

Chemotherapy in Advanced Colorectal Cancer

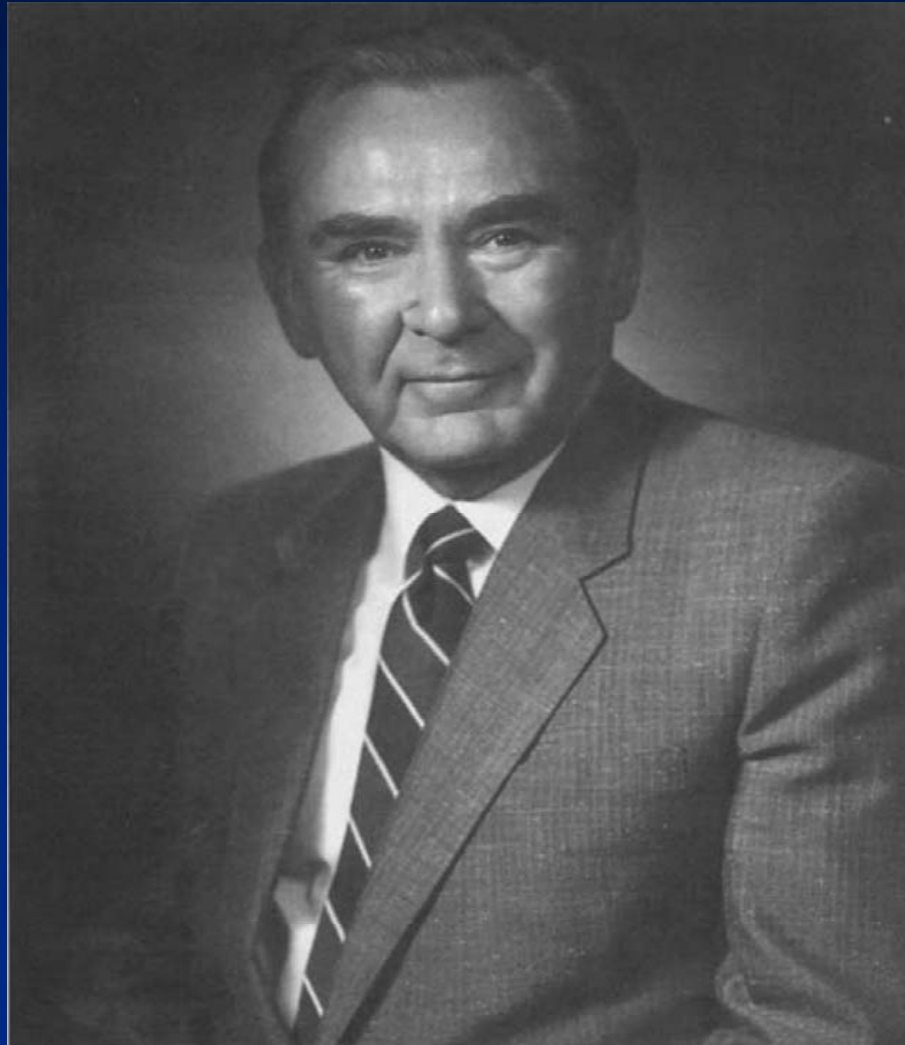
– an historical overview of the past 25
years

Professor John R Zalcbeg OAM

Peter MacCallum Cancer Centre
Melbourne, Australia



Charles G Moertel (1927 – 1994)



Charles Erlichman



“A randomised phase III adjuvant study of 5FU and high dose folinic acid vs. observation in colon cancer”

Principal Investigator:
John R Zalcborg



Key Issues

1. Does chemotherapy improve survival?
2. Does chemotherapy improve QoL?
3. When should chemotherapy be administered in asymptomatic patients?
4. What is optimal initial chemotherapy?

Does chemotherapy improve survival?

- 3 studies compare chemotherapy to no chemotherapy (BSC)
- Median survival significantly increased by chemotherapy

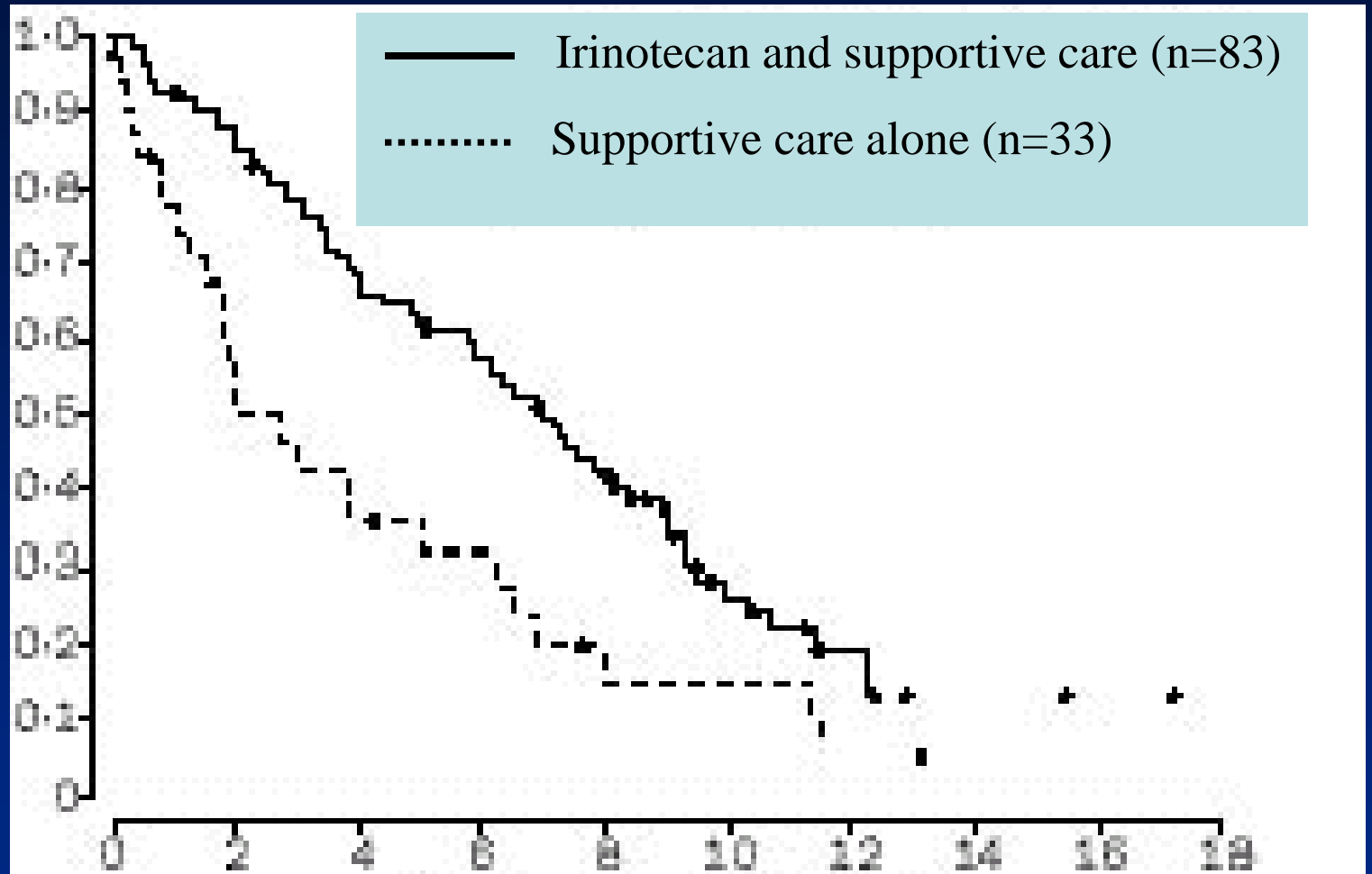
Group (entry, Author, Year	Treatment chemotherapy	Control	Patients entered (evaluated)		Median survival in months	
			Chemo	Control		
GOAL (91-93) Beretta G 1994	5FU +FA +Supportive care	Supportive care only	80 (78)	83 (79)	7.5	5.5
Vienna (88-89) Schielthauer W, 1993	Vienna (88-89) Schielthauer W, 1993	Vienna (88- 89) Schielthauer W, 1993	40(24)	40 (12)	11	5
CRC, UK (88- 93) Allen-Mersh TG 1994	FUDR 0.2mg/1g/24hr by hepatic arterial infusion for 14 days every 28 days	Control	51 (51)	49 (49)	13	8

Does chemotherapy improve QoL?

- Conclusively demonstrated in a number of trials (1st/2nd line)

Significant improvement in pain, PS in patients receiving chemotherapy

Probability



Pain free survival

When should chemotherapy be administered in asymptomatic patients?

1. Nordic Study
2. AGITG/NCIC study

A meta-analysis of two randomised trials of early chemotherapy in asymptomatic metastatic colorectal cancer

SP Ackland^{1,2,3}, M Jones^{1,3}, D Tu⁴, J Simes^{1,3}, J Yuen^{1,3}, A-M Sargeant⁴, H Dhillon^{1,3}, RM Goldberg⁵, E Abdi^{1,7},
L Shepherd⁴ and MJ Moore^{4,5}

¹Australasian Gastro-Intestinal Trials Group and NSW Clinical Oncology Group, Locked Bag 77, Camperdown, NSW 1450, Australia; ²Newcastle Mater Misericordiae Hospital, Locked Bag 7, Hunter Region Mal Centre, NSW 2310, Australia; ³National Health and Medical Research Council, Locked Bag 77, Camperdown, NSW 1450, Australia; ⁴National Cancer Institute of Canada Clinical Trials Group, 10 Alcom Avenue, Suite 200, Toronto, Ontario, Canada M4V 3B1; ⁵Princess Margaret Hospital, 610 University Avenue, Toronto, Canada M5G 2M9; ⁶North Central Cancer Treatment Group, Operations Office, 200 First Street SW, Rochester, MN 55905, USA; ⁷Department of Medical Oncology, Northern Rivers Area Health Services, Tweed Hospital, Powell Street, Tweed Heads, NSW 2485, Australia

Meta-analysis of AGITG and NCIC studies

	Immediate (months)	Delayed (months)	HR
MS	13	11	1.15 CI – 0.79-1.72 p=0.49
PFS	10.2	10.8	1.08 CI – 0.71-1.64 p=0.73

What is optimal initial chemotherapy?

- 5FU / LV
- CPT 11 (irinotecan)
- Oxaliplatin
- The role of single agents
- Biological Agents with or without chemotherapy
- The integration of chemo with surgery for metastatic disease

5FU Regimens

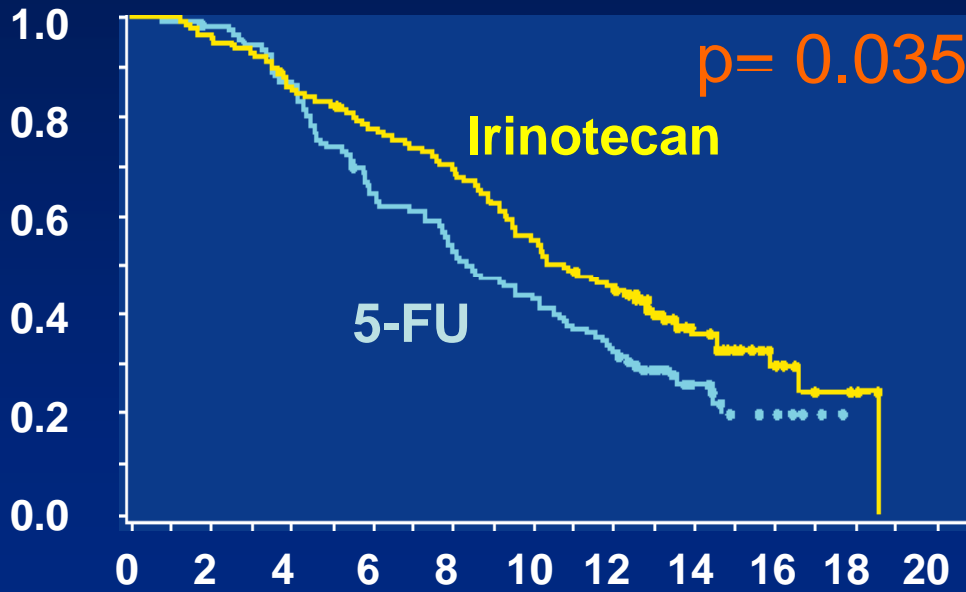
- Roswell Park
- Mayo Clinic
- Machover
- de Gramont
- Oral 5FU
(capecitabine)

What is optimal initial chemotherapy?

- 5FU / LV
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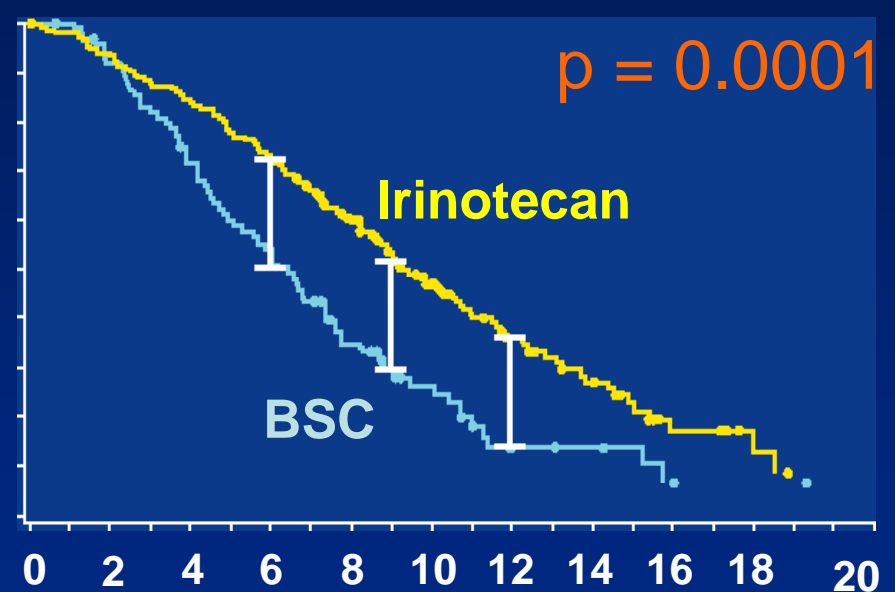
Survival in 2nd line phase III studies with irinotecan

Probability



Irinotecan vs 5-FU

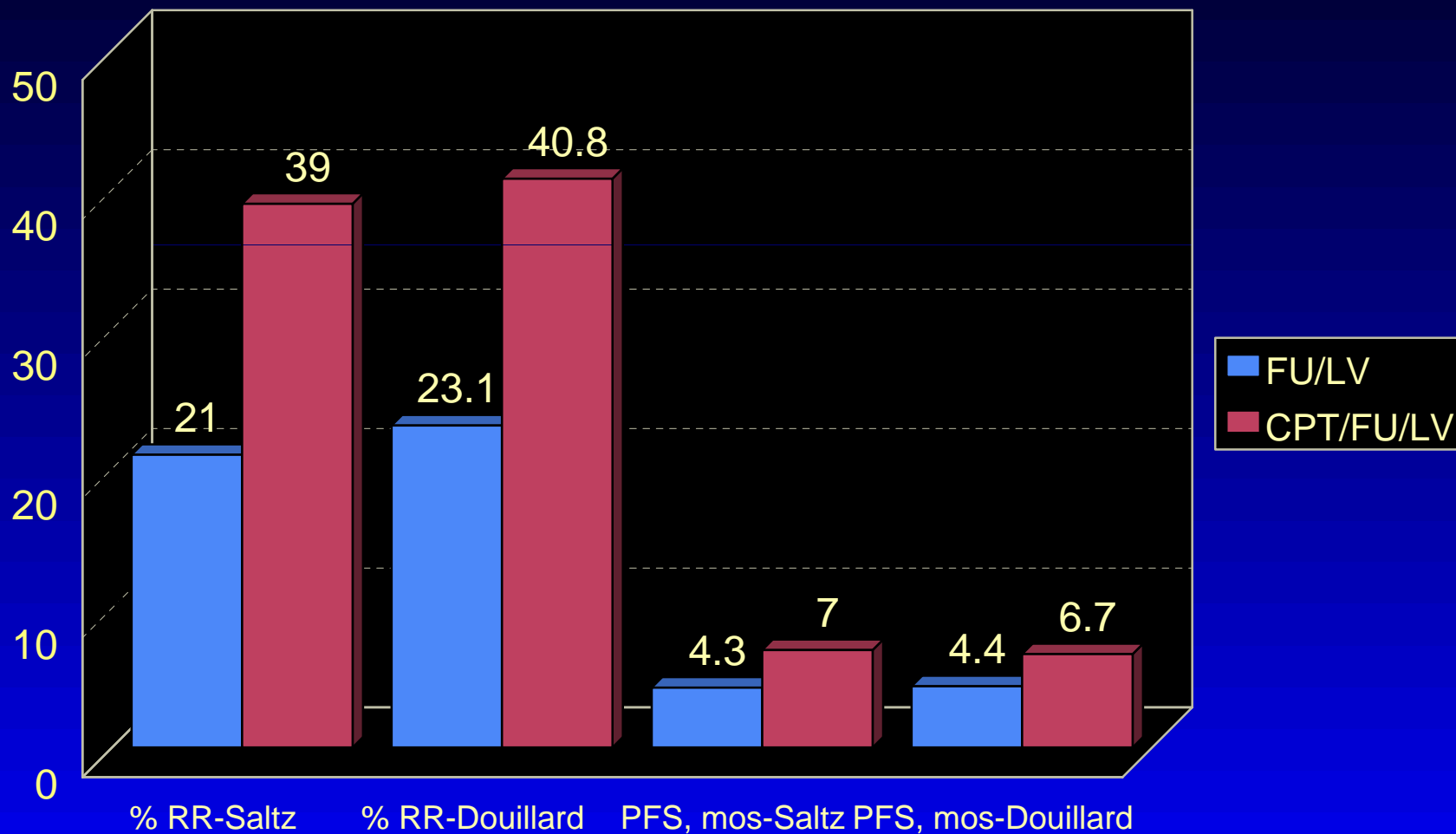
Probability



Irinotecan vs BSC

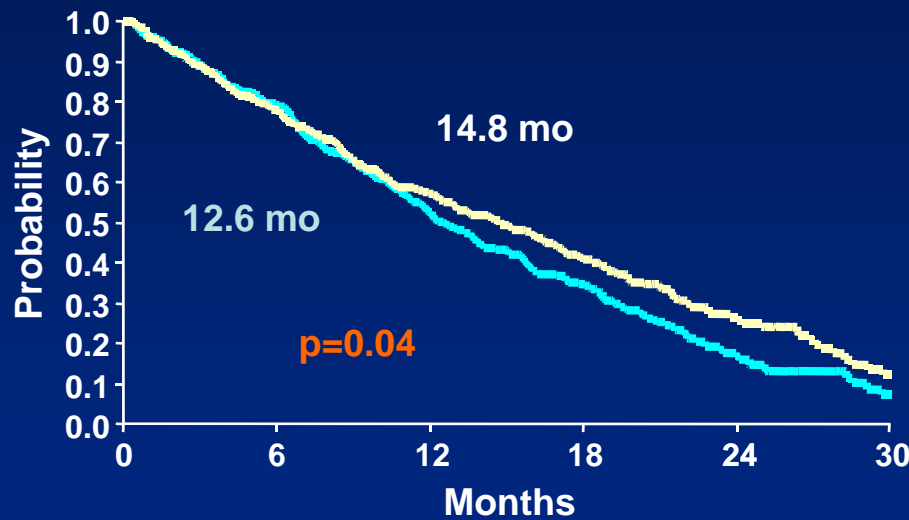
Efficacy of CPT-11/FU/LV

0038 (Saltz) / V303 (Douillard)



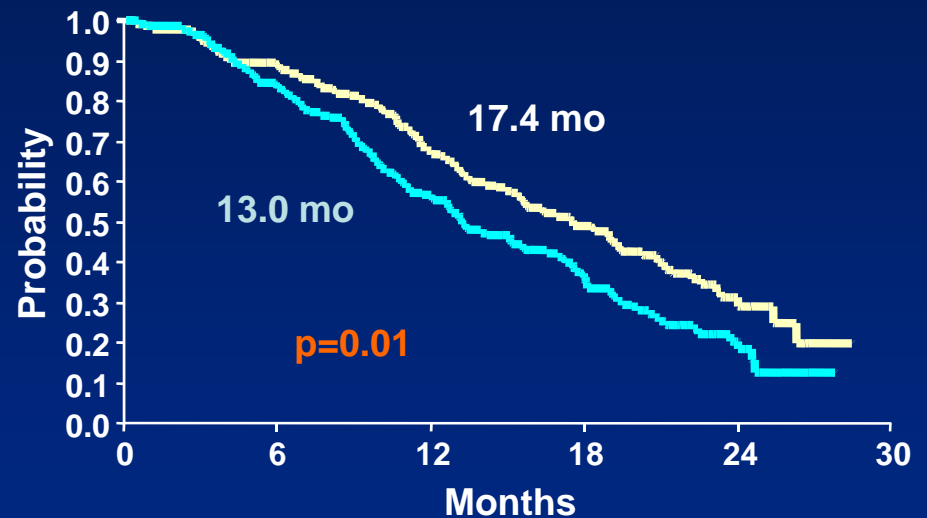
Survival in 1st line phase III studies with 5FU/CPT-11

Bolus IFL (308)



— Saltz CPT-11/5-FU/LV (N=231)
— Mayo Clinic 5-FU/LV (N=226)

Infusional (V303)

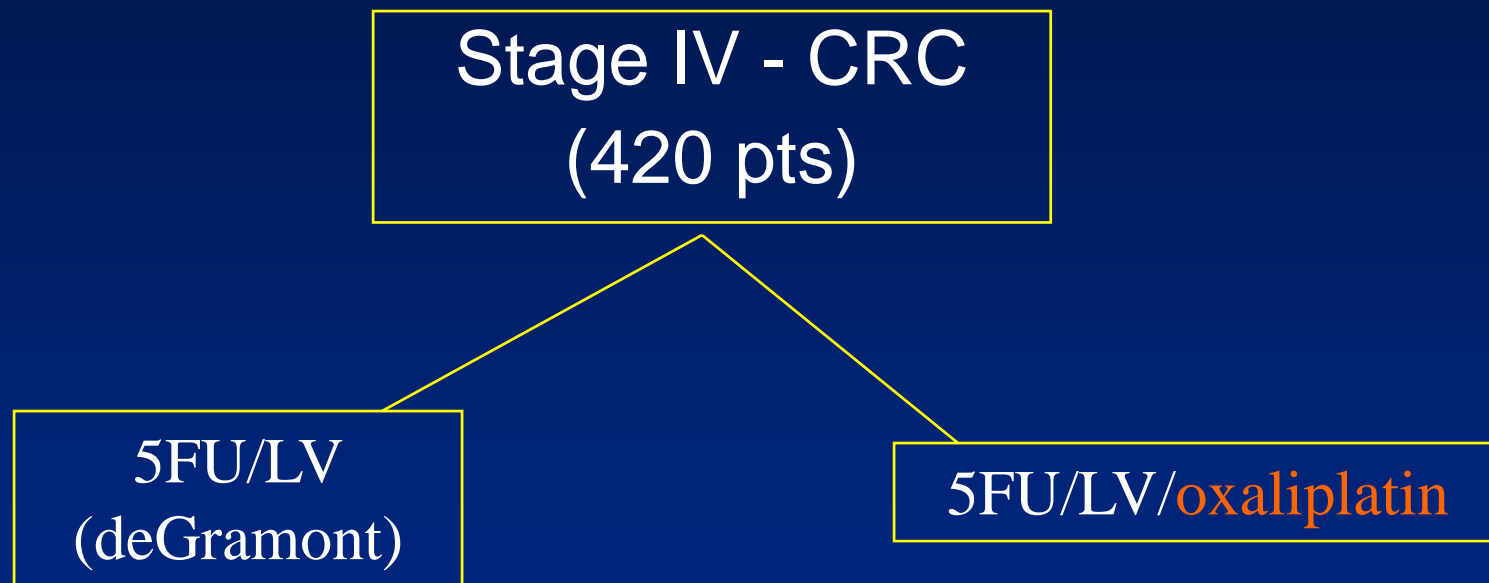


— Douillard CPT-11/5-FU/LV (N=145)
— de Gramont 5-FU/LV (N=143)

What is optimal initial chemotherapy?

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Randomized study of oxaliplatin in 1st line metastatic colorectal cancer



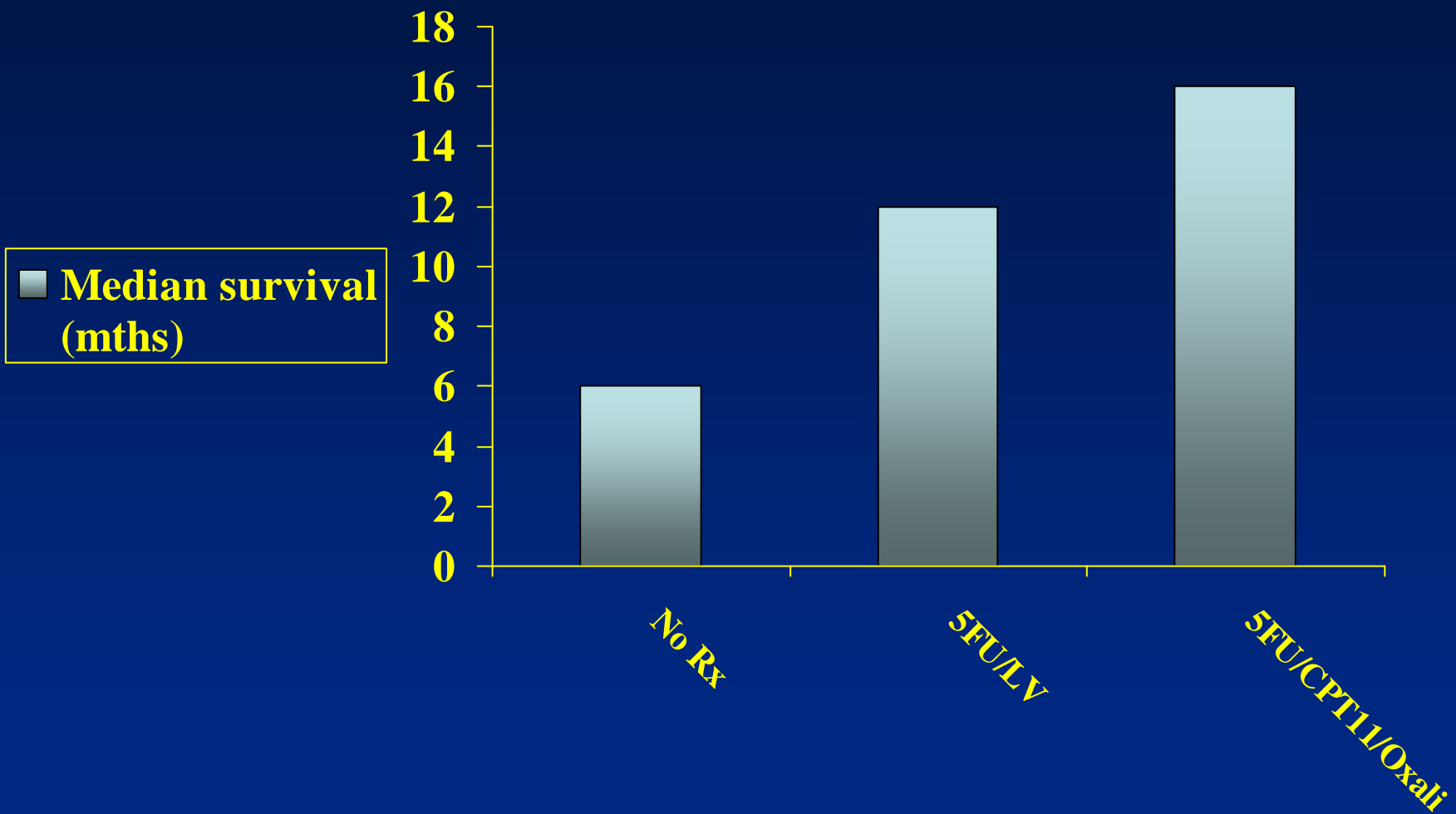
Oxaliplatin in 1st line metastatic colorectal cancer

	5FU/LV	5FU/LV/oxaliplatin
ORR	22.3%	50.7%, p= 0.0001
PFS (mths)	6.2	9.0, p=0.0003
OS (mths)	14.7	16.2, p=0.12

Response rate/Survival data

- 5FU based regimens
 - RR 20%
 - MS 12-14 months

- 5FU/CPT11 or 5FU/oxaliplatin
 - RR 40-50%
 - MS 14-18 months

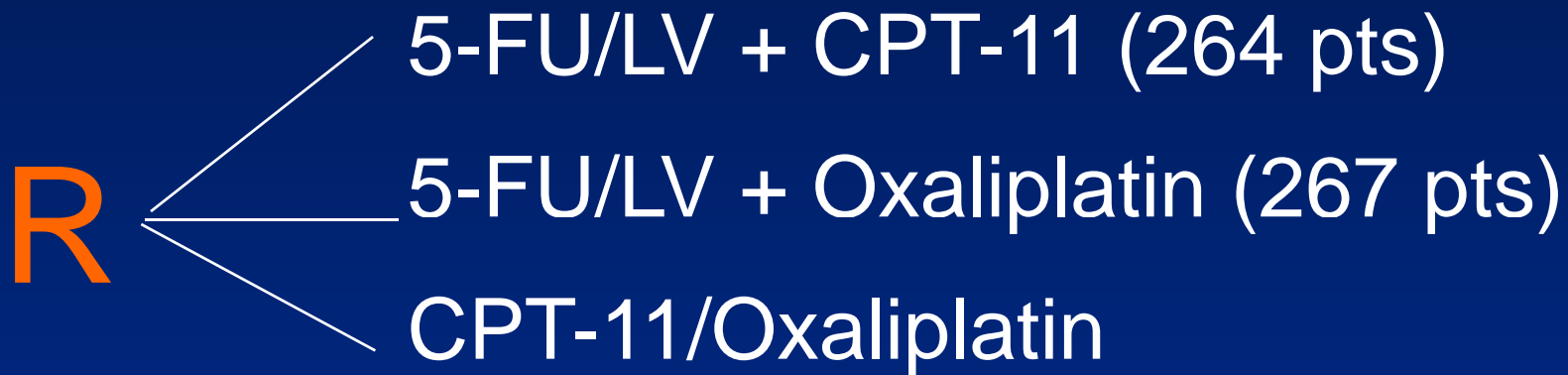


If both 5FU/oxaliplatin and 5FU/CPT11 are active, how should we choose between them?

- N9741 (Goldberg et al)
- V308 (Tournigard et al)

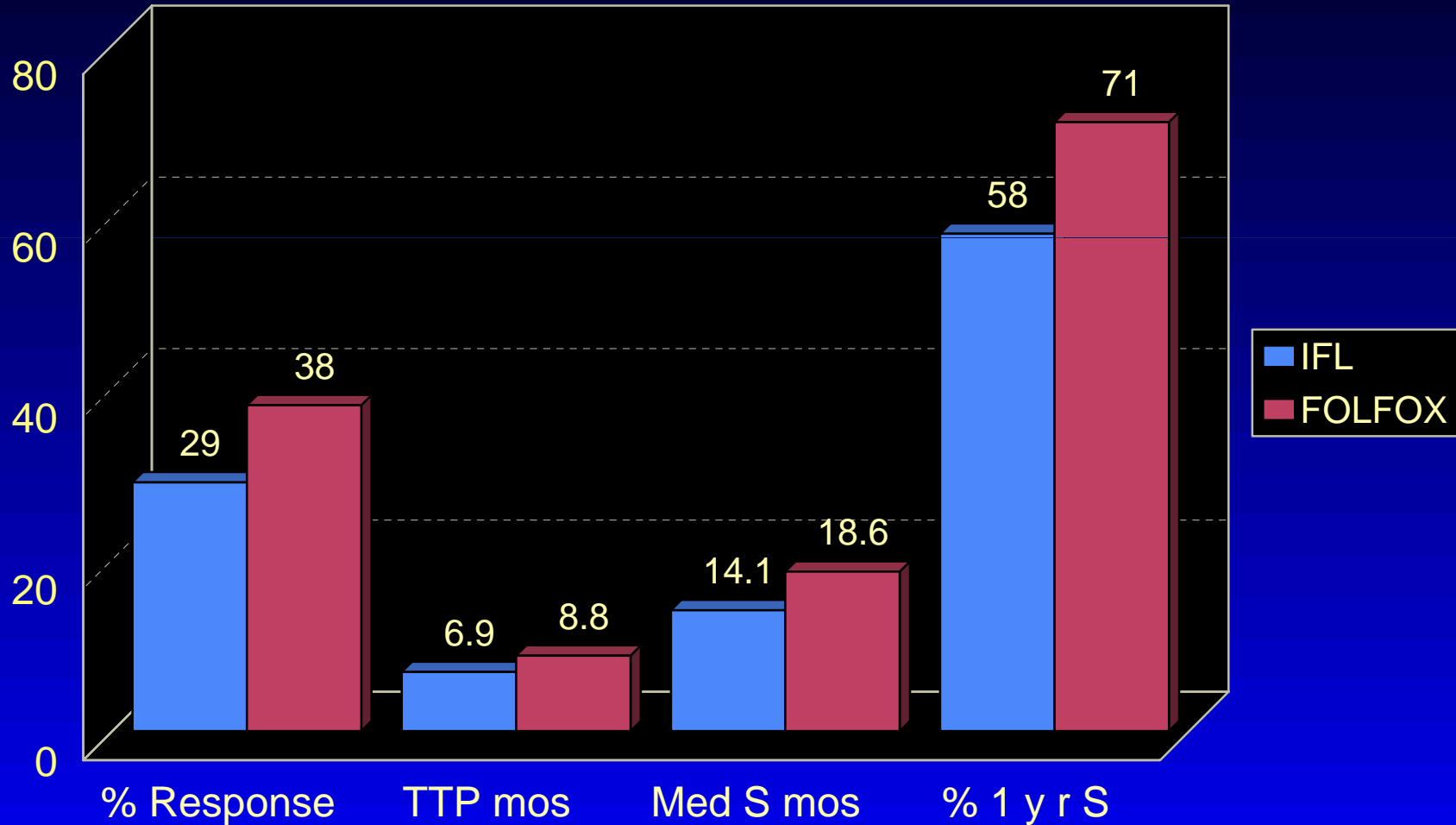
N9741: Schema

Actual Accrual: 795 patients

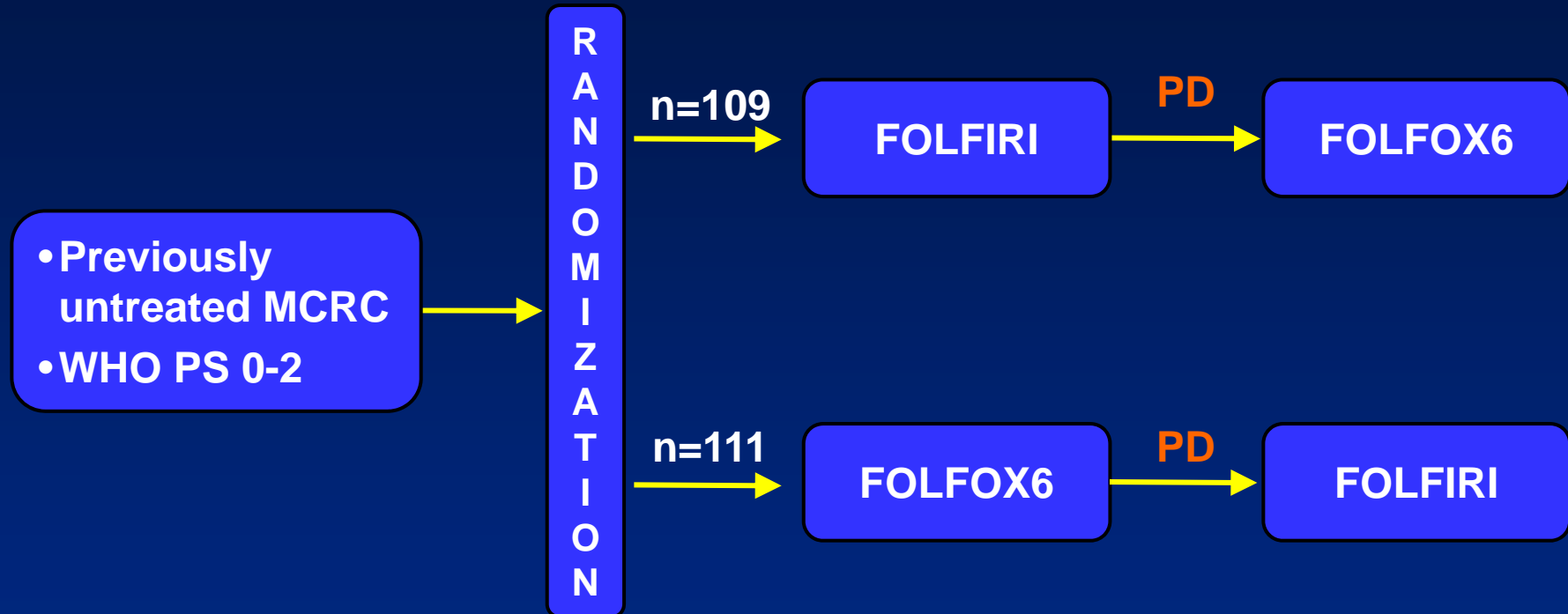


Efficacy of FOLFOX/IFL

N9741



GERCOR C97-3: Comparison of Infused 5-FU Combinations



- Primary end point: TTP on second-line therapy
- Secondary end points: ORR, OS, PFS, and safety

GERCOR C97-3; Efficacy Data

End Point	FOLFIRI	FOLFOX	P-value
RR	56	54	.26
TTP	8.5	8.0	.26
OS	21.5	20.6	.99

Any there any differences between FOLFOX and FOLFIRI?

Study	Year	Patient numbers	Median PFS/TTP	Median OS	Weighted PFS average	Weighted OS average
FOLFIRI						
Douillard	2000	199	6.7 mo	17.4 mo	7.6 mo	18.9 mo
Tournigand	2004	113	8.5 mo	20.9 mo		
Colucci	2005	164	7.0 mo	14.0 mo		
Kohne	2005	214	8.5 mo	20.1 mo		
Fuchs (BICC)	2007	144	7.6 mo	23.1 mo		
FOLFOX/XELOX						
de Gramont	2000	210	9.0 mo	16.2 mo	8.2 mo	18.2 mo
Goldberg	2004	267	8.7 mo	19.5 mo		
Tournigand	2004	111	8.0 mo	21.5 mo		
Colucci	2005	172	7.0 mo	15.0 mo		
Cassidy FOLFOX	2006	317	7.7 mo	17.7 mo		
Cassidy XELOX	2006	317	7.3 mo	18.8 mo		
Ducreux FOLFOX	2007	150	9.7 mo	18.4 mo		
Ducreux XELOX	2007	150	9.3 mo	19.9 mo		

Conclusions

- Activity
 - FOLFOX \approx FOLFIRI
- Toxicity
 - FOLFOX: Neuropathy and neutropenia
 - FOLFIRI: GI, alopecia

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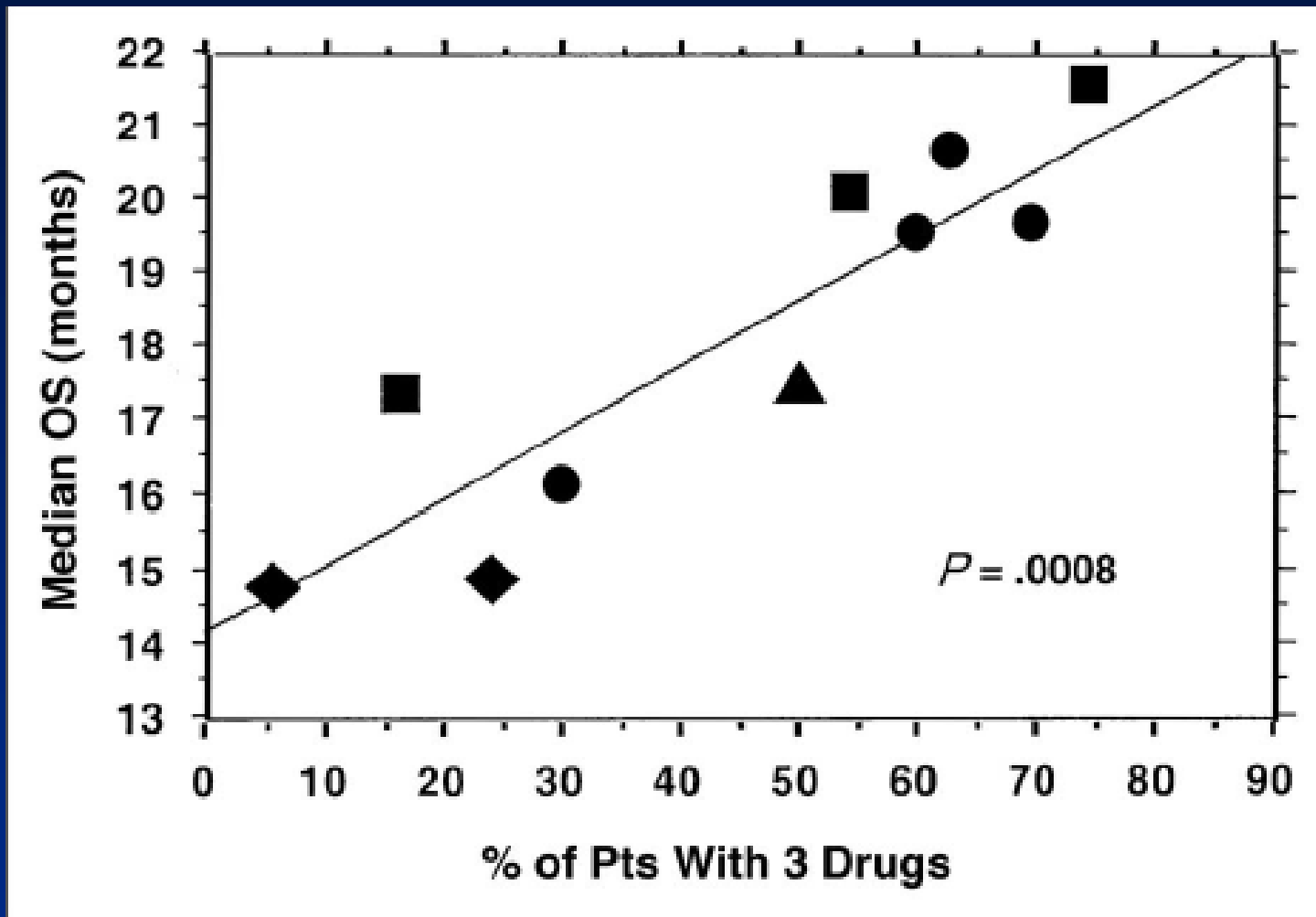
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Survival of Patients With Advanced Colorectal Cancer Improves With the Availability of Fluorouracil-Leucovorin, Irinotecan, and Oxaliplatin in the Course of Treatment

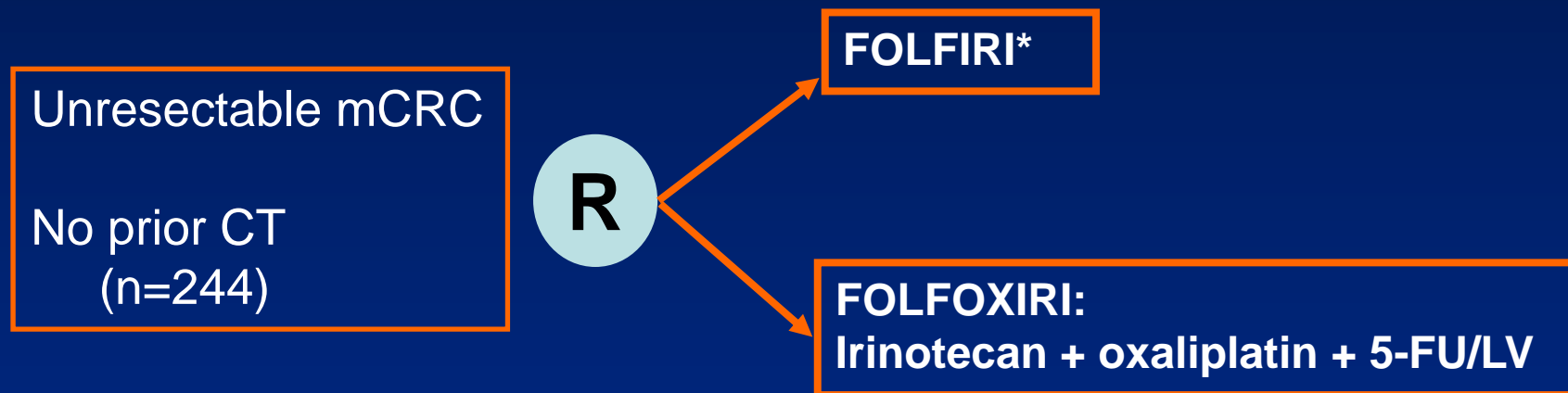
Axel Grothey, Daniel Sargent, Richard M. Goldberg, and Hans-Joachim Schmoll





1st line FOLFOXIRI vs. FOLFIRI for mCRC

Gruppo Oncologico Nord Ovest (GONO) trial (Phase 3)



***An oxaliplatin-containing regimen was recommended after progression on FOLFIRI**

Response rate for FOLFOXIRI vs. FOLFIRI

Response, % patients	FOLFIRI	FOLFOXIRI
ORR [CR+ PR] ^a	41	66
CR	6	8
PR	35	58
SD	33	21
PD	24	11
Not evaluable	2	2
Confirmed response rate ^b	34	60

^ap=0.0002; ^bexternal review panel, p<0.0001

The logo for Peter Mac, featuring a stylized 'i' and 'i' in red and blue, followed by the name 'Peter Mac' in a blue cursive script.

What is optimal initial chemotherapy?

- 5FU / LV
- CPT 11 (irinotecan)
- Oxaliplatin
- **The role of single agents**
- Biological agents with or without chemotherapy
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Focus

(2100 pts)

Strategy A

- 5FU followed by salvage treatment

Strategy B

- 5FU followed by either FOLFIRI or FOLFOX

Strategy C

- FOLFIRI or FOLFOX at start of treatment

Overall survival

Plan	First 2 drugs schedule	Median OS
A	FU then Ir	13.9
B(ir)	FU then FU/Ir	14.8
B(ox)	FU then FU/Ox	15.2
C(ir)	1 st -line FU/Ir	16.3
C(ox)	1 st -line FU/Ox	15.2

Focus

Number of patients receiving
salvage treatment

- Strategy A + B 43%
- Strategy C 55%

Focus

Number of patients that received
all 3 drugs **

- Strategy A 16%
 - Strategy B 19%
 - Strategy C 33%
- No difference whether irinotecan or oxaliplatin given first

** Seymour et al, Lancet July 2007

Randomized study of sequential versus combination chemotherapy with capecitabine, irinotecan and oxaliplatin in advanced colorectal cancer

a study of the Dutch Colorectal Cancer Group (DCCG)

CJA Punt et al.

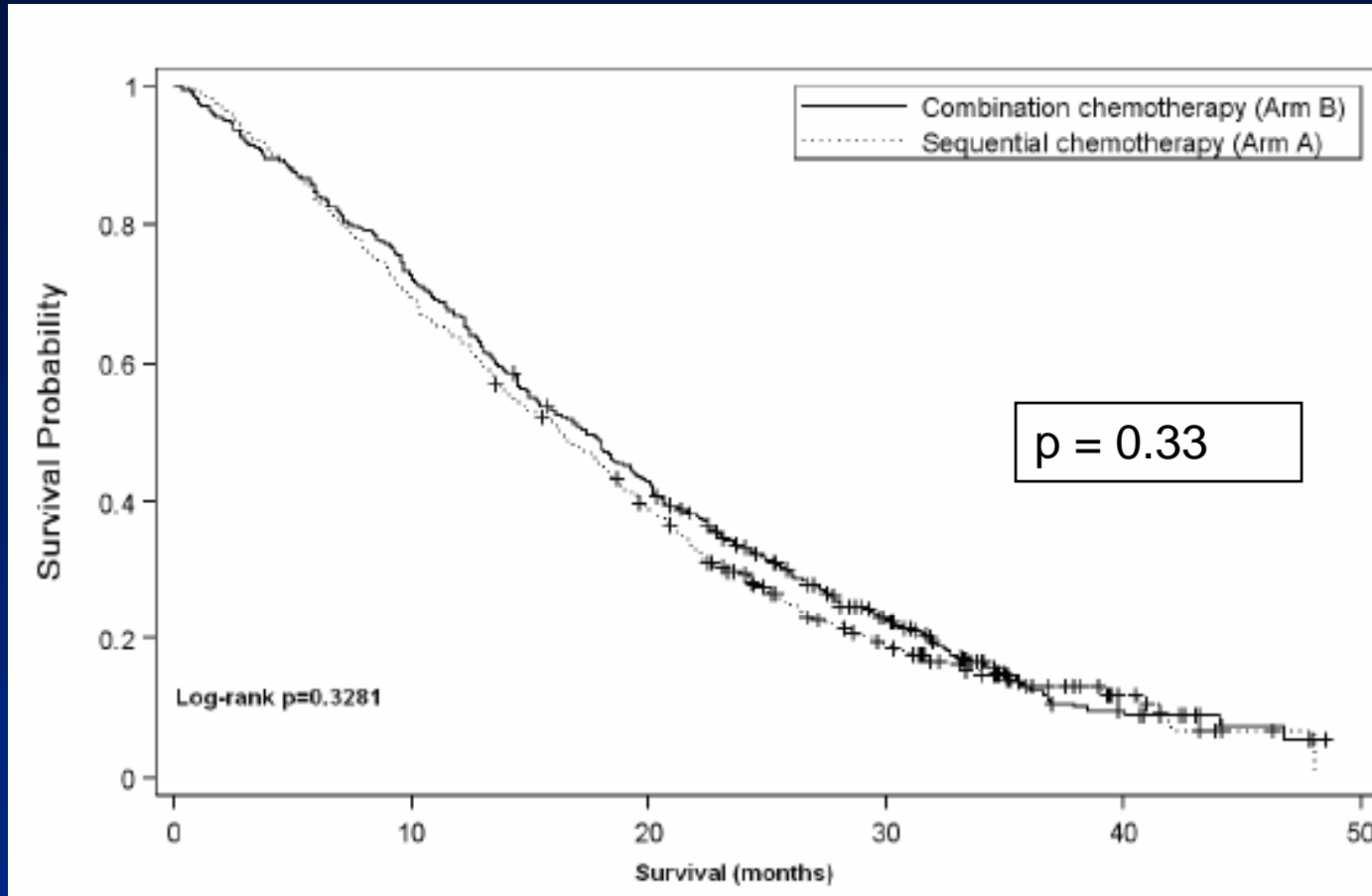
ASCO 2007



Efficacy

End Point	Singles N=397	Combo N=398	P-value
Response rate (%)	20%	41%	na
PFS (mos)	5.8	7.8	0.0002
OS (mos)	16.3	17.4	0.33

Median Overall Survival

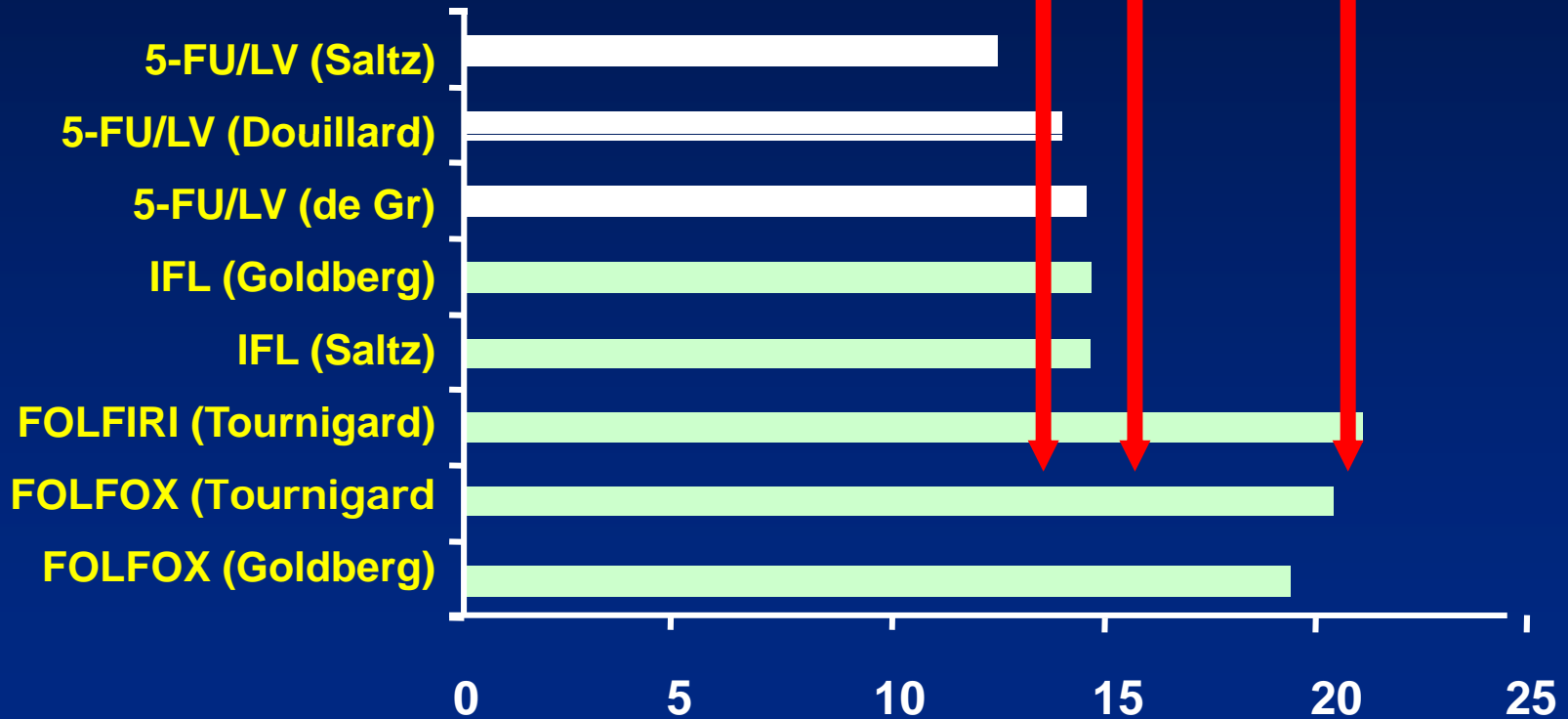


————— **Combination treatment 17.4 months (15.2-19.2)**

----- **Sequential treatment 16.3 months (14.3-18.2)**

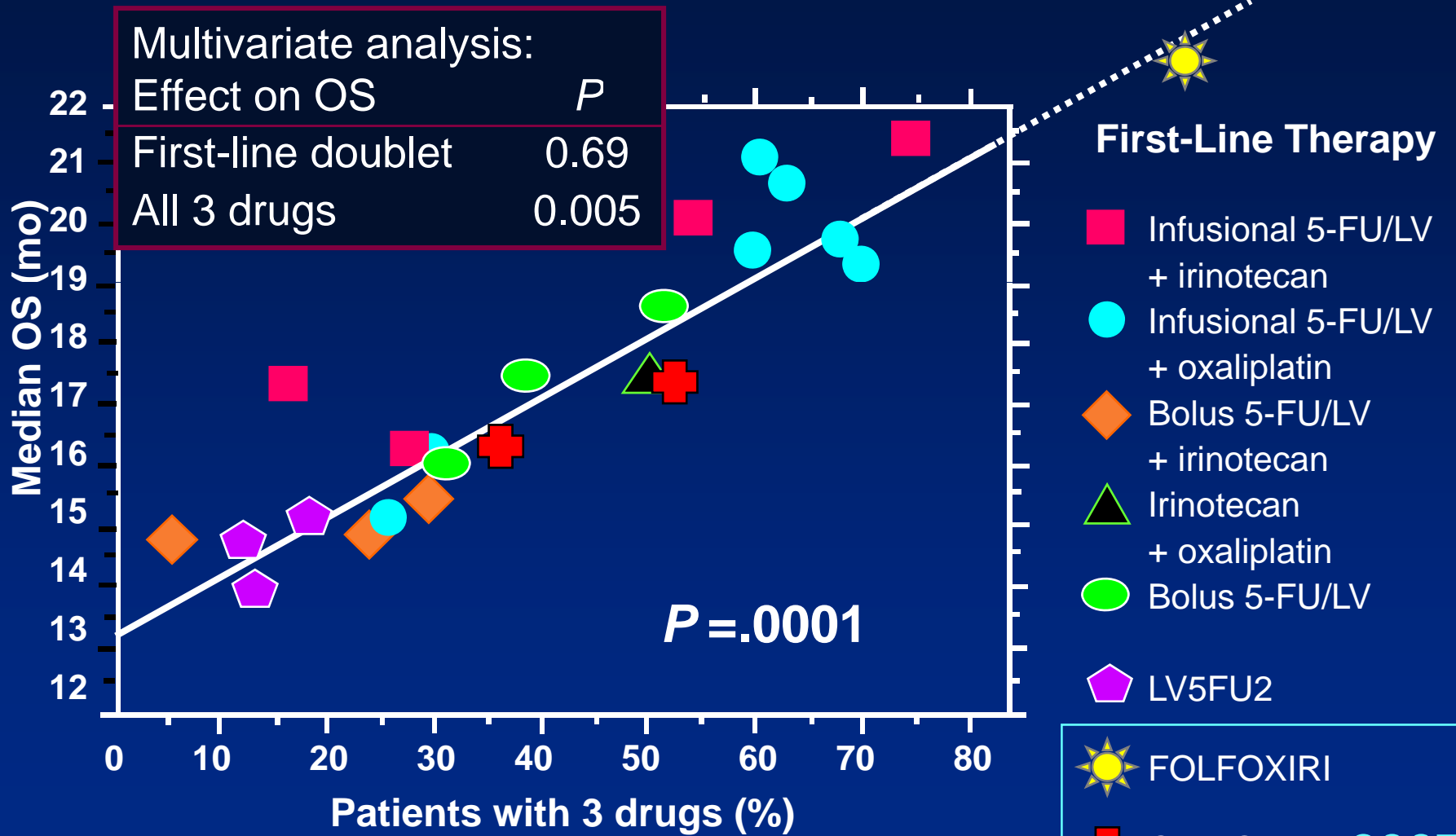
Best OS for 1st Line: 1,2, or 3 Agents

FOCUS CAIRO FOLFOX, FOLFIRI



Concept of "All-3-Drugs" - Update 2005

11 Phase III Trials, 5768 Patients



$OS (mos) = 13.2 + (\%3drugs \times 0.1), R^2 = 0.85$

2007

Single agent fluorouracil for first-line treatment of advanced colorectal cancer as standard?

**Hans-Joachim Schmoll, Daniel Sargent*

www.thelancet.com Vol 370 July 14, 2007

Peter Mac

Single agent fluorouracil for first-line treatment of advanced colorectal cancer as standard?

- Who should get upfront **combination** therapy?
 - Patients who may become resectable with a good response
 - Patients whose quality of life may improve with a tumor response
 - Patients who are unlikely to get second and third line treatment regimens (e.g., aggressive tumors)

Single agent fluorouracil for first-line treatment of advanced colorectal cancer as standard?

- Who should get upfront **single agent** therapy?
 - Patients who have relatively indolent disease, and who can expect to receive additional lines of therapy
 - Patients with good quality of life who are not interested in trading it for improvements in the therapy's efficacy

What is optimal initial chemotherapy?

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- Oxaliplatin
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- **Biological agents with or without chemotherapy**
- The integration of chemo with surgery for metastatic disease

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JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

JUNE 3, 2004

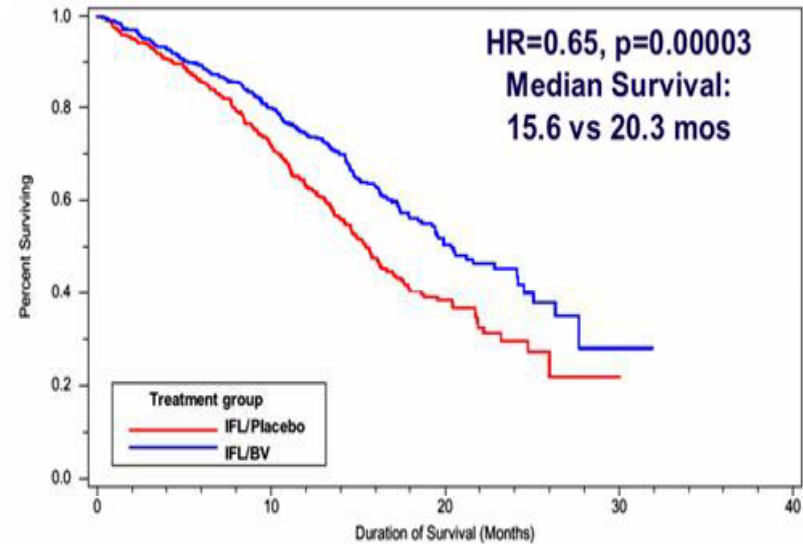
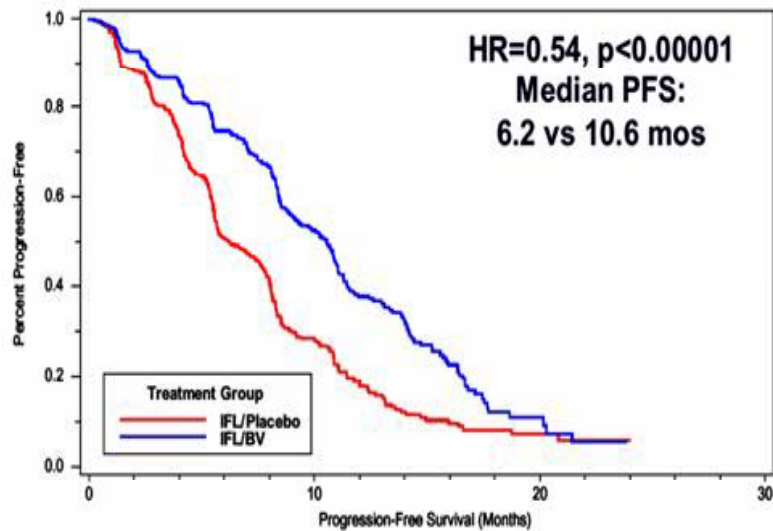
VOL. 350 NO. 23

Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin
for Metastatic Colorectal Cancer

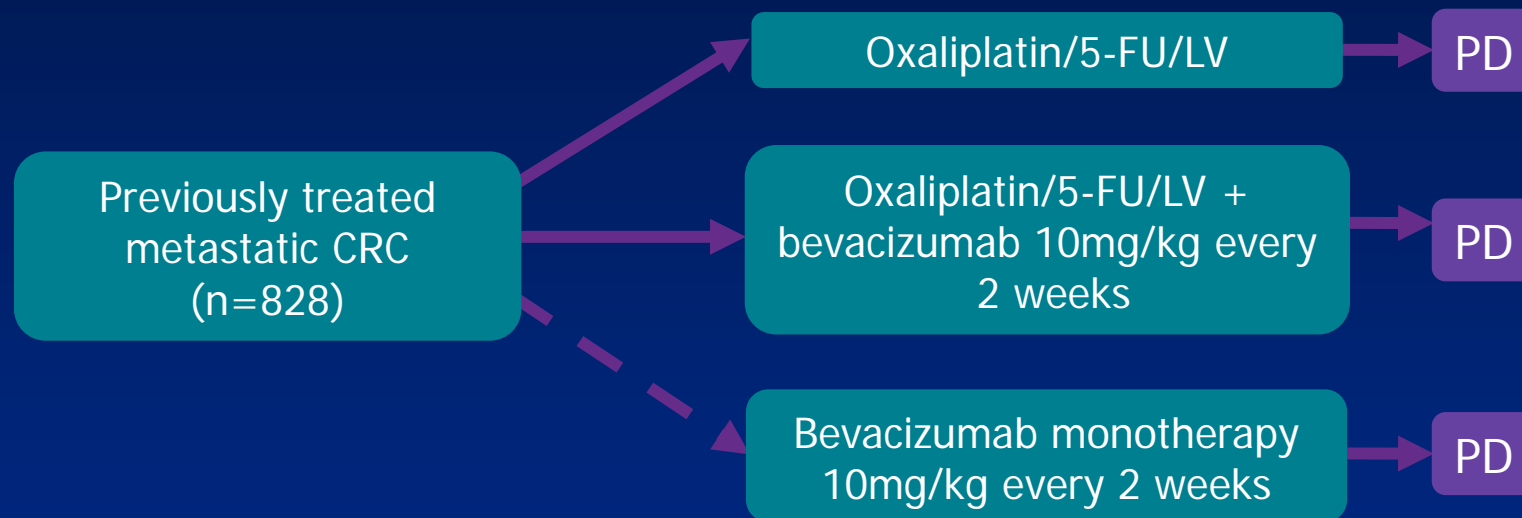
Herbert Hurwitz, M.D., Louis Fehrenbacher, M.D., William Novotny, M.D., Thomas Cartwright, M.D.,
John Hainsworth, M.D., William Heim, M.D., Jordan Berlin, M.D., Ari Baron, M.D., Susan Griffing, B.S.,
Eric Holmgren, Ph.D., Napoleone Ferrara, M.D., Gwen Fyfe, M.D., Beth Rogers, B.S., Robert Ross, M.D.,
and Fairooz Kabbinavar, M.D.

Peter Mac

CPT 11/ 5-FU + Bevacizumab in 1st CRC: PFS and OS

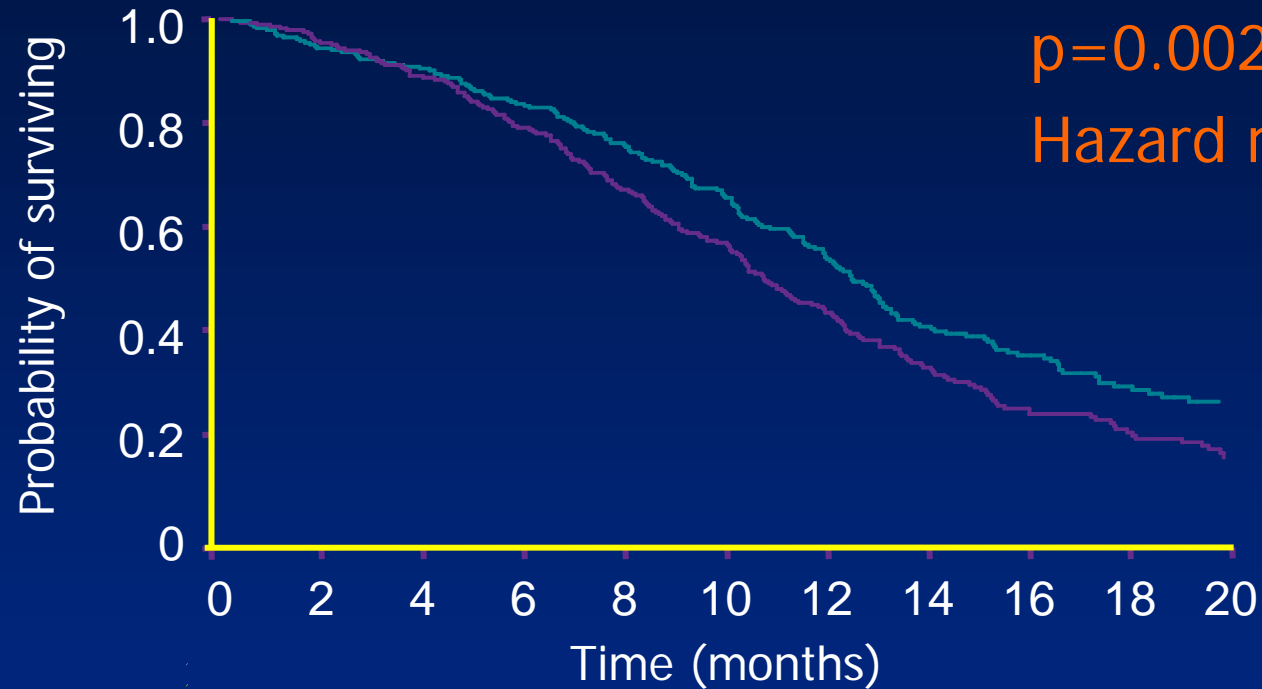


Phase III trial of FOLFOX4 ± bevacizumab in 2nd line CRC: E3200



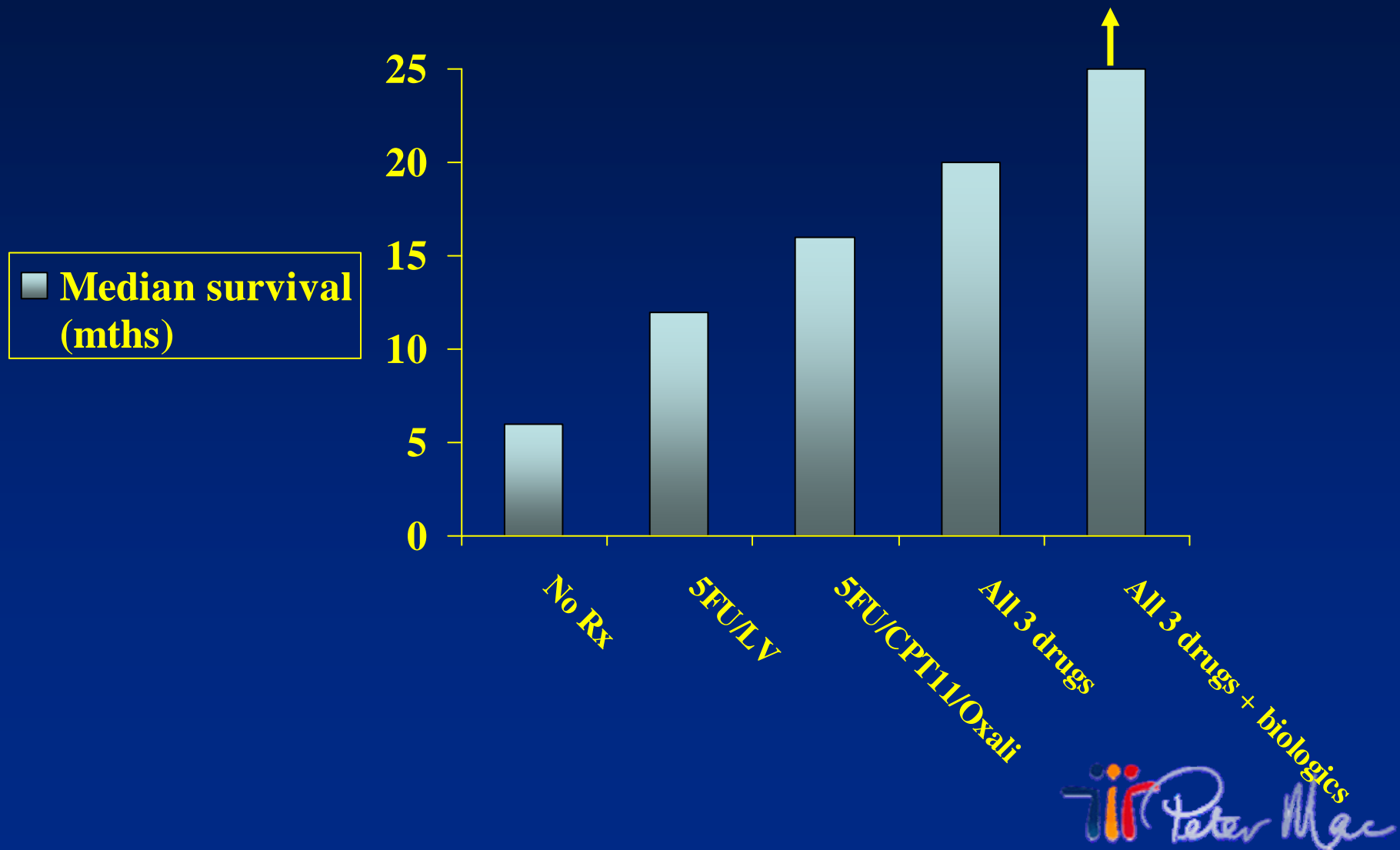
Primary endpoint: survival

E3200: overall survival



	Total	Median
 FOLFOX4 + bevacizumab	290	12.5
 FOLFOX4	289	10.7

Impact of Chemotherapy



Timing issues for chemo and bevacizumab

- Duration of chemo
- Duration of bevacizumab

Duration of chemo

- GISCAD study
- Optimox 1
- Optimox 2
- CONcePT

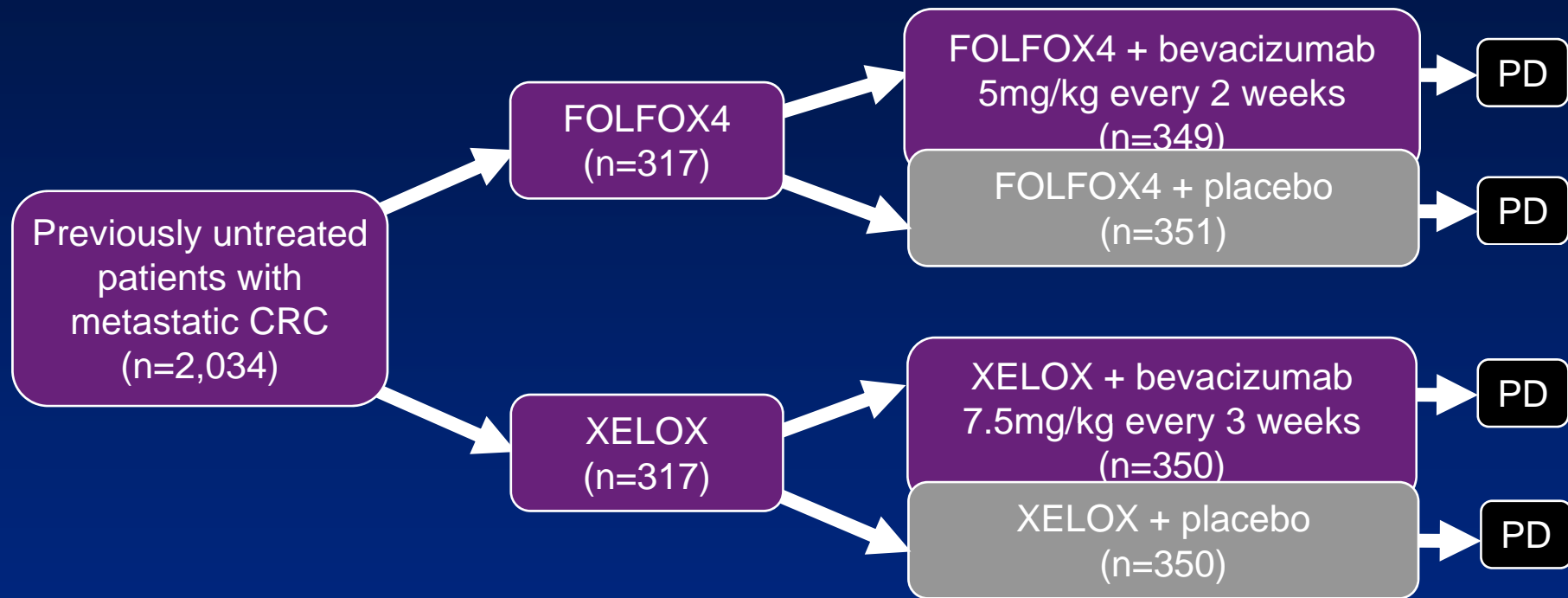
Conclusion:

Intermittent chemo +/- maintenance is an acceptable option; cumulative toxicity is reduced and efficacy is maintained

Timing issues for chemo and bevacizumab

- Duration of chemo
- Duration of bevacizumab

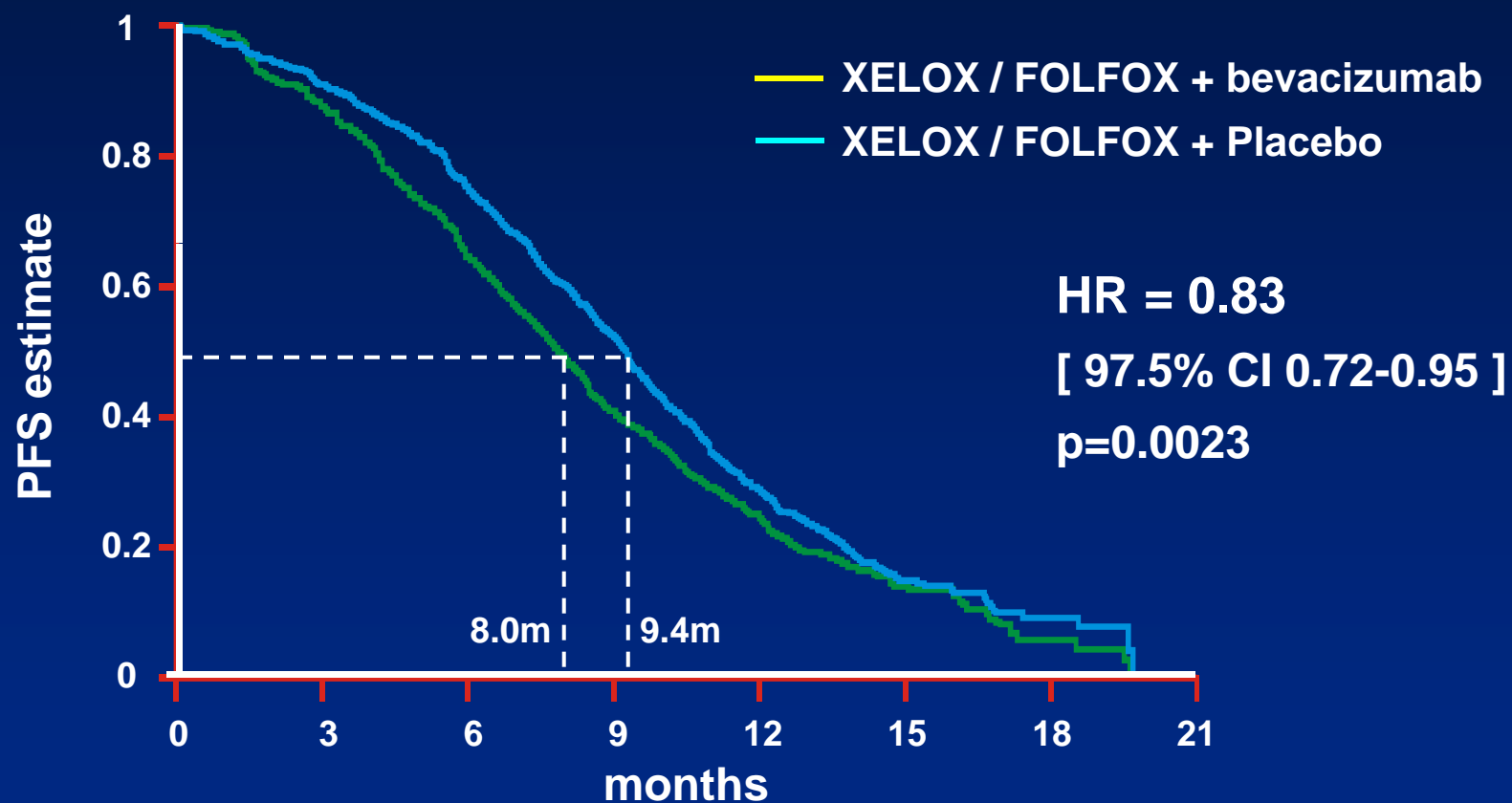
Phase III trial of XELOX/FOLFOX4 ± bevacizumab (NO16966): study design



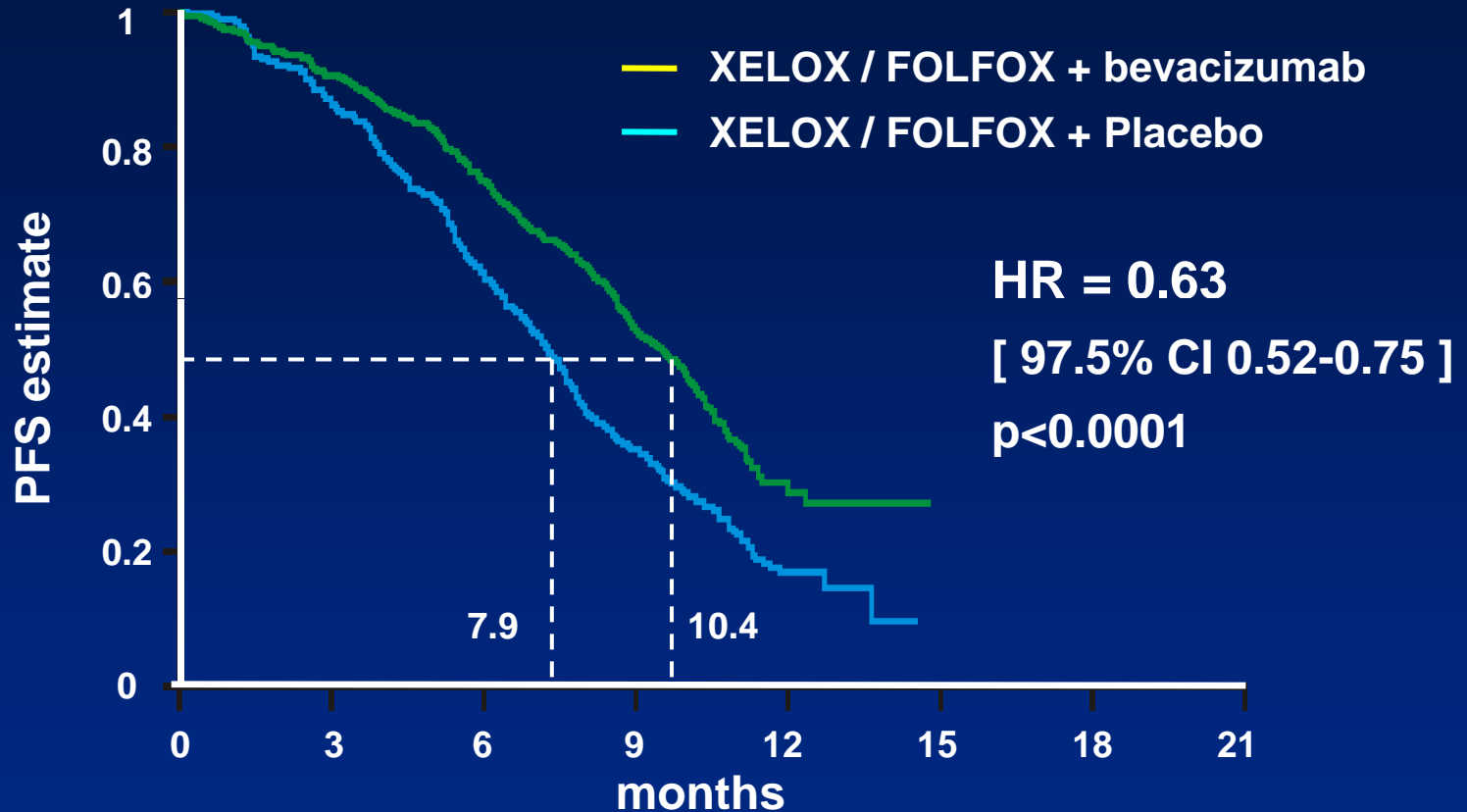
Cassidy et al. ESMO 2006 (Abst LBA3) Cassidy et al. ASCO 2007 (Abst 4030) Saltz et al ASCO 2007

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NO16966: PFS with oxali-based chemo plus bevacizumab



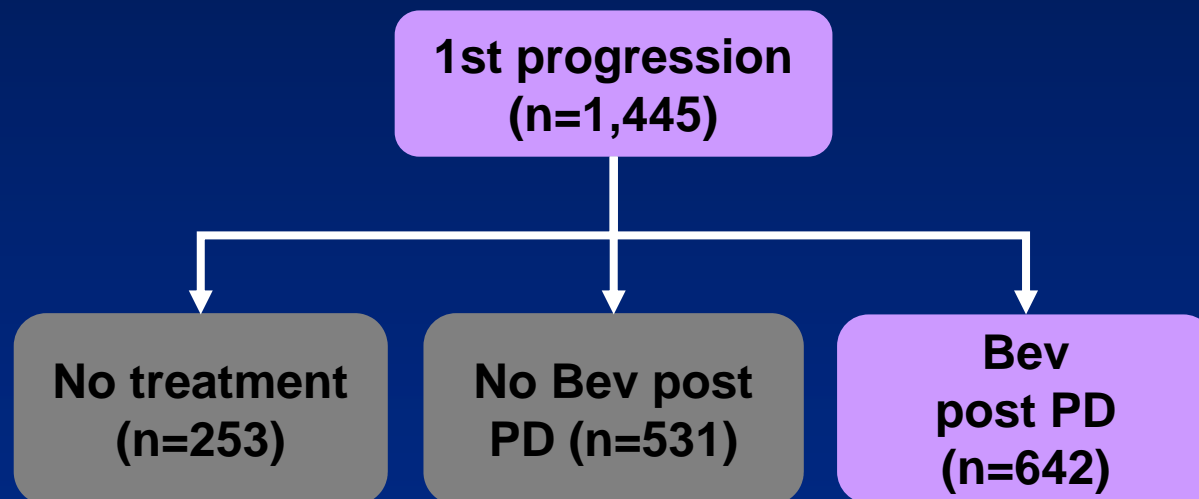
NO16966: 'on treatment' PFS with oxali-based chemo



On treatment PFS = pts who received treatment with bev until progression
This was a pre-specified analysis set up to test the effect of continued bev

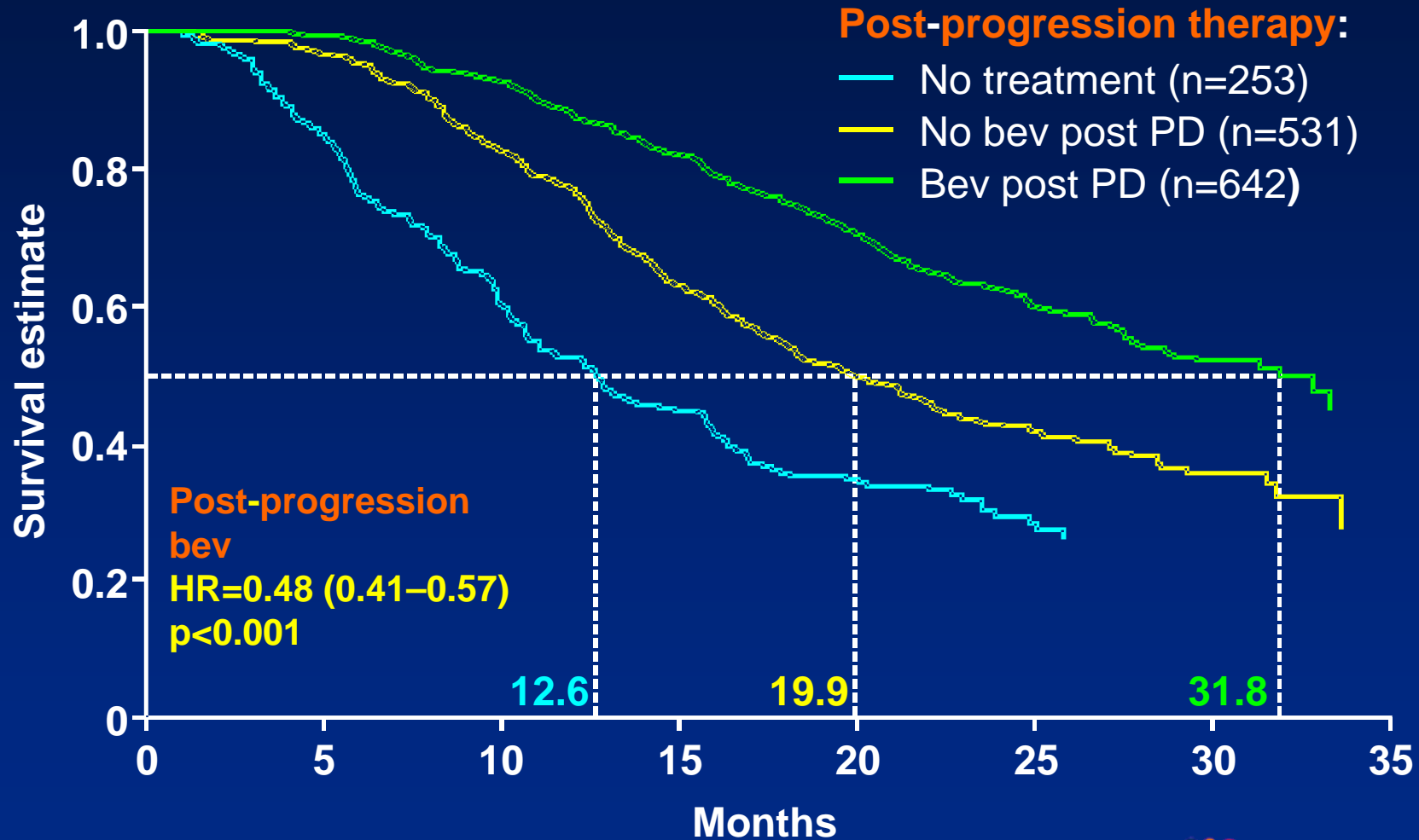
BRiTE: post-progression treatment evaluation

- All patients (previously untreated, unresectable mCRC) received 1st-line bevacizumab + standard CT (n=1,953)
- Prospective analysis to examine effect of post-progression bev

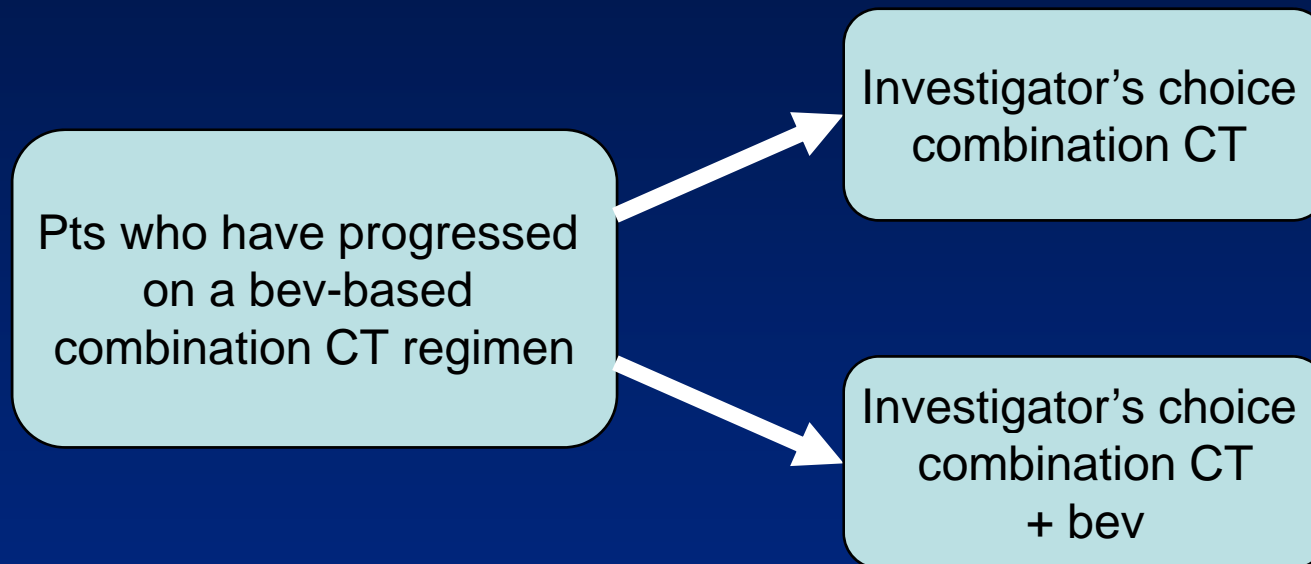


932 deaths (reported as of the 21 January, 2007 data cut-off)
Median follow-up time 19.6 months

BRiTE: Bevacizumab post 1st progression



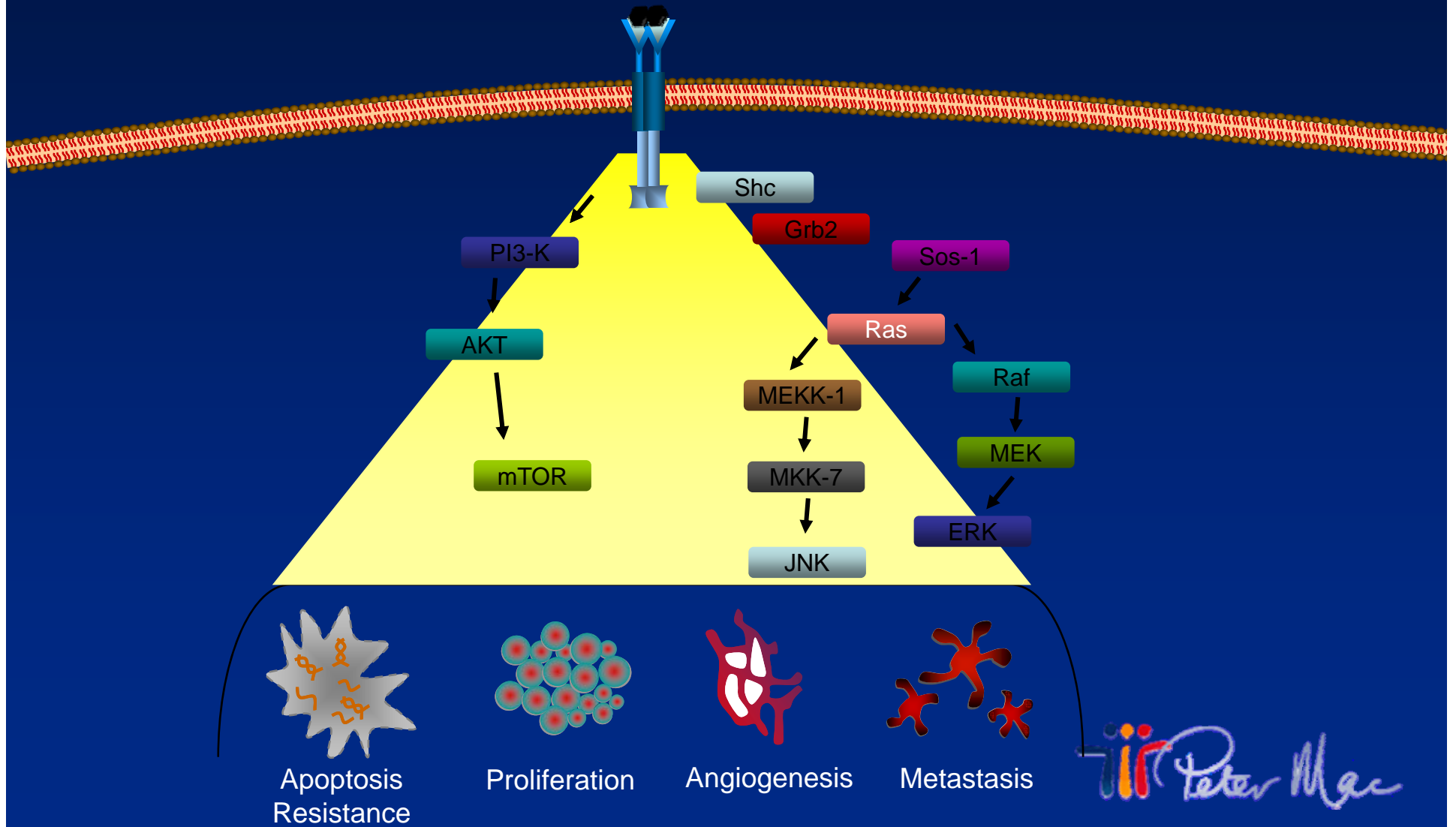
AIO 0504 – phase III randomised study to test role of continuation of bevacizumab



AGITG/NCIC Studies

- The biologic era continued

The EGF Receptor Pathway



AGITG/NCIC CRC Studies

- Asymptomatic CRC
- CO.17
- CO.20

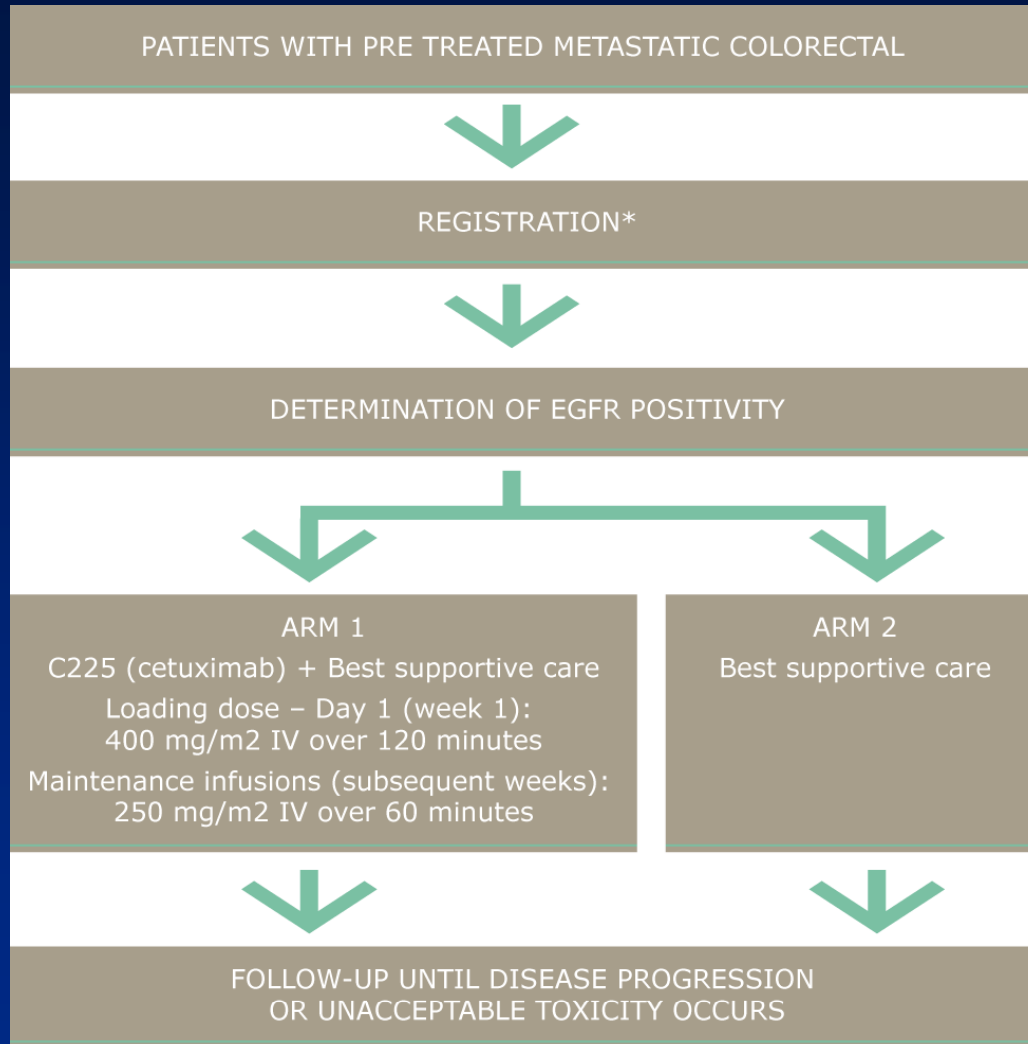
THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

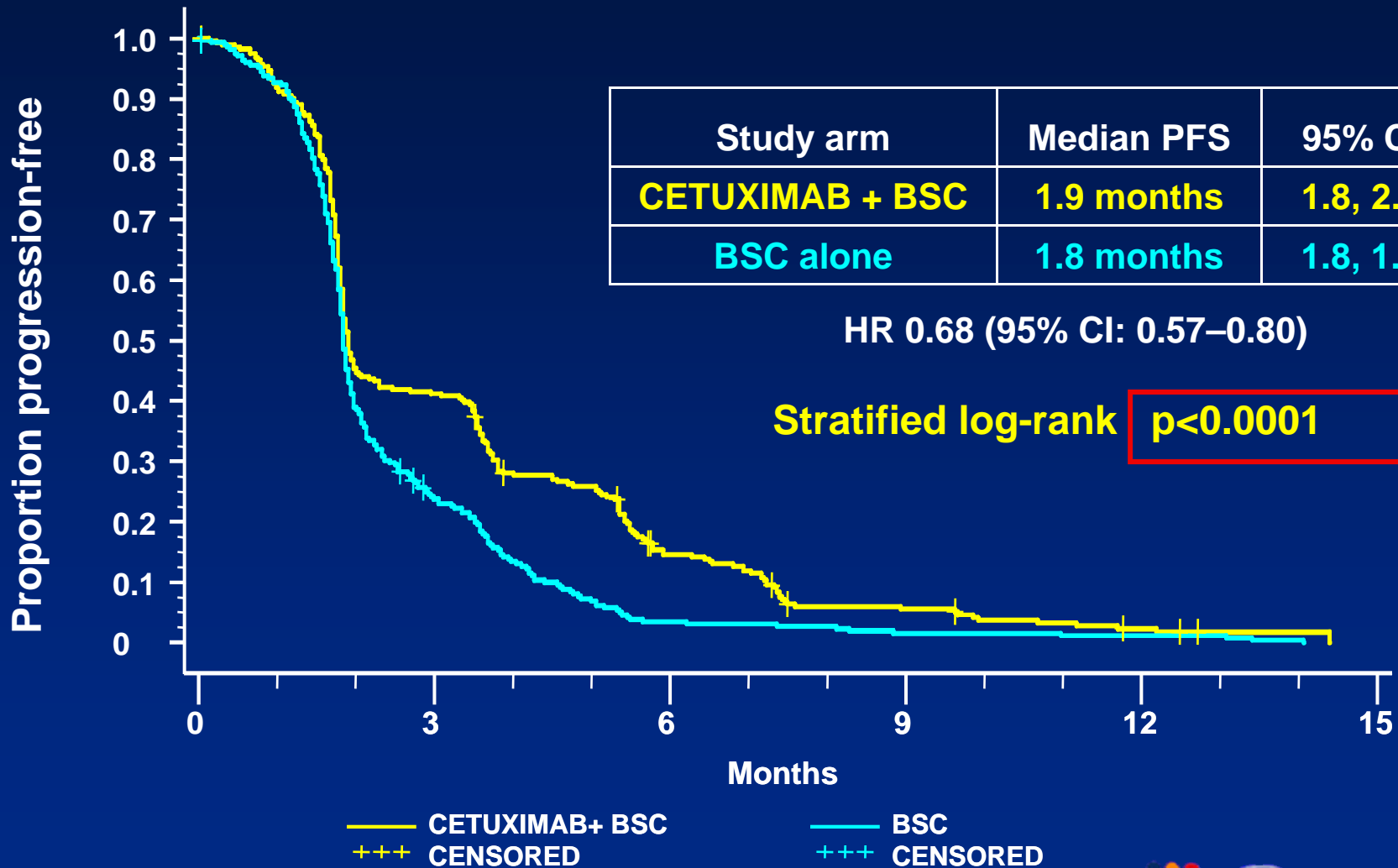
Cetuximab for the Treatment of Colorectal Cancer

Derek J. Jonker, M.D., Chris J. O'Callaghan, Ph.D., Christos S. Karapetis, M.D.,
John R. Zalcborg, M.D., Dongsheng Tu, Ph.D., Heather-Jane Au, M.D.,
Scott R. Berry, M.D., Marianne Krahn, M.D., Timothy Price, M.D.,
R. John Simes, M.D., Niall C. Tebbutt, M.D., Guy van Hazel, M.D.,
Rafal Wierzbicki, M.D., Christiane Langer, M.D., and Malcolm J. Moore, M.D.*

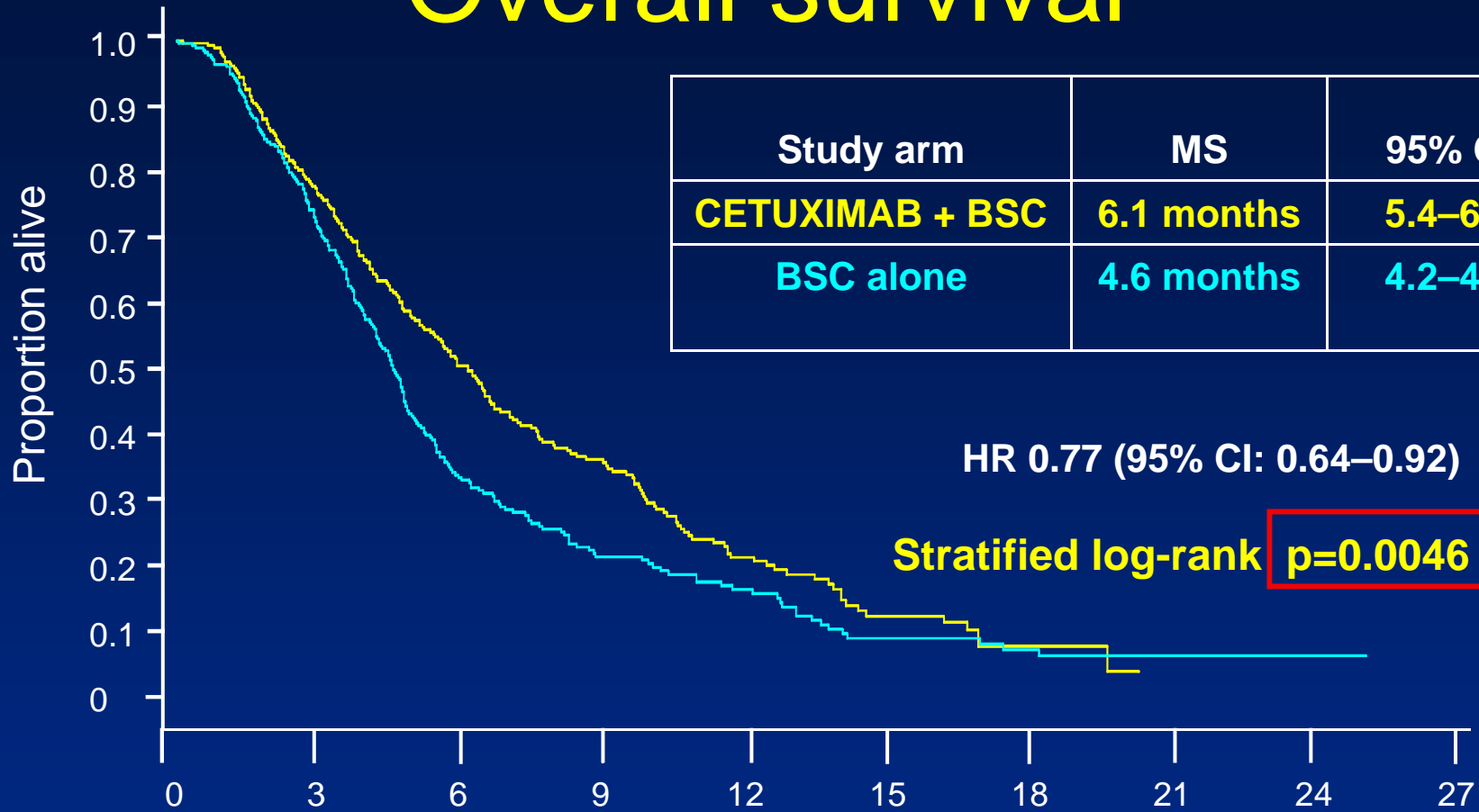
CO.17 Schema



Progression-free survival



Overall survival



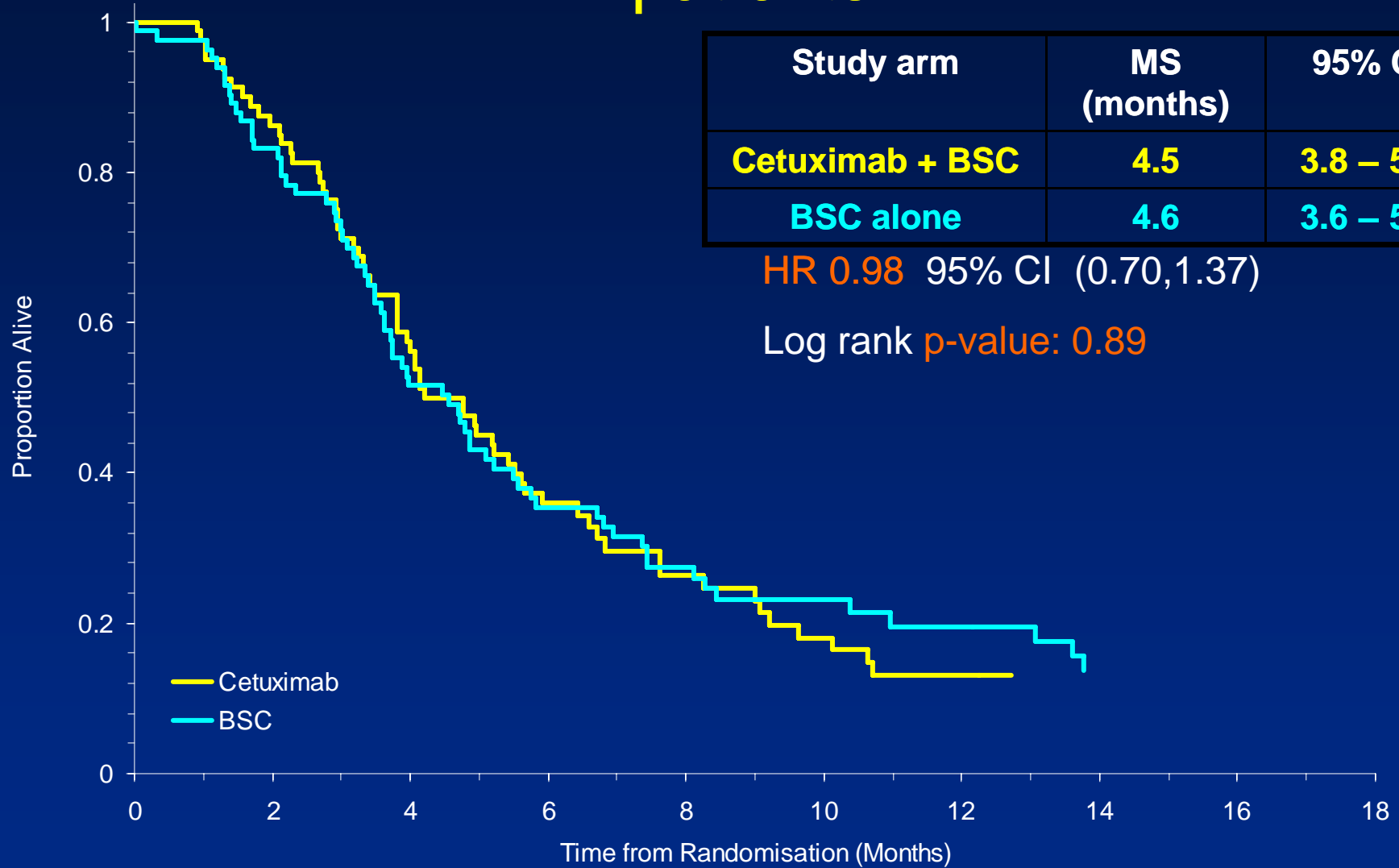
Study arm	MS	95% CI
CETUXIMAB + BSC	6.1 months	5.4–6.7
BSC alone	4.6 months	4.2–4.9

	0	3	6	9	12	15	18	21	24	27
Subjects at risk										
CETUXIMAB+BSC	287	217	136	78	37	14	4	0	0	0
BSC alone	285	197	85	44	26	12	8	2	1	0

— CETUXIMAB + BSC
+++ CENSORED

— BSC
+++ CENSORED

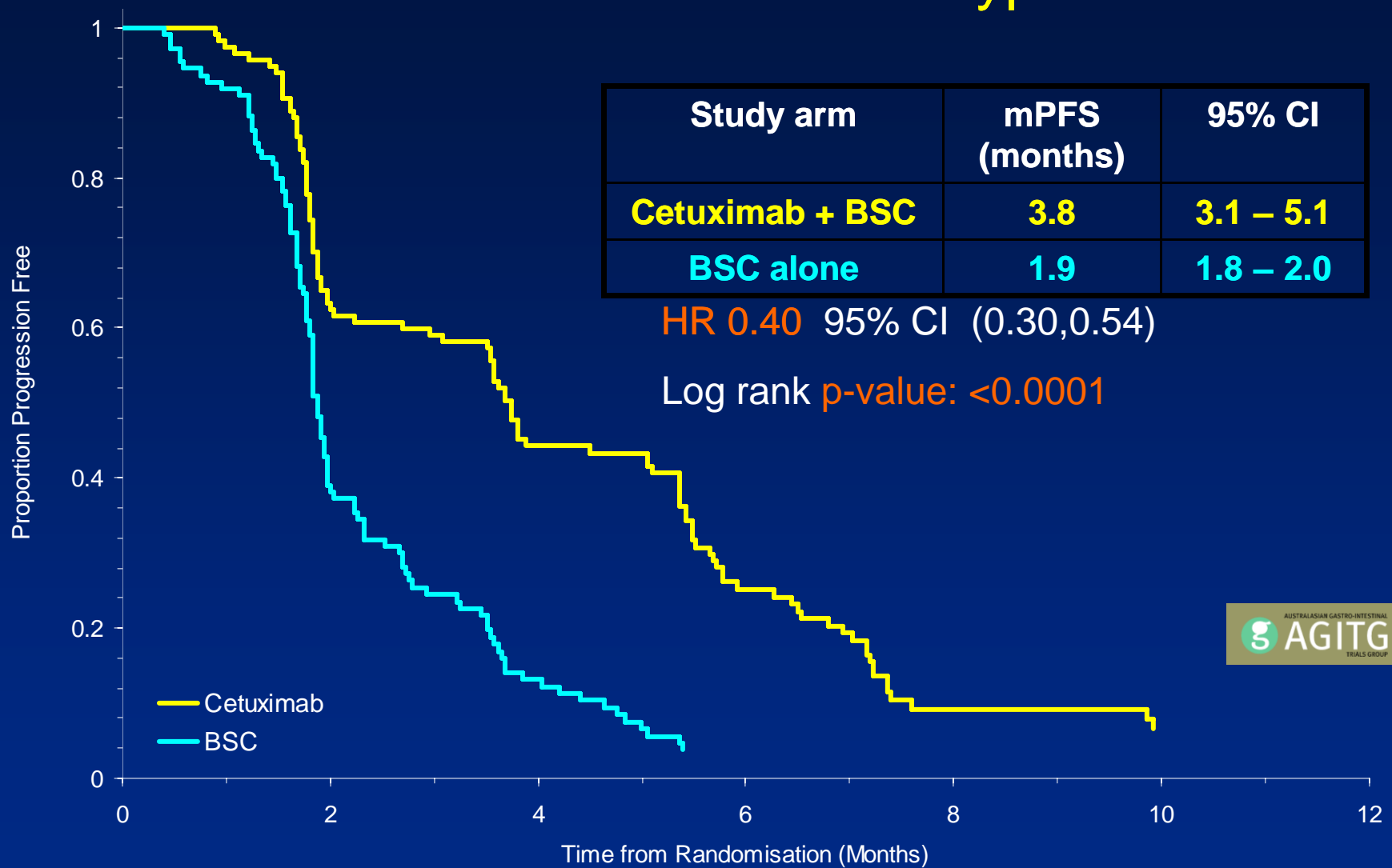
C0.17: Overall survival in K-Ras Mutant patients



Study arm	MS (months)	95% CI
Cetuximab + BSC	4.5	3.8 – 5.6
BSC alone	4.6	3.6 – 5.5

Cetuximab	81	69	46	27	16	11	7	4
BSC	83	69	42	28	20	13	11	7

C0.17: PFS in the K-Ras Wild-Type Patients

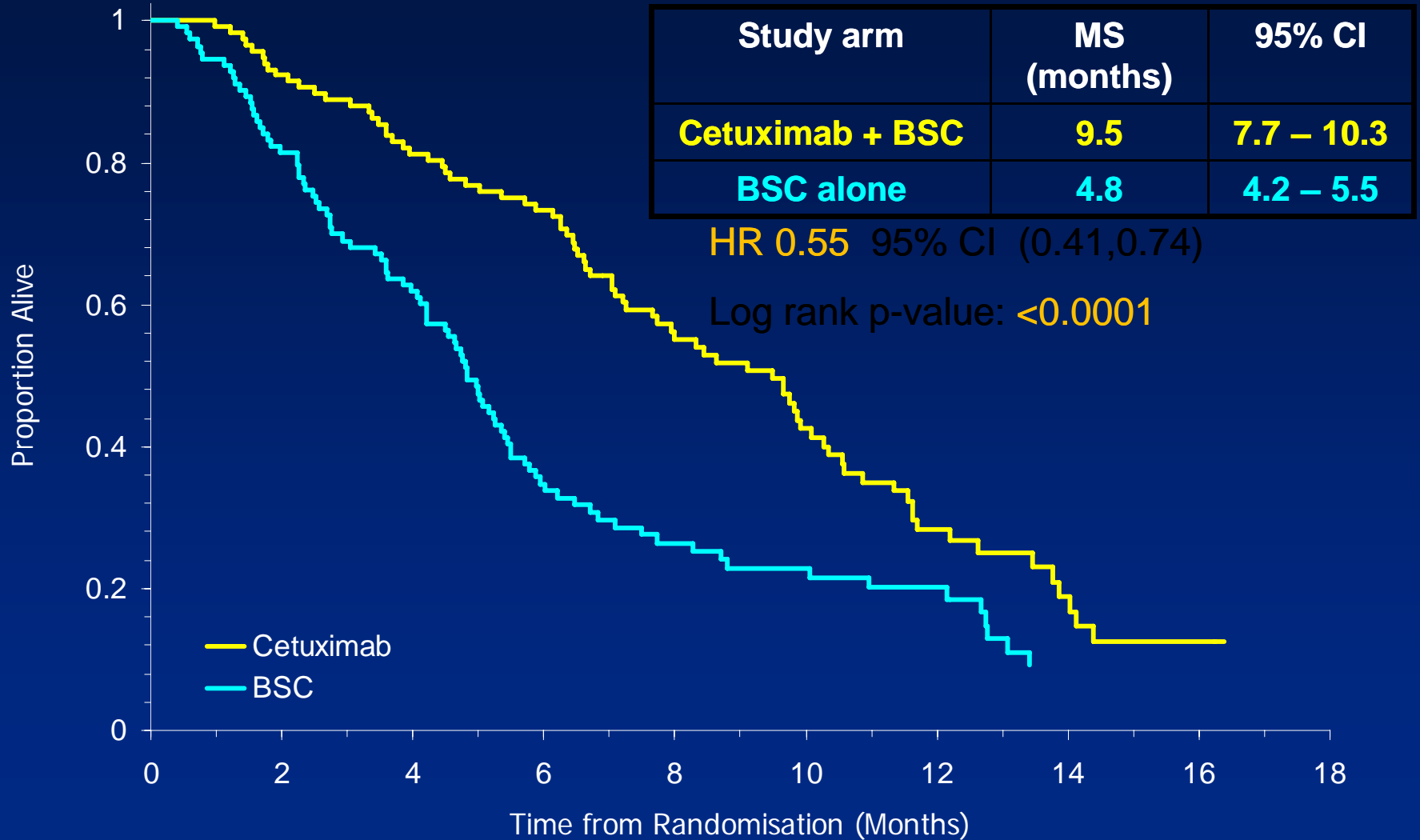


Study arm	mPFS (months)	95% CI
Cetuximab + BSC	3.8	3.1 – 5.1
BSC alone	1.9	1.8 – 2.0

Cetuximab	117	74	50	26	8	5
BSC	113	43	14	2	1	1



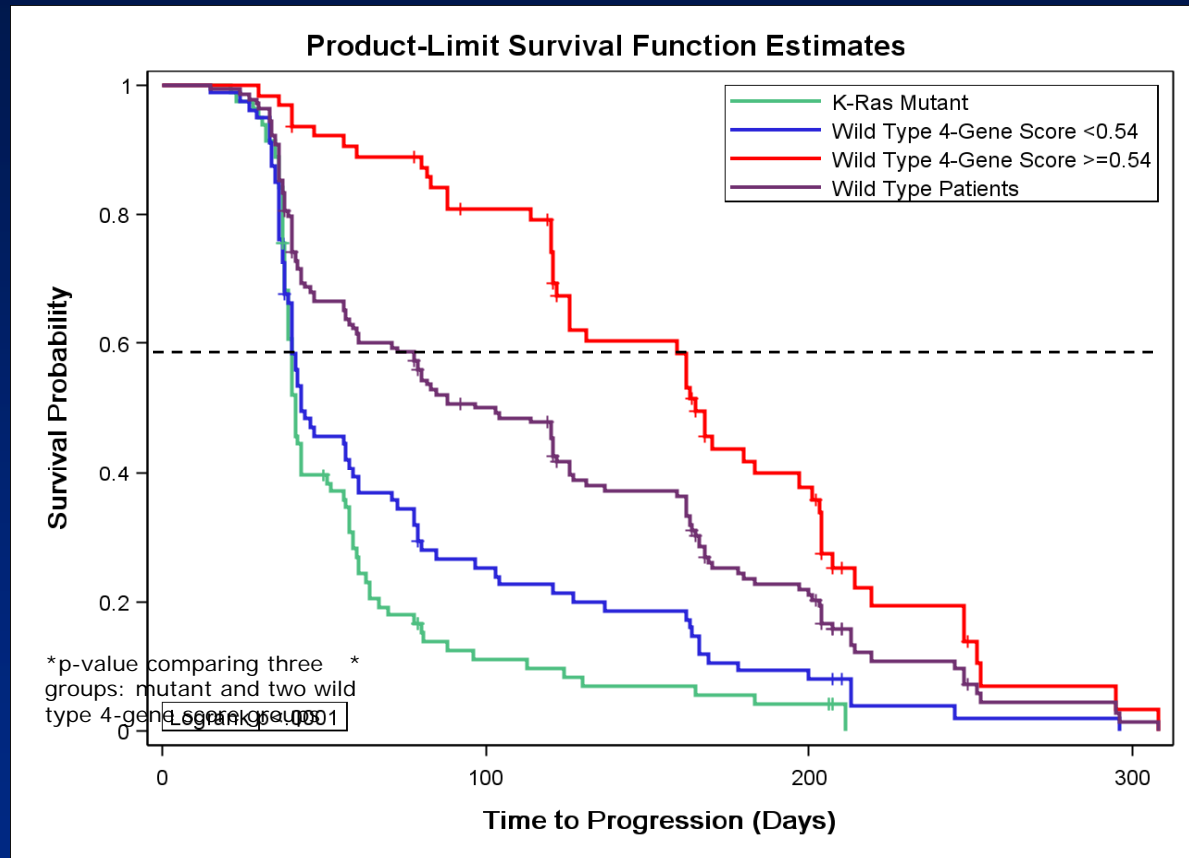
C0.17: Overall survival in K-Ras Wild-Type patients



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

Multi-gene Models for Prediction of Cetuximab Benefit in PFS

- *K-Ras* + 4 Gene Score applied to all patients to evaluate progression-free survival
- The addition of the 4 genes to *K-ras* status, identifies a subset of patients with a significant increase in median time to progression (163 days v. ~40 days)



- Is there an advantage to using both classes of biological agent with chemotherapy?

Study Design CAIRO2



Randomization

Arm A

Capecitabine
Oxaliplatin
Bevacizumab

Arm B

Capecitabine
Oxaliplatin
Bevacizumab
Cetuximab

Efficacy results

	Arm A n = 368	Arm B n = 368	p value
Median PFS (months) (HR; 95% CI)	10.7 (9.7-12.5)	9.6 (8.5-10.7)	0.018 (1.21;1.03-1.45)
Median OS (months) (HR; 95% CI)	20.4 (18.1-26.1)	20.3 (17.9-21.6)	0.21 (1.15;0.93-1.43)
Response rate (CR + PR)	44%	44%	0.88
Disease control rate (CR + PR + SD)	83%	81%	0.39

Results were confirmed in the subgroup of patients with EGFR+ tumors



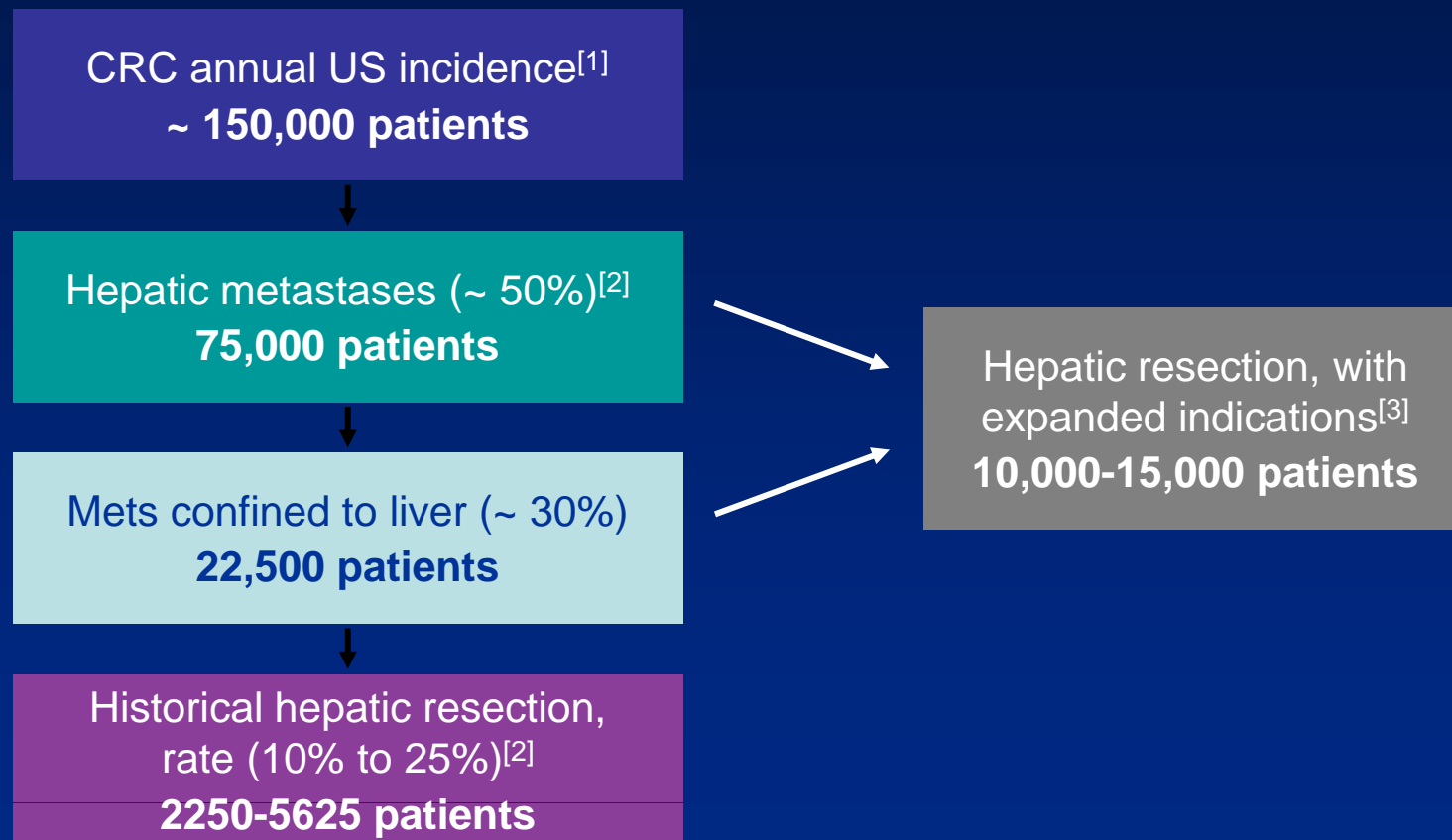
KRAS genotyping (n=501)

	Wildtype n = 305 (61%)	Mutation n = 196 (39%)	p value
Arm A	152 (50%)	103 (53%)	
Arm B	153 (50%)	93 (47%)	
Median PFS (months)			
Arm A	10.7	12.5	0.92
Arm B	10.5	8.6	0.47
p value	0.10	0.043	

What is optimal initial chemotherapy?

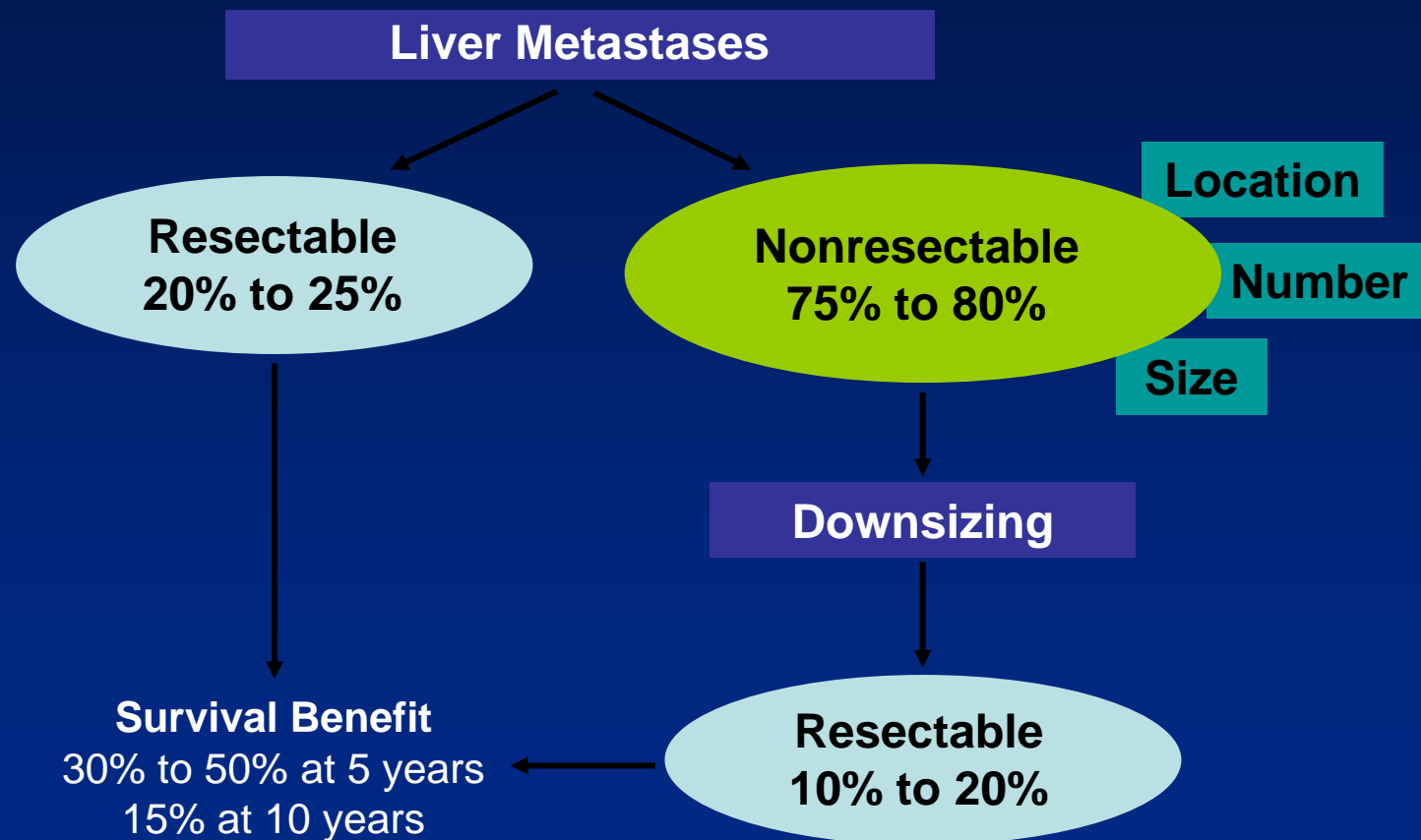
- 5FU / LV
- CPT 11 (irinotecan)
- Oxaliplatin
- The role of single agents
- Biological Agents with or without chemotherapy
- The integration of chemo with surgery for metastatic disease

Hepatic Metastases From Colorectal Carcinoma (cco.com)



1. Jemal A, et al. CA Cancer J Clin. 2007;57:43-66. 2. Leonard GD, et al. J Clin Oncol. 2005;23:2038-2048. 3. Pawlik TM, et al. J Gastrointest Surg. 2007;11:1057-1077.

Hepatic Metastases From Colorectal Carcinoma (cco.com)



Two-stage Hepatectomy Approach for Initially Unresectable Colorectal Hepatic Metastases

René Adam, MD, PhD^{a,d,e,*}, Rafael Miller, MD^{a,b},
Marcos Pitombo, MD^a, Dennis A. Wicherts, MD^{a,c},
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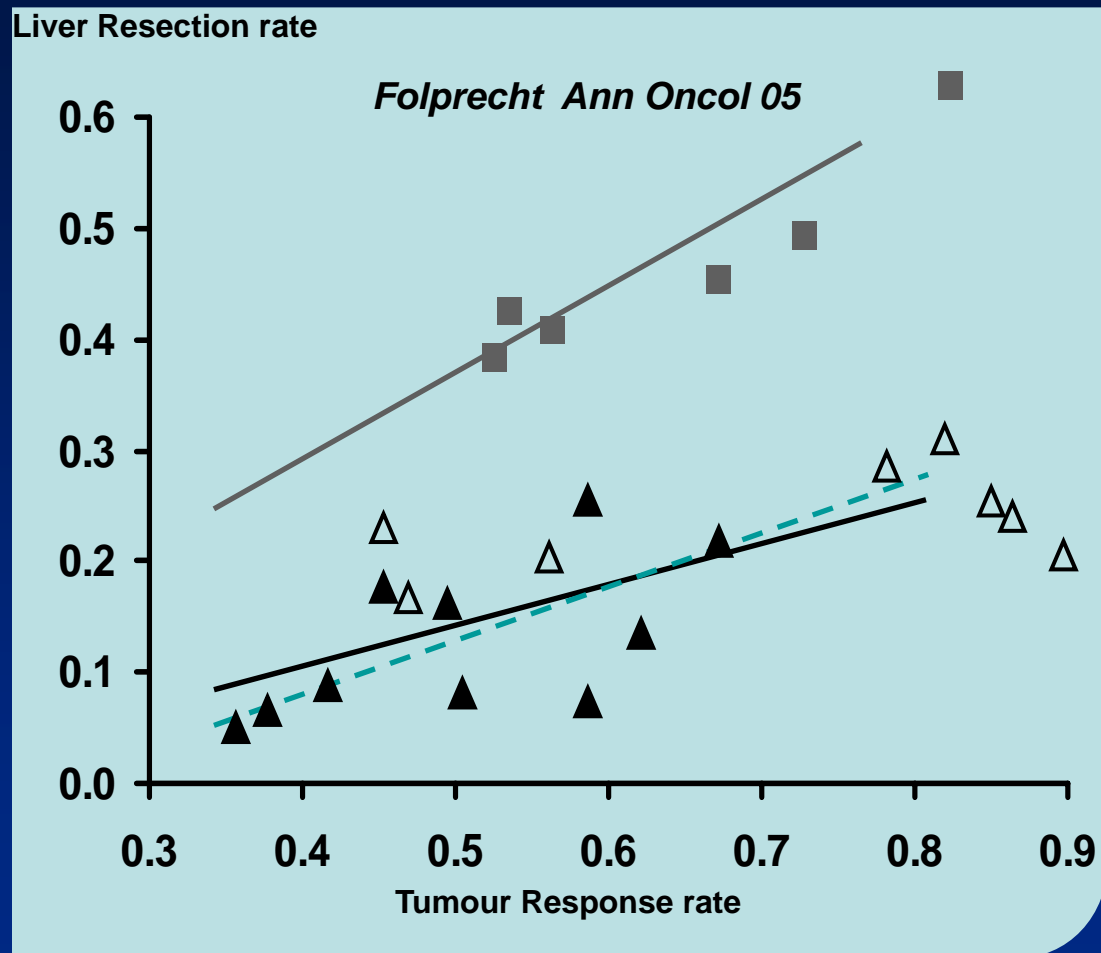
ORIGINAL REPORT

Is Hepatic Resection Justified After Chemotherapy in Patients With Colorectal Liver Metastases and Lymph Node Involvement?

René Adam, Robbert J. de Haas, Dennis A. Wicherts, Thomas A. Aloia, Valérie Delvert, Daniel Azoulay, Henri Bismuth, and Denis Castaing

The logo for Peter Mac consists of three stylized human figures in red, orange, and blue, followed by the text "Peter Mac" in a white, cursive script.

Curative therapy needs Combinations



New agents

Systematic review of trials in metastatic CRC*

- 102 trials active/goal is 20,000 patients
- Only 13% are testing agents currently unapproved by the FDA
- Only 13 trials had an enrichment design
 - CEA (5), EGFR (5), TS (2), PI3K (1)

*Kopetz, JCO, April 2008



Peter Mac

New agents

- Angiogenesis inhibitors; ZD 6474, AG-013736, AZD 2171, IMC-A12, Brivinib, XL999, VEGF Trap
- Novel targets; AMG 655 (death receptor), Ticilimumab (T cells)
- Growth Factor inhibitors; EGFRi, IGF1Ri

Thank You

