectable	138	124	69	37	18	12
Resectable	335	282	168	90	32	17

Original article

Annals of Oncology 16: 1311–1319, 2005
doi:10.1093/annonc/mdi246
Published online 3 May 2005

Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates

G. Folprecht[1], A. Grothey[2], S. Alberts[2], H.-R. Raab[3] & C.-H. Köhne[3]*



Je höher die CTx Ansprechrate, desto höher die Resektionsrate

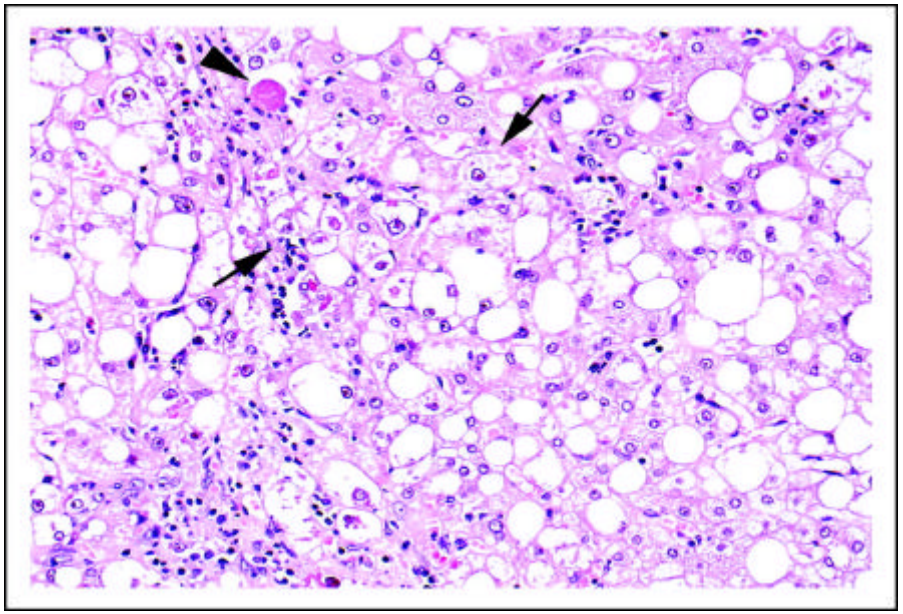
Ansprechraten Kolorektalkarzinom

CTx-Schema	Responserate	Literatur
5-FU/LV (de Gramont)	22%	De Gramont 2000
FOLFOX	50%	
FOLFOX	38%	Cassidy 2007
FOLFOX-Bevacizumab	39%	
FOLFIRI	38%	Van Cutsem 2007
FOLFIRI-Cetuximab	47%	
FOLFIRI	33%	Falcone 2007
FOLFOXIRI	60%	

Chemotherapie - Lebertoxizität

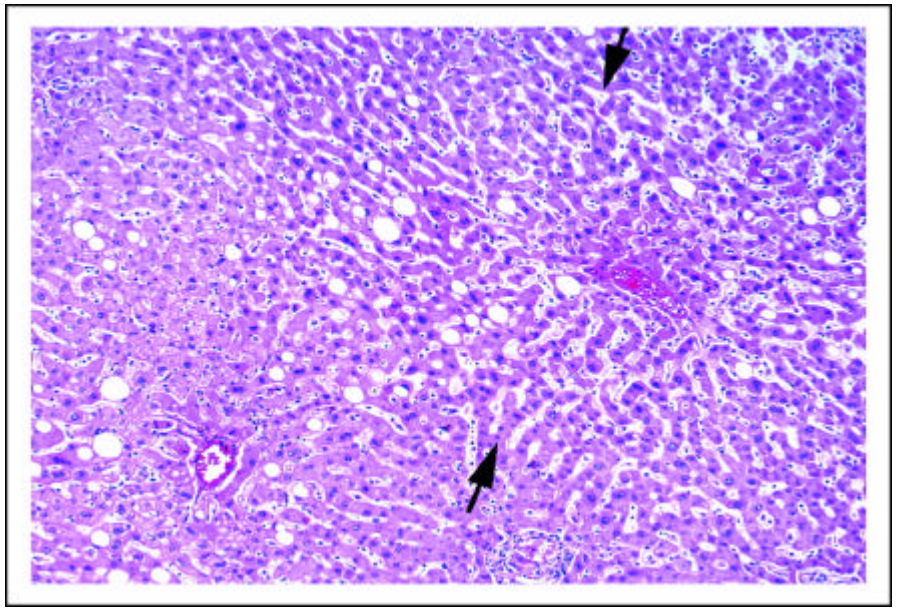
Irinotecan

Steatohepatitis
20,2%



Oxaliplatin

Sinusoidalobstruktion
18,9 %



Potentiell erhöhte post-op. Letalität

Vauthey et al. *J Clin Oncol* 2006; 24: 2065-2072

1st-line Monotherapie versus Kombination

- **Wer benötigt unbedingt eine Erstlinien-Kombinationstherapie?**
  - **Patienten mit potenziell resektabler Tumorerkrankung**
  - **Patienten mit hoher Tumorlast**

1st line Monotherapie versus Kombination

- **Analyse 3852 Patienten (5-FU-Therapie)**

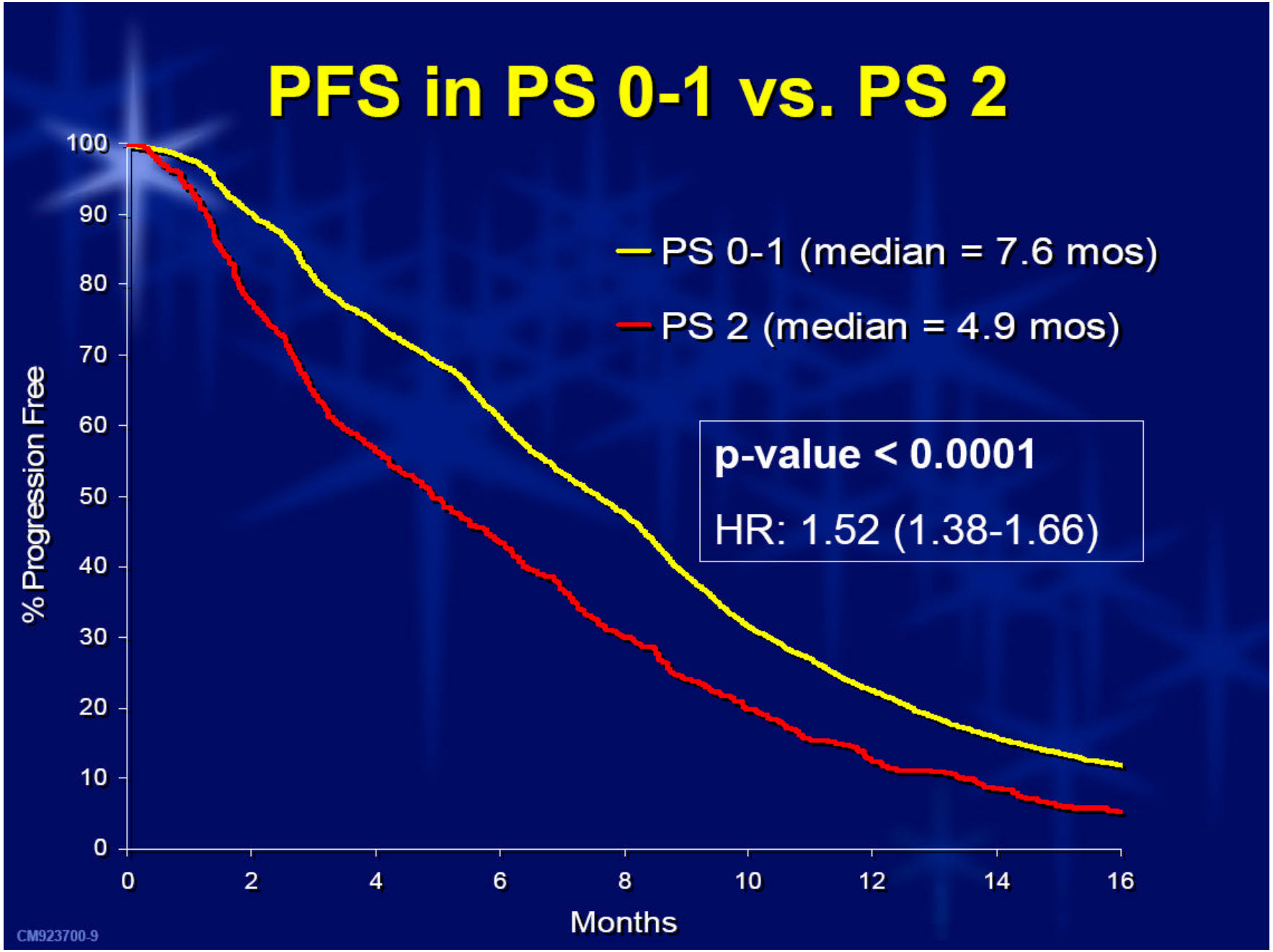
3 Risiko-Kollektive: medianes Überleben

- ‚good risk‘	15,0 Monate
- ‚intermediate risk‘	10,7 Monate
- ‚high risk‘	6,1 Monate

anhand 4 klinischer Risikofaktoren

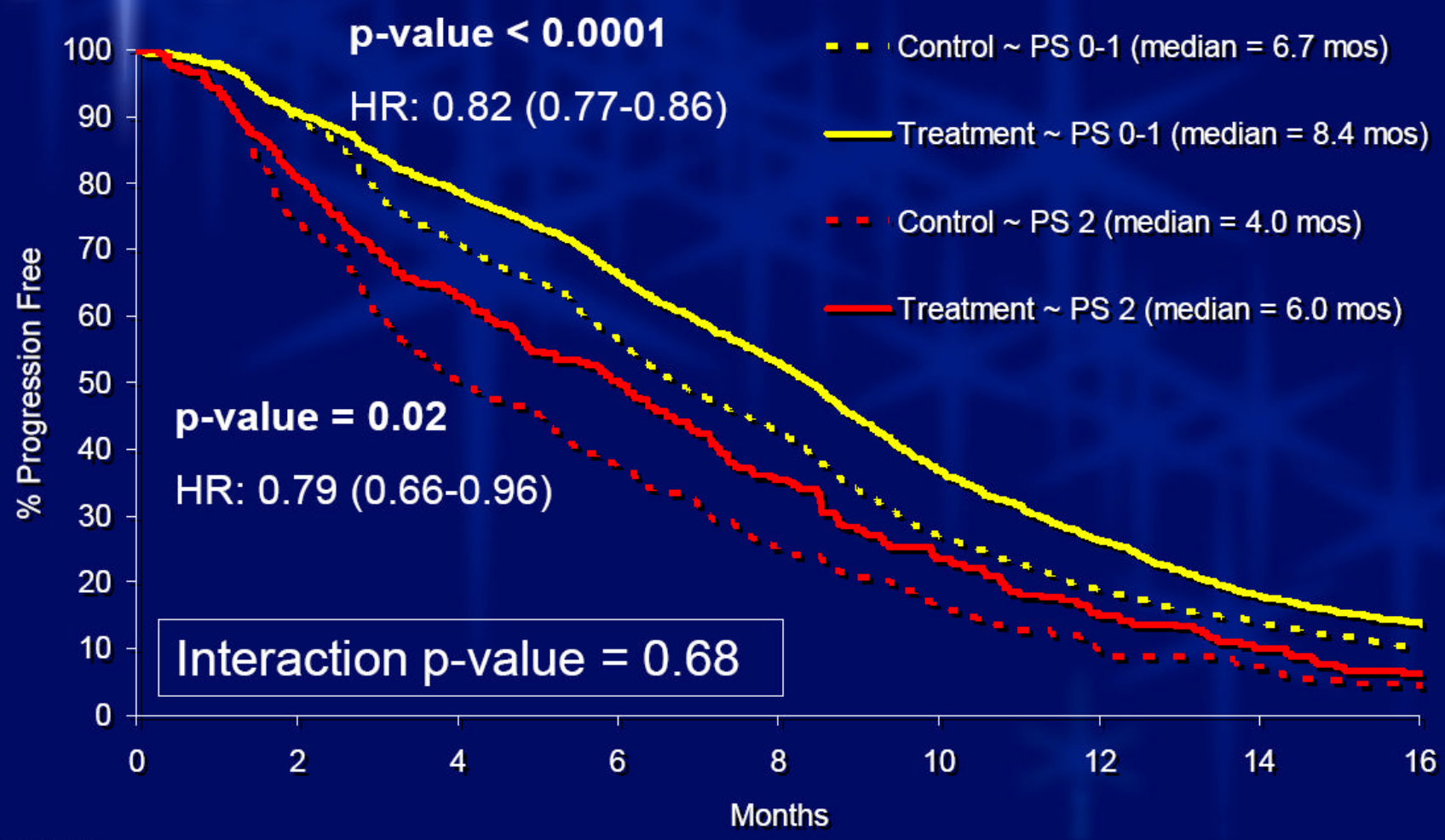
- Allgemeinzustand (ECOG)
- Anzahl betroffener Organe
- Leukozyten (Blut)
- Alkalische Phosphatase (Serum)

Köhne CH et al. *Ann Oncol* 2002; 13: 308-317



Goldberg R et al. *ASCO* 2007; abstract 4011

PFS – Treatment by PS



CM923700-15

Goldberg R et al. *ASCO* 2007; abstract 4011

„…to maximise the potential benefit for each patient, an approach based on prognosis and disease presentation with initial combination chemotherapy for most patients, reserving single-agent fluorouracil for patients with less aggressive or never-resectable disease, should be the standard of care for for first-line treatment of of metastatic colorectal cancer.“

H.J. Schmoll

Schmoll HJ & Sargent D. *Lancet* 2007; 370: 105-107

Erstlinientherapie – aktuelle Fragen

- Mono-Chemotherapie oder Kombinationen?
- Welche Zytostatika first-line?
- Therapiedauer?
- Stellenwert von Bevacizumab?
- Stellenwert von Cetuximab?

VOLUME 22 · NUMBER 2 · JANUARY 15 2004

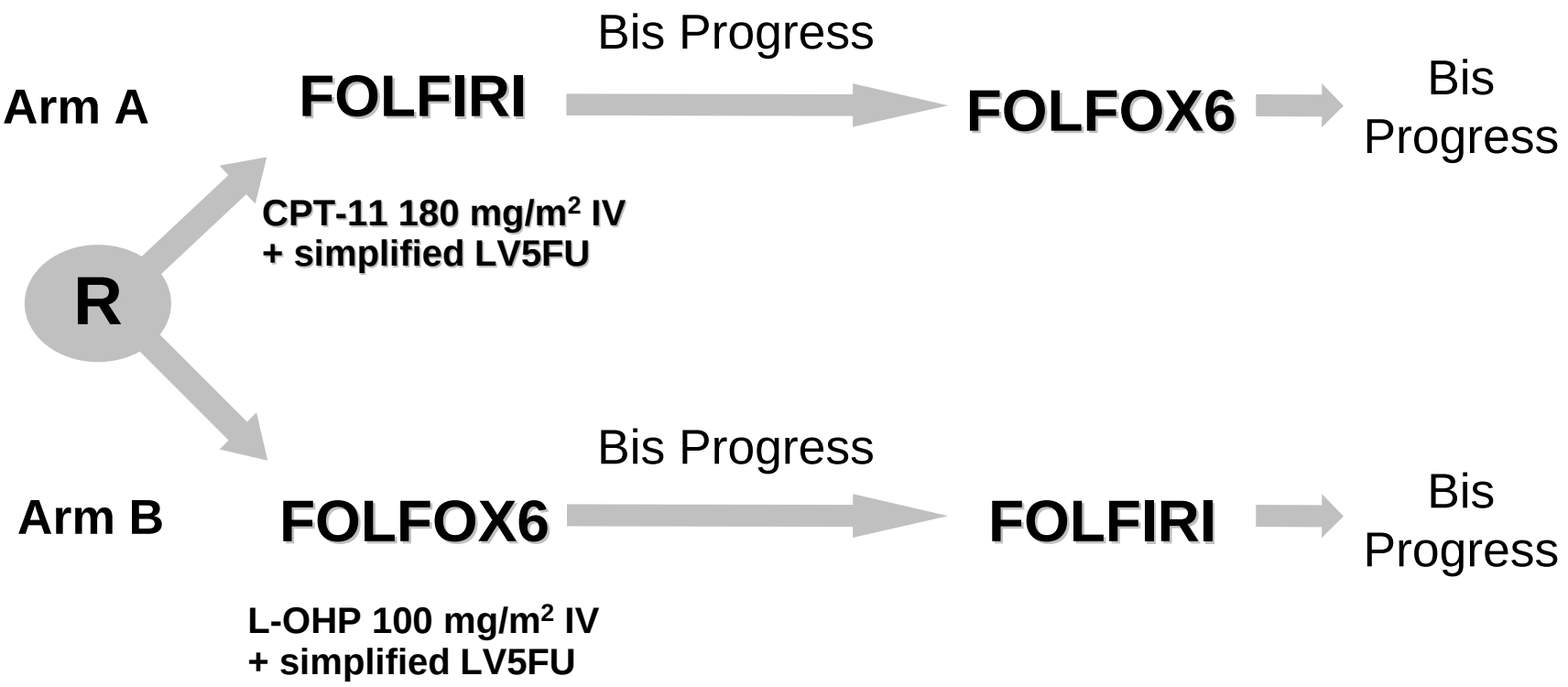
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

NCT

FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR Study

Christophe Tournigand, Thierry André, Emmanuel Achille, Gérard Lledo, Michel Flesh, Dominique Mery-Mignard, Emmanuel Quinaux, Corinne Couteau, Marc Buyse, Gérard Ganem, Bruno Landi, Philippe Colin, Christophe Louvet, and Aimery de Gramont



Welche Erstlinienkombination?

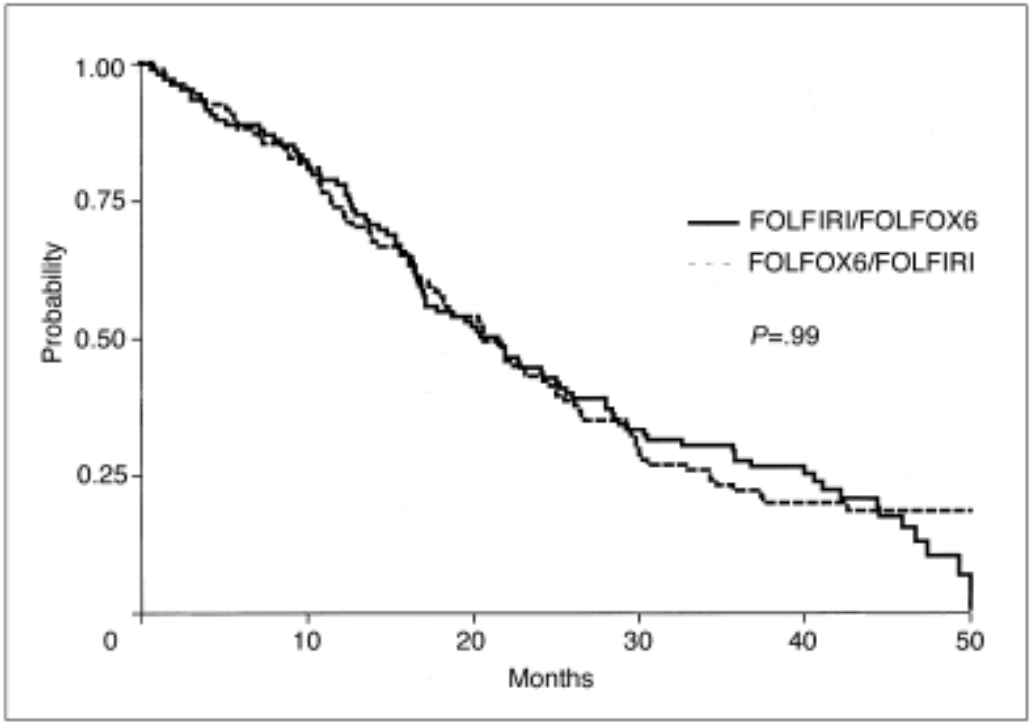


Fig 4. Overall survival curves. FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin.

Medianes Überleben
21,5 vs 20,6 Monate

Tournigand C et al. *J Clin Oncol* 2004; 22: 229-237

→ FOLFIRI oder FOLFOX first-line, konsequentes cross-over 2nd-line

Auswahlkriterien für 1st-line CTx?

Fluoropyrimidin	DPD (Genmutationen) TS (Thymidylat-Synthetase) TP (Thymodon-Phosphorylase) MSI (Mikrosatelliten-Status) LOH-18 (Heterozygotie-Verlust)
Irinotecan	UGT1A1
Oxaliplatin	ERCC1 GST (Glutathion-S-Transferase)

Bislang keine ausreichend validierten prädiktiven Marker!

Auswahlkriterien für 1st-line CTx?

Sensorische PNP limitiert Oxaliplatin-Therapiedauer

Erstlinientherapie – aktuelle Fragen

- Mono-Chemotherapie oder Kombinationen?
- Welche Zytostatika first-line?
- Therapiedauer?
- Stellenwert von Bevacizumab?
- Stellenwert von Cetuximab?

VOLUME 24 · NUMBER 3 · JANUARY 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

OPTIMOX1: A Randomized Study of FOLFOX4 or FOLFOX7 With Oxaliplatin in a Stop-and-Go Fashion in Advanced Colorectal Cancer—A GERCOR Study

Christophe Tournigand, Andres Cervantes, Arie Figer, Gérard Lledo, Michel Flesch, Marc Buyse, Laurent Mineur, Elisabeth Carola, Pierre-Luc Etienne, Fernando Rivera, Isabel Chirivella, Nathalie Perez-Staub, Christophe Louvet, Thierry André, Isabelle Tabah-Fisch, and Aimery de Gramont

Random

FOLFOX-4 **bis Progression**

620 Patienten
Primärer Endpunkt: Dauer der Erkrankungskontrolle
Sekundärer Endpunkt: Überleben

FOLFOX-7 **3 Monate**

5-FU/LV Monotherapie 6 Monate

FOLFOX-7 Reintroduktion

Optimox-1 Konzept

Überleben

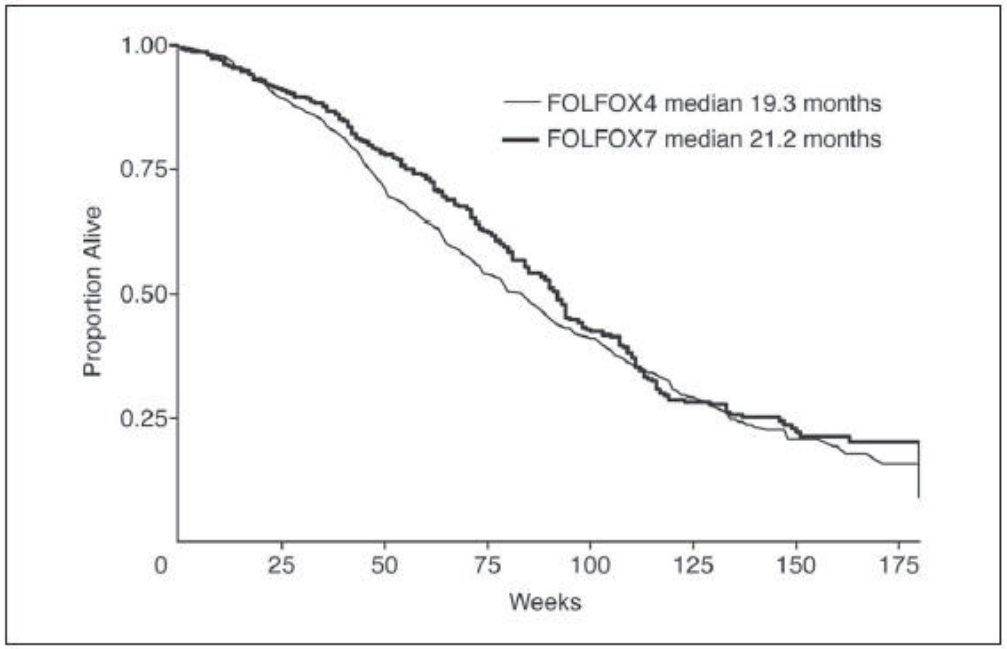
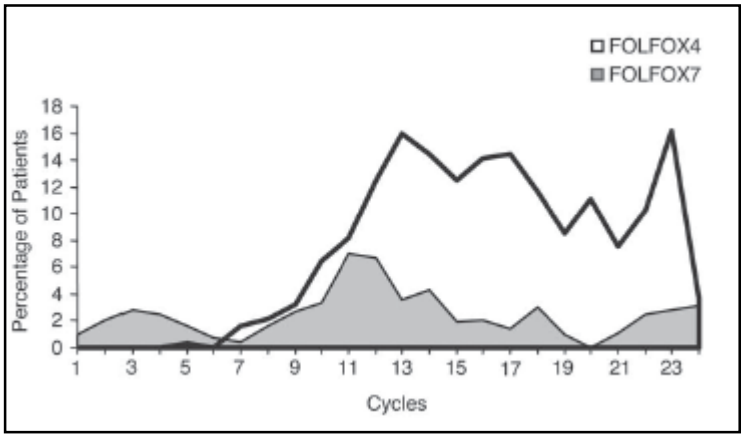


Fig 4. Overall survival curves. FOLFOX, leucovorin, fluorouracil, and oxaliplatin.

Neuropathie



Tournigand C et al. *J Clin Oncol* 2006; 24: 394-400

Optimox-2 Konzept

Random

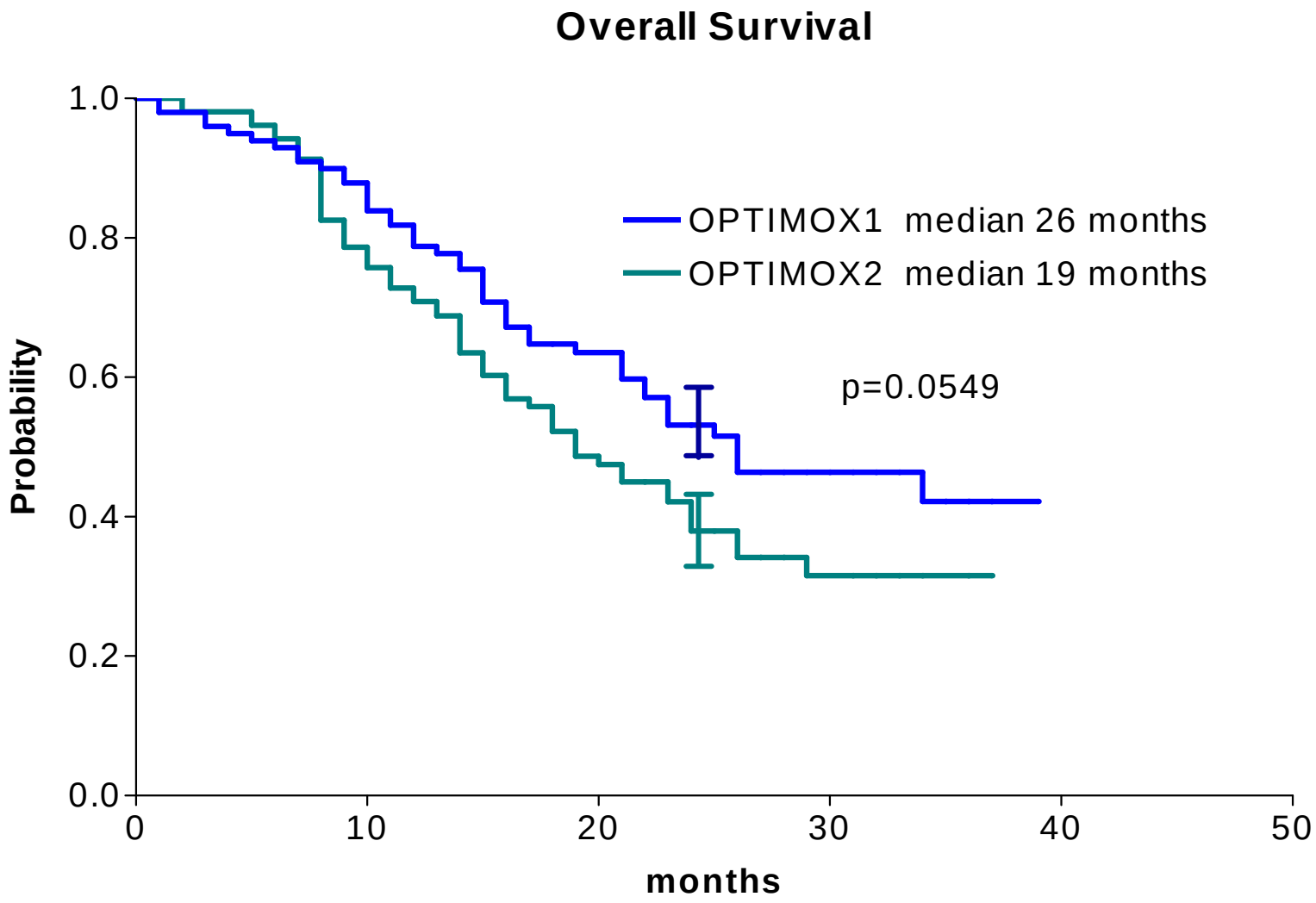
FOLFOX-7 3 Monate
5-FU/LV Monotherapie bis Progression
FOLFOX-7 Reintroduktion

200 geplante Patienten (Phase II)
Primärer Endpunkt: Dauer der Erkrankungskontrolle

FOLFOX-7 3 Monate
Keine Erhaltungstherapie
FOLFOX-7 Reintroduktion

Maindrault-Goebel et al. *ASCO* 2007; abstract 4013

Optimox-2 Konzept



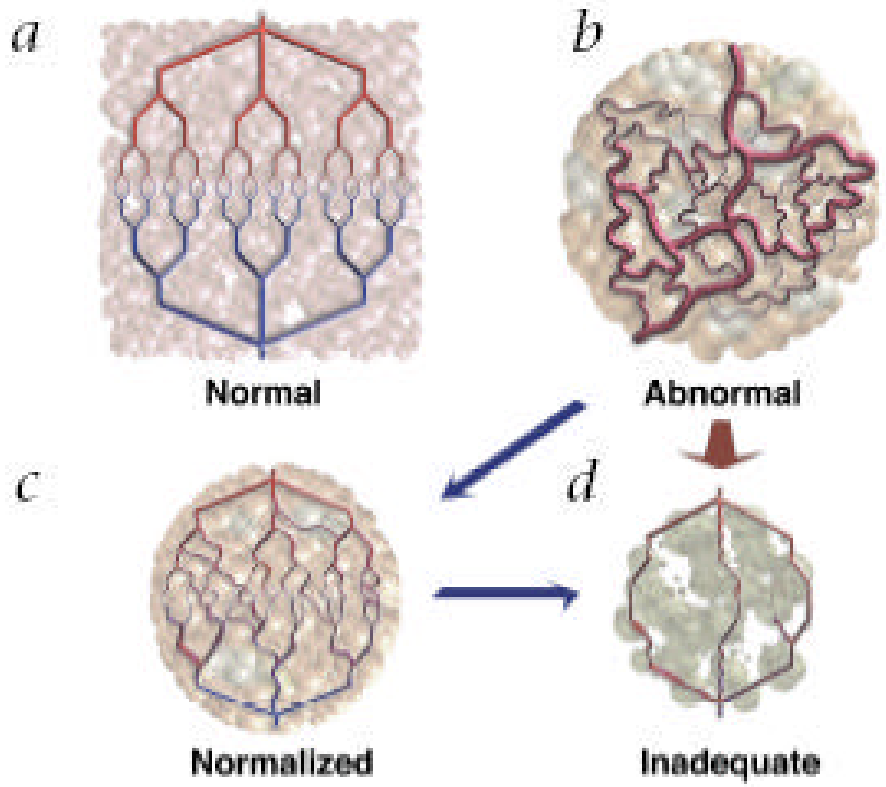
Maindrault-Goebel et al. *ASCO* 2007; abstract 4013

Erstlinientherapie – aktuelle Fragen

- Mono-Chemotherapie oder Kombinationen?
- Welche Zytostatika first-line?
- Therapiedauer?
- Stellenwert von Bevacizumab (Avastin)?
- Stellenwert von Cetuximab?

Bevacizumab

Anti-VEGF-mAK: Normalisierung der Tumorgefäßarchitektur



Im Tumor:

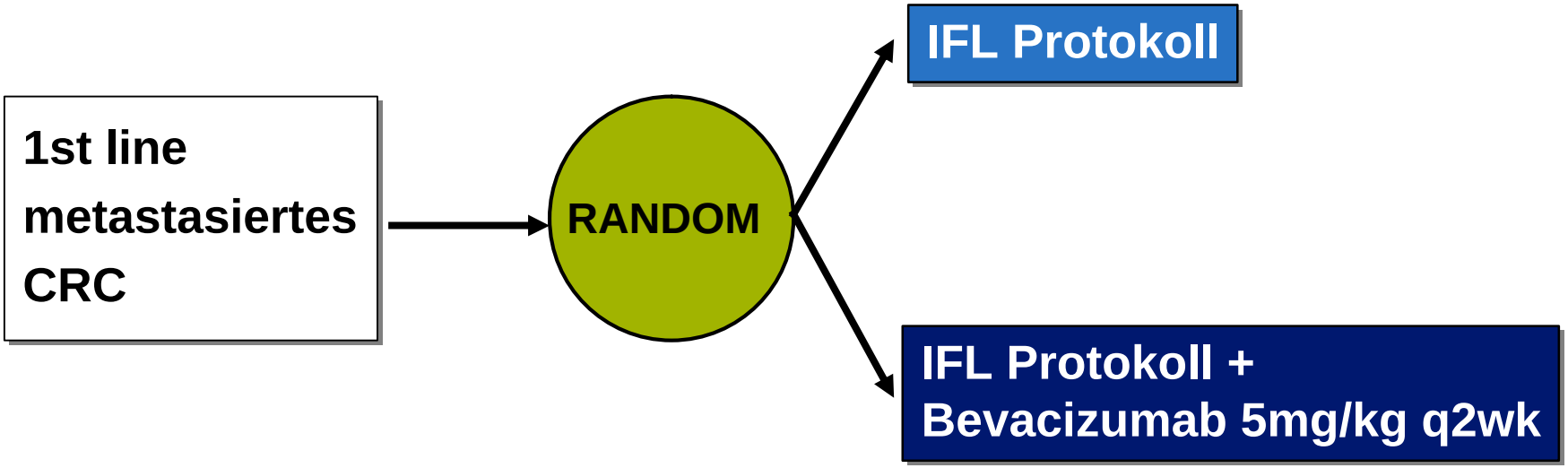
- dilatierte, abnorme Gefäße
- Überschuss Endothelzellen
- hohe Permeabilität
- interstitieller Hochdruck
- Hypoxie

VEGF Blockade:

- Abnahme Gefässdurchmesser, -dichte und –permeabilität
- Zunahme Sauerstoffpartialdruck

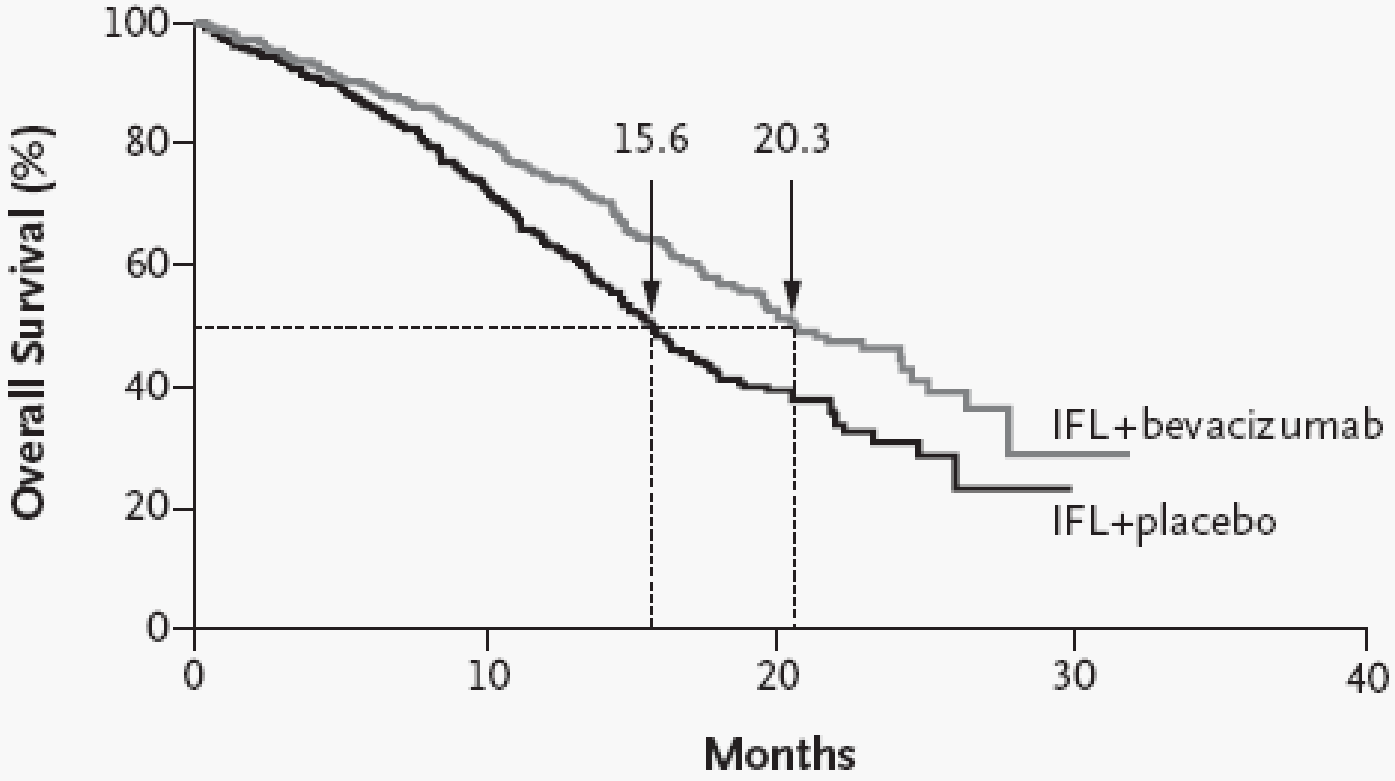
Jain. *Science* 2005: 307: 58-62

Bevacizumab: Hurwitz-Studie



Hurwitz et al. *NEJM* 2004; 350: 2335-2342

Bevacizumab: Hurwitz-Studie



No. at Risk

IFL+bevacizumab	402	362	320	178	73	20	1	0
IFL+placebo	411	363	292	139	51	12	0	0

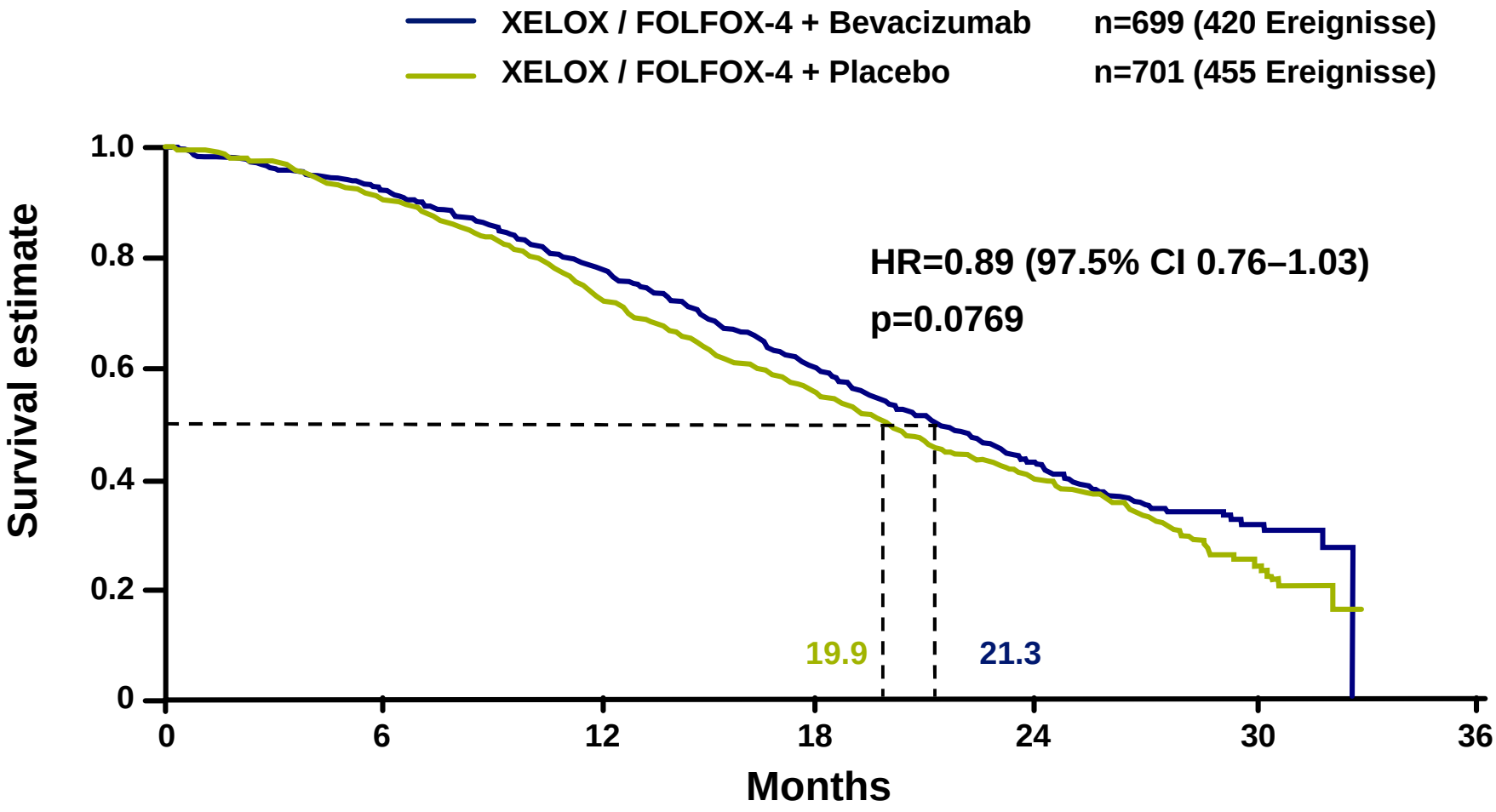
Hurwitz et al. *NEJM* 2004; 350: 2335-2342

Bevacizumab auch aktiv mit anderen Schemata?

Verbesserung der Prognose

Kabbinavar et al. JCO 2005 (gepoolte Analyse)	**5-FU / LV Mono (1st line)**
Giantonio et al. ASCO 2005 (ECOG 3200, Phase III)	**FOLFOX (2nd line)**
Saltz et al. ASCO 2007 (NO16966, Phase III)	**FOLFOX / Xelox (1st-line)**

FOLFOX/Xelox +/- Bevacizumab (NO16966)



Saltz et al. *ASCO* 2007; 350: abstract

FOLFOX/Xelox +/- Bevacizumab

	Chemotherapie + Placebo (n=701)	Chemotherapie + Bevacizumab (n=699)
Behandlungsabbruch[a]	601	582
Progressionsereignis[a]	334 (56%)	221 (38%)
Erkrankungsprogression	327	205
Tod	7	16
Nicht-Progression Events[a]	267 (44%)	361 (62%)
Nebenwirkung	140	213
Protokollverletzung	3	1
Behandlungsverweigerung	53	59
Andere	74	88

Saltz et al. *ASCO* 2007; 350: abstract

Bevacizumab first-line

Die wahrscheinlich besten Kombinationspartner sind noch nicht abschließend in Phase III untersucht

- FOLFIRI
- OPTIMOX

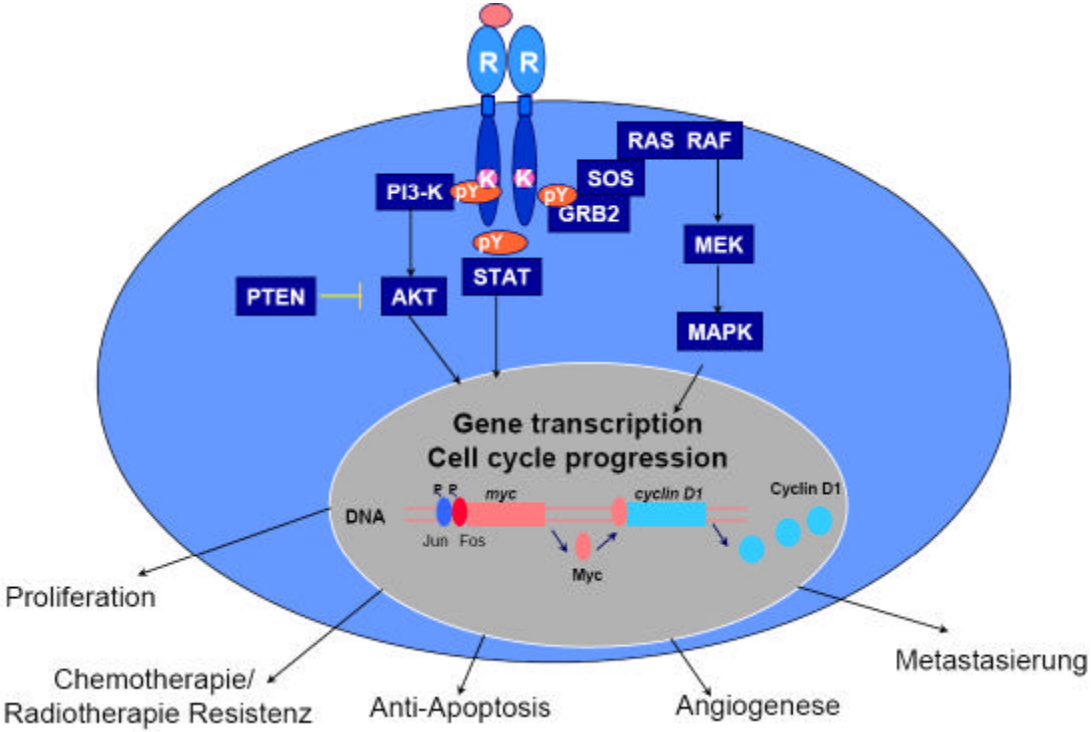
Erstlinientherapie – aktuelle Fragen

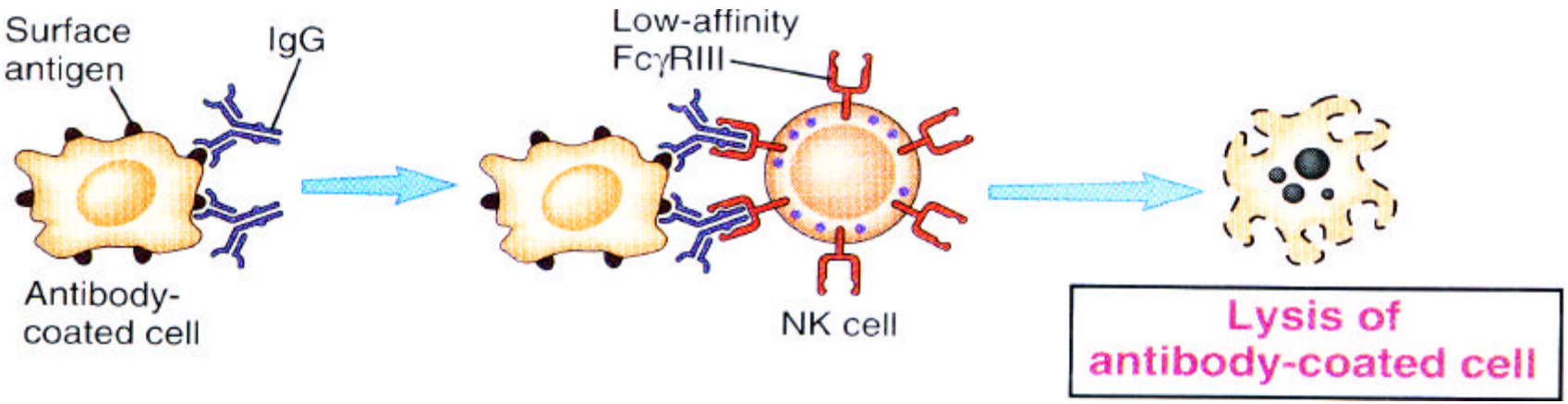
- Mono-Chemotherapie oder Kombinationen?
- Welche Zytostatika first-line?
- Therapiedauer?
- Stellenwert von Bevacizumab?
- Stellenwert von Cetuximab (Erbitux)?

Cetuximab

Anti-EGFR AK (IgG1)

- EGFR Signalkaskade
- ADCC





CRYSTAL: Chemotherapie +/- Cetuximab

EGFR-exprimierendes metastasiertes CRC

R

Cetuximab + FOLFIRI

Cetuximab IV 400 mg/m^2 an Tag 1,
dann 250 mg/m^2 wöchentlich
+ Irinotecan (180mg/m^2)
+ 5-FU (400 mg/m^2 Bolus +
2400 mg/m^2 als 46-hr
kontin. Infusion)
+ FA alle 2 Wochen

FOLFIRI

Irinotecan (180 mg/m^2)
+ 5-FU 400 mg/m^2 Bolus +
2400 mg/m^2 als 46-hr
kontin. Infusion)
+ FA alle 2 Wochen

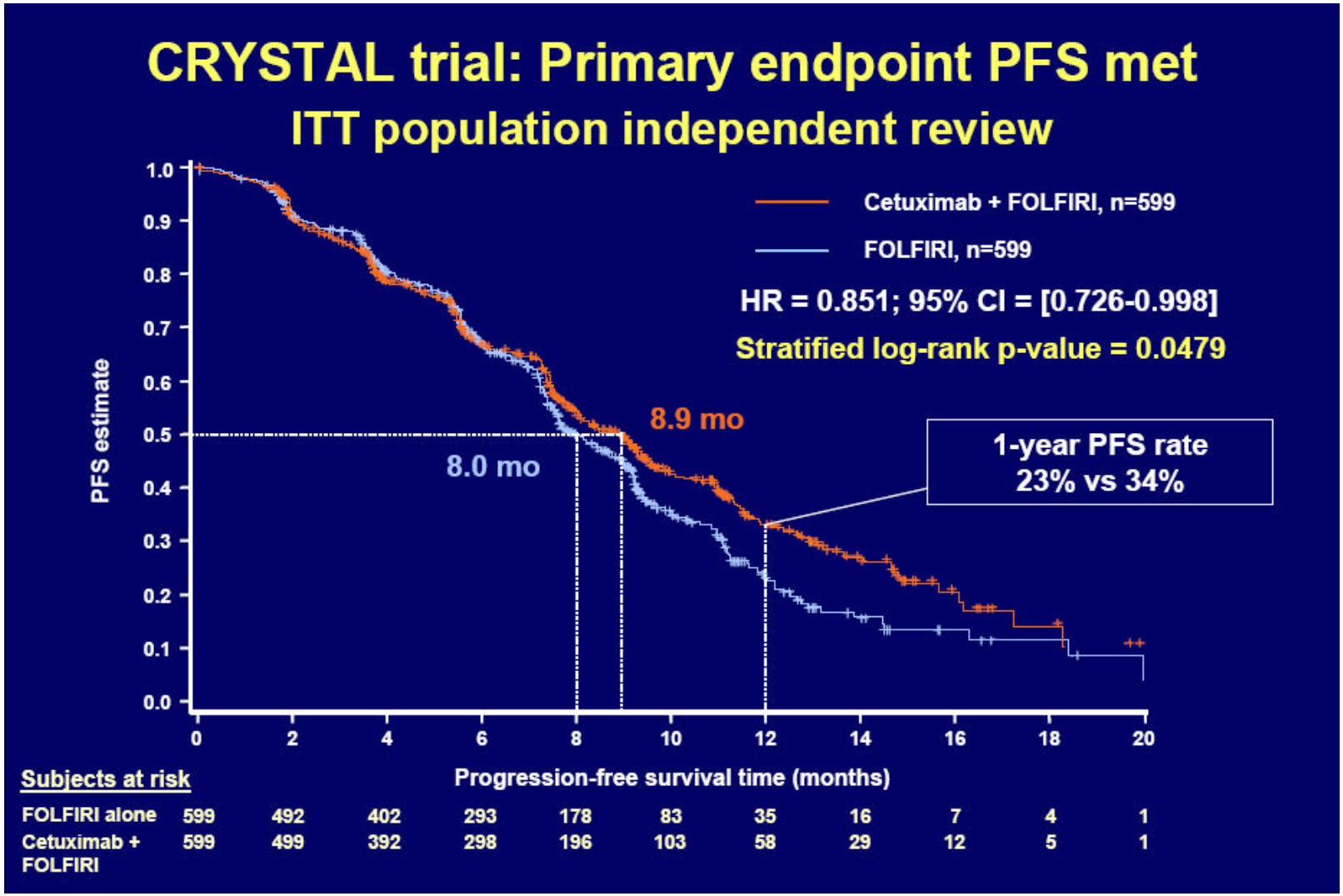
Stratificationsfactoren:

- **Region**
- **ECOG PS**

Populationen

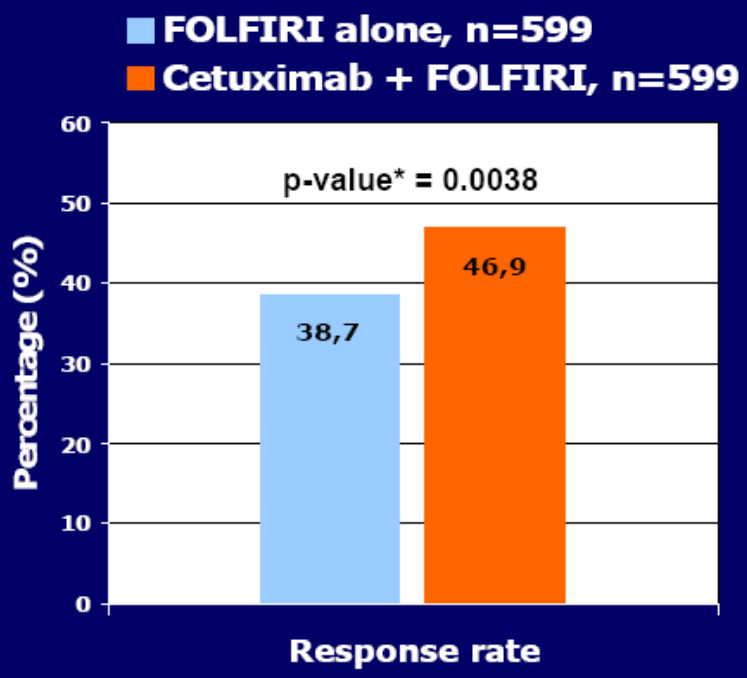
- **Randomisierte Patienten n=1217**
- **Sicherheits Population n=1202**
- **ITT Population: n=1198**

VanCutsem E et al. *ASCO* 2007; abstract 4000



VanCutsem E et al. *ASCO* 2007; abstract 4000

CRYSTAL trial:
Independent assessment of response

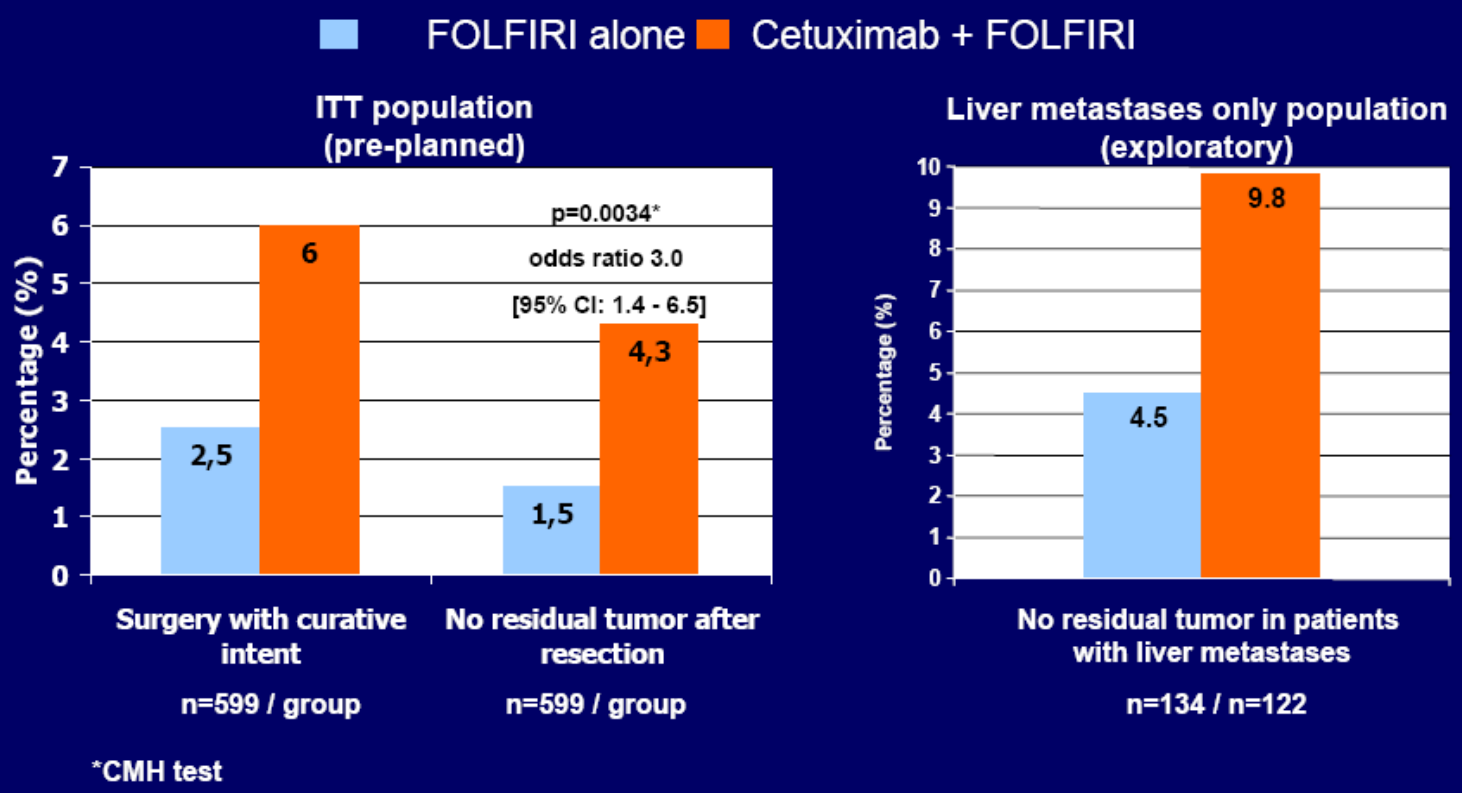


	FOLFIRI %	Cetuximab + FOLFIRI %
CR	0.3	0.5
PR	38.4	46.4
SD	46.7	37.4
PD	9.0	8.8
ORR 95%CI	38.7 [34.8 - 42.8]	46.9 [42.9 - 51.0]
DCR**	85.5	84.3

*Cochran-Mantel-Haenszel (CMH) test ** DCR: disease control rate

VanCutsem E et al. *ASCO* 2007; abstract 4000

CRYSTAL trial:
Surgery with curative intent



VanCutsem E et al. *ASCO* 2007; abstract 4000

Zusammenfassung 1st-line Therapie mCRC

- Kombinationschemotherapie Standard für die meisten Patienten
- Mögliche Ausnahmen: - wenig aggressive Erkrankung / begrenzte Tumorlast
  - und definitiv irresektable Erkrankung
- Immer: Resektabilität im Verlauf erneut prüfen!
- FOLFIRI first-line oder Optimox first-line führen zu den besten Ergebnissen
- Kombination mit Bevacizumab verlängert Progressionszeit (und Überleben)
- Kombination mit Cetuximab erhöht die Ansprechrate und Progressionszeit
- In der Auswahl der 1st-line-Therapie werden berücksichtigt
  - individuelle Therapieziele
  - Komorbiditäten
  - Aggressivität der Erkrankung
  - Vorbehandlung in der adjuvanten Situation