

Colorectal cancer

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**Adjuvant treatment of colorectal cancer:
which regimen, which patients?**

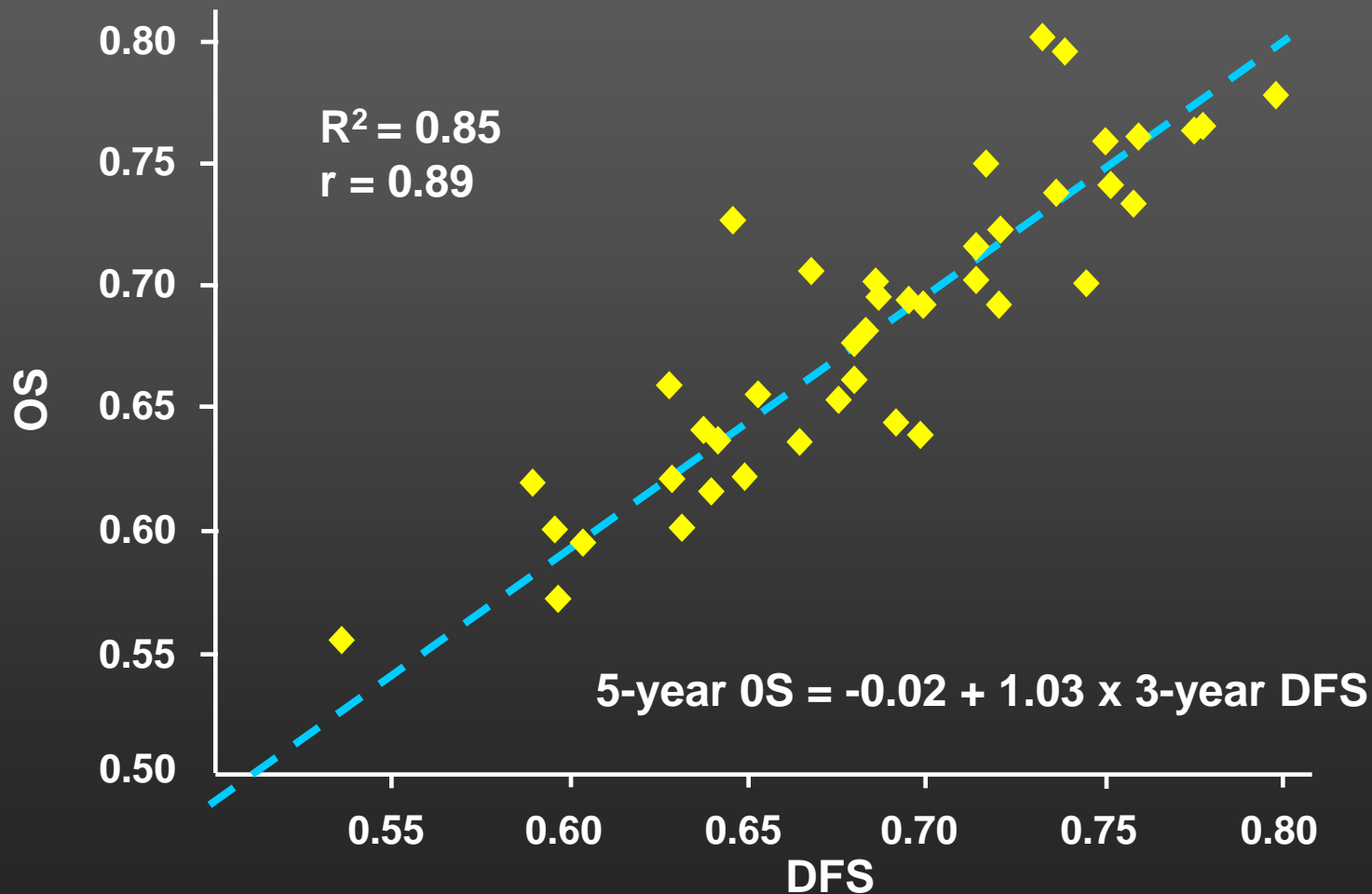
Overview of presentation

- ❑ DFS vs OS as a primary endpoint
- ❑ Fluoropyrimidine monotherapy
- ❑ Irinotecan-based combinations
- ❑ Oxaliplatin-based combinations
- ❑ Risk stratification and rational patient selection
- ❑ Rectal cancer

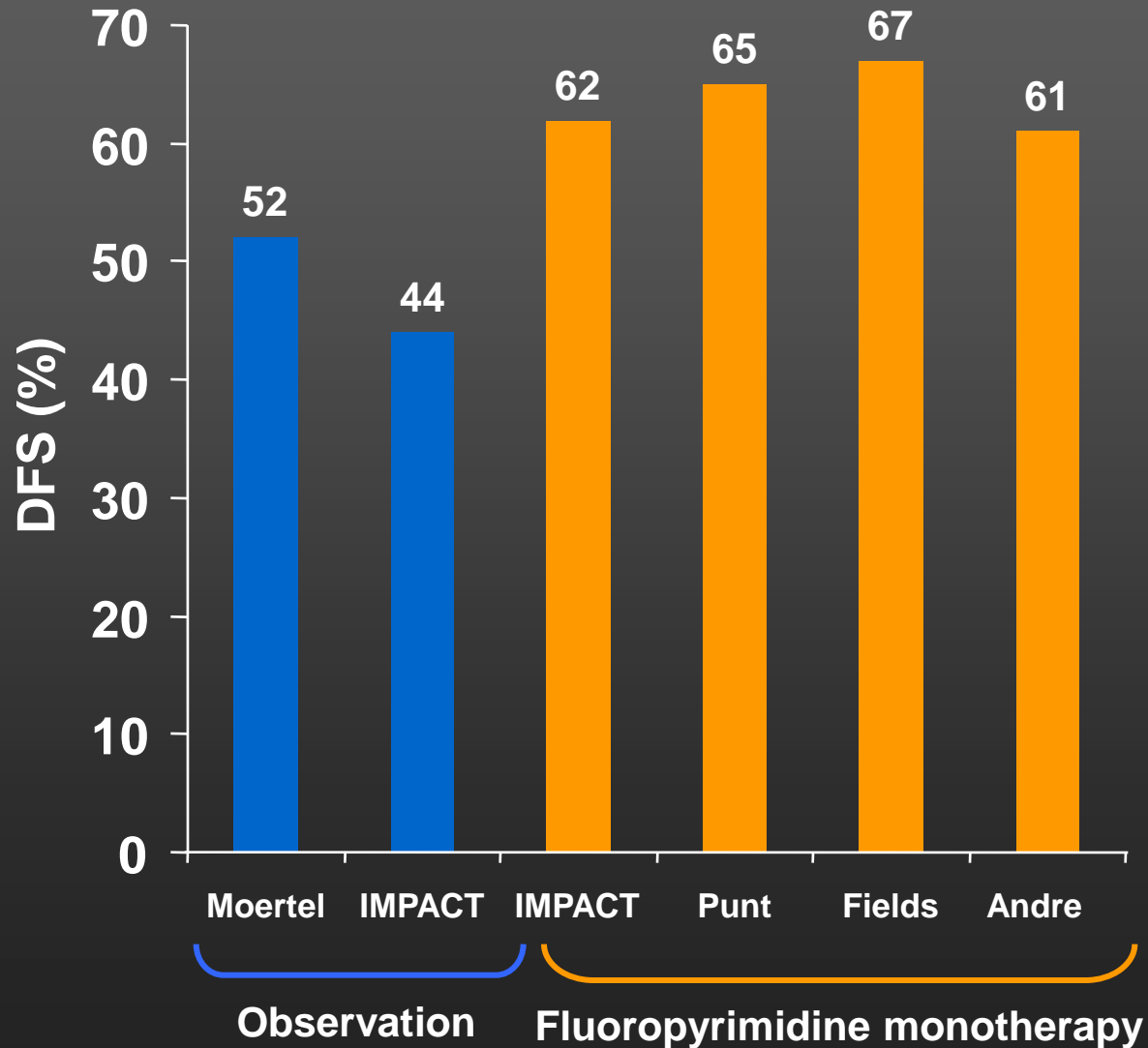
DFS vs OS as an endpoint for adjuvant colon cancer studies

- Pooled analysis of 18 Phase III trials
 - 43 different treatment arms
 - n=20,898
- Evaluated 3-year DFS as a surrogate for 5-year OS
- 3-year DFS and 5-year OS were highly correlated both within patients and across trials
 - Formal measures of surrogacy satisfied
- Conclusion: 3-year DFS is an appropriate endpoint for adjuvant colon cancer trials of 5-FU-based regimens

Pooled analysis: 3-year DFS vs 5-year OS by study arm



3-year DFS in stage III CRC



Fluoropyrimidines: what do we know?

■ GERCOR C96

- LV5FU2 is equivalent to bolus 5-FU/LV, but is less toxic¹

■ MRC

- 3 months' protracted infusion of 5-FU is equivalent to 6 months of monthly bolus 5-FU/LV²

■ X-ACT

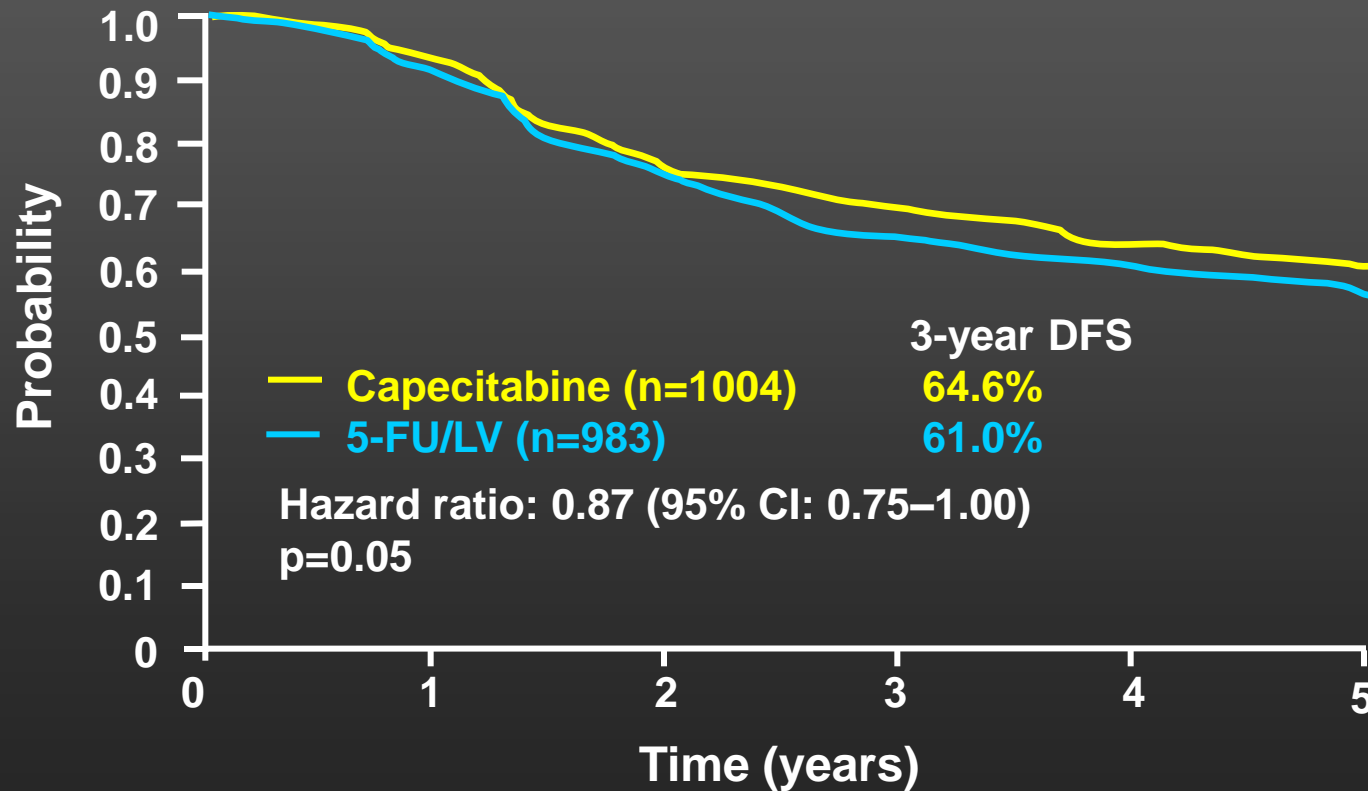
- Capecitabine compared to 5-FU/LV (Mayo) in 1987 stage III patients³

1. André T, et al. ASCO 2005 (Abstract 3522);

2. Chau I, et al. Ann Oncol 2005,16:549–557; 3. Twelves C, et al, ASCO 2005 (Abstract 3521).

Fluoropyrimidines: X-ACT DFS

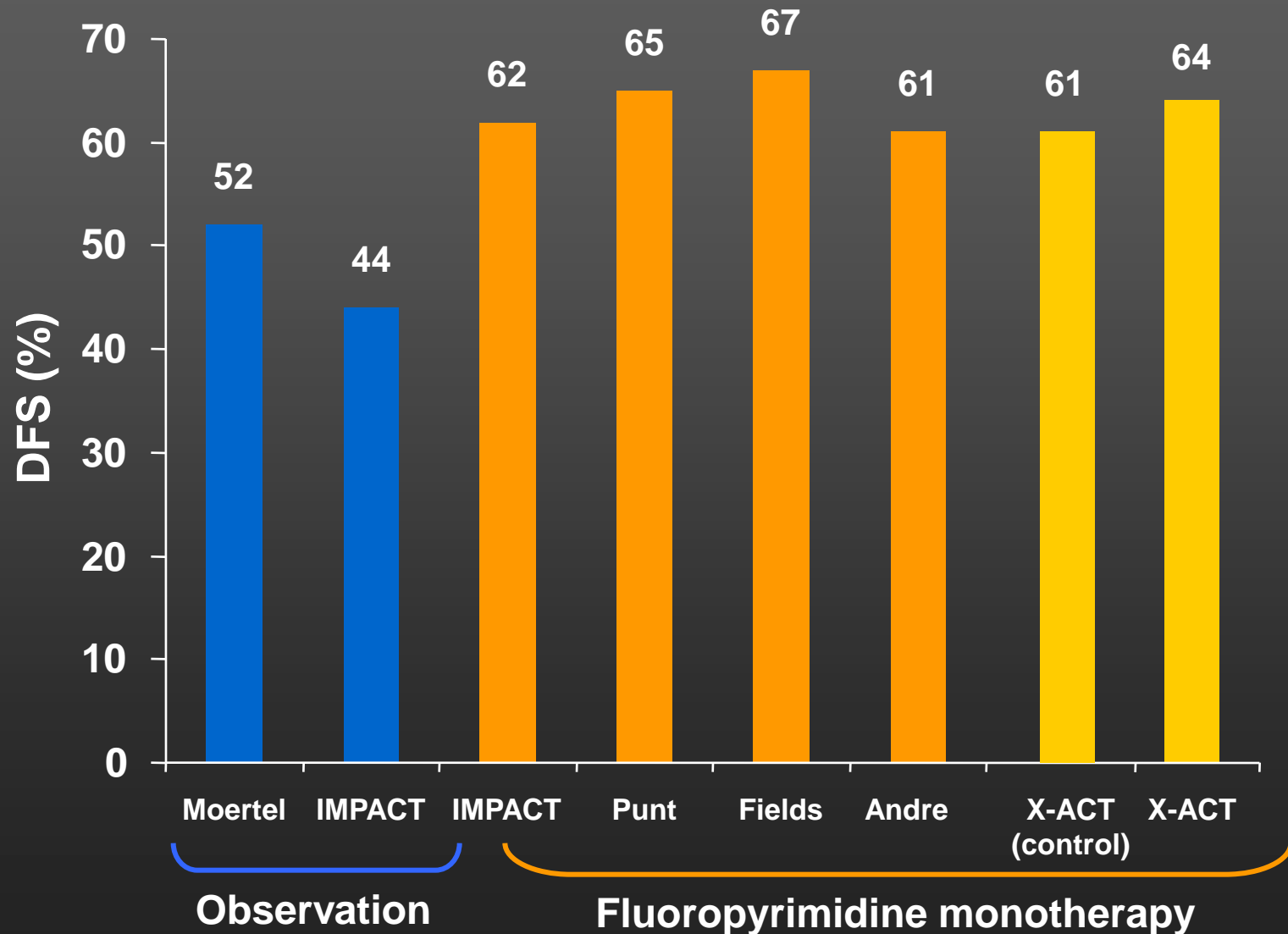
Median follow-up: 4.3 years (ITT population)



Fluoropyrimidines: X-ACT safety

	Patients (%)		p-value
	Capecitabine (n=993)	5-FU/LV (n=974)	
Diarrhoea	46	64	<0.001
Nausea/vomiting	36	51	<0.001
Stomatitis	22	60	<0.001
Hand-foot syndrome	62	10	<0.001
Fatigue	23	23	NS
Alopecia	6	22	<0.001
Abdominal pain	10	13	NS
Lethargy	10	9	NS
Anorexia	9	10	NS

Fluoropyrimidines: 3-year DFS in stage III CRC



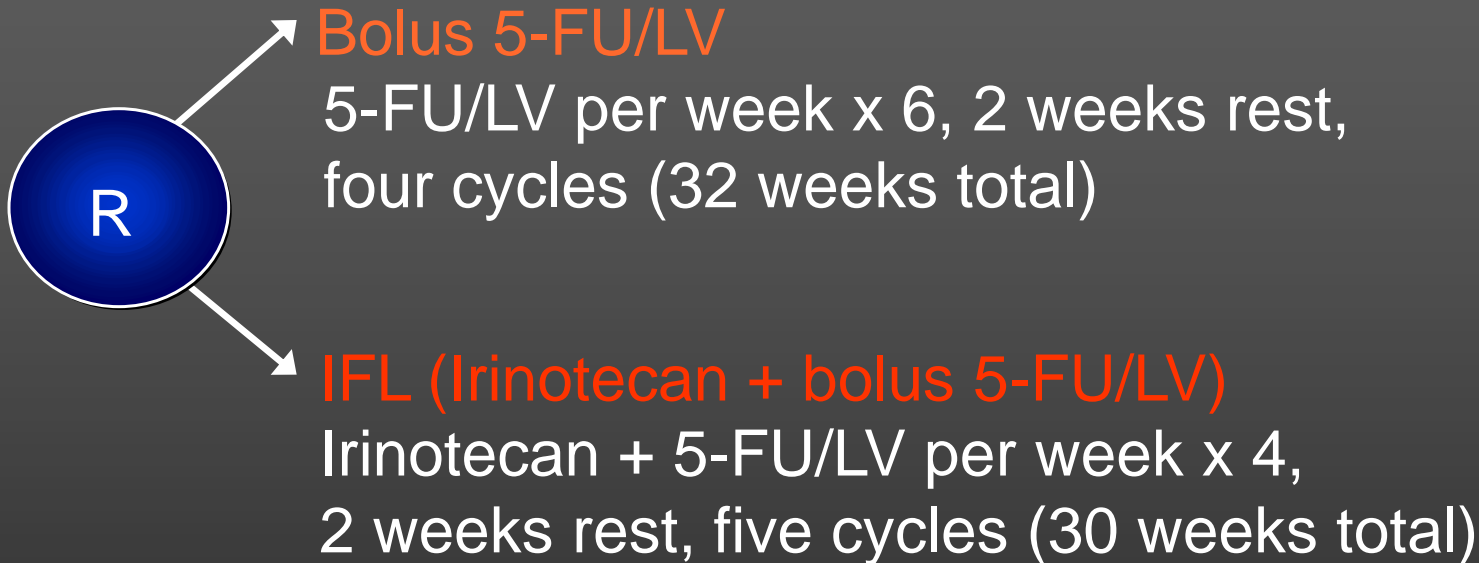
Irinotecan combinations: Phase III studies in colon cancer

Study	CALGB C89803¹	ACCORD-2²	PETACC-3³
Regimen	Irinotecan + bolus 5-FU/LV vs bolus 5-FU/LV	Irinotecan + LV5FU2 vs LV5FU2	Irinotecan + LV5FU2 vs LV5FU2
No. of patients	1264	400	3278
Patient profile	Stage III	High-risk stage III	Stage II and III
Results	p=0.80 for FFS analysis (median follow-up 2.6 years)	p=0.22 for 3-year DFS analysis	Stage III patients (n=2333): p=0.091 for 3-year DFS analysis p=0.045 for 3-year RFS analysis

DFS = disease-free survival; FFS = failure-free survival; RFS = relapse-free survival.

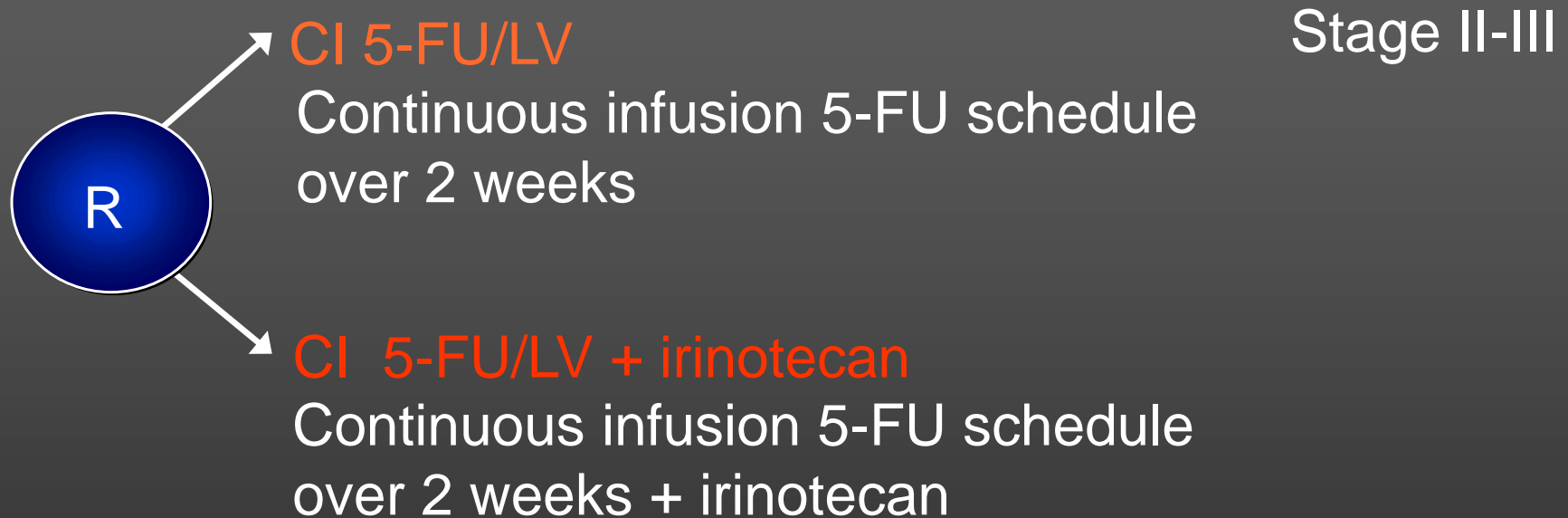
CALGB C89804: study design

Stage III



- Phase III trial in 1,263 patients
- Primary endpoint: overall survival. Negative results
- Excess in early deaths reported in IFL arm (0.8% vs 2.2%)

PETACC-3 (V307): study design

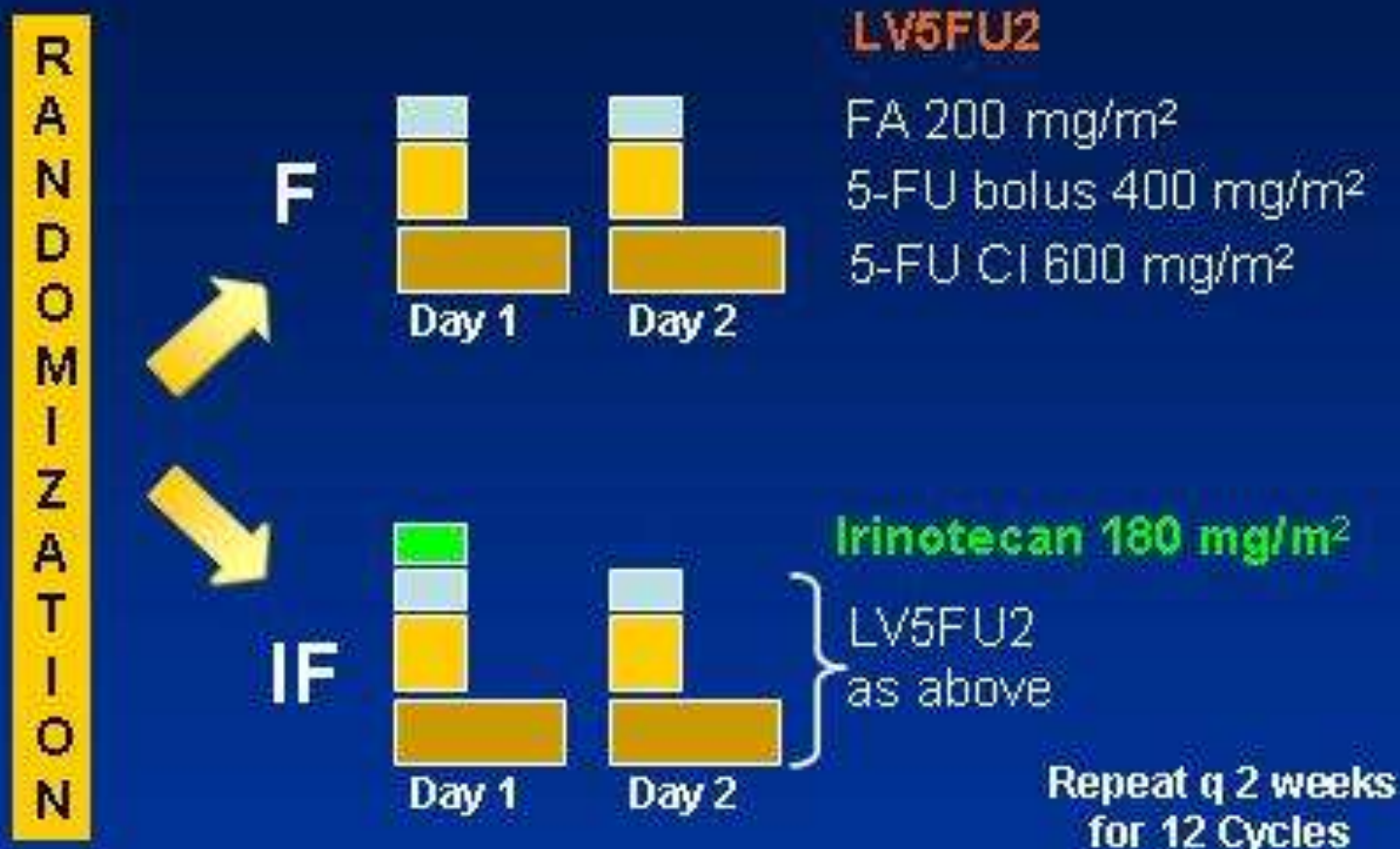


- Phase III trial in 1,794 patients
- Primary endpoint: disease-free survival
- Negative study for the primary endpoint

Study Design

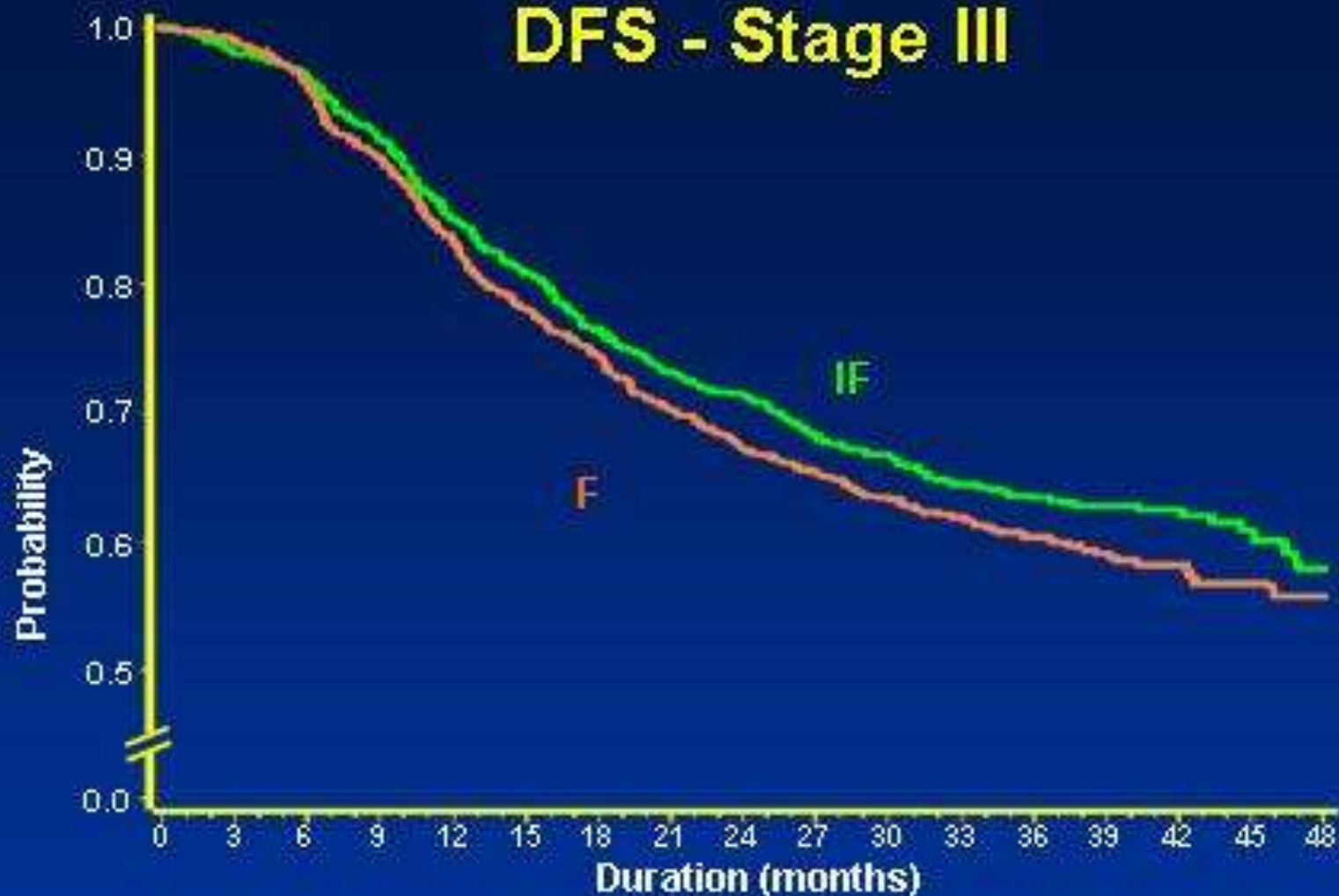
Stratification:

- Stage II vs. III
- Center



210 pts treated with the AIO regimen ± irinotecan within given centers will be presented later.

DFS - Stage III



	IF (n=1044)	F (n=1060)	HR	95% CI	p-value
	3-yr DFS	3-yr DFS			
risk adjusted	65.2	60.4	0.85	0.74-0.98	0.021
observed	63.3	60.3	0.89	0.77-1.11	0.091

Summary

Efficacy for Stage III Colon Cancer

- Although there was a trend for improved 3 yr DFS in favour of IF, the primary endpoint was not met:

DFS: HR = 0.89 (p = 0.091)

- Secondary endpoint was met:

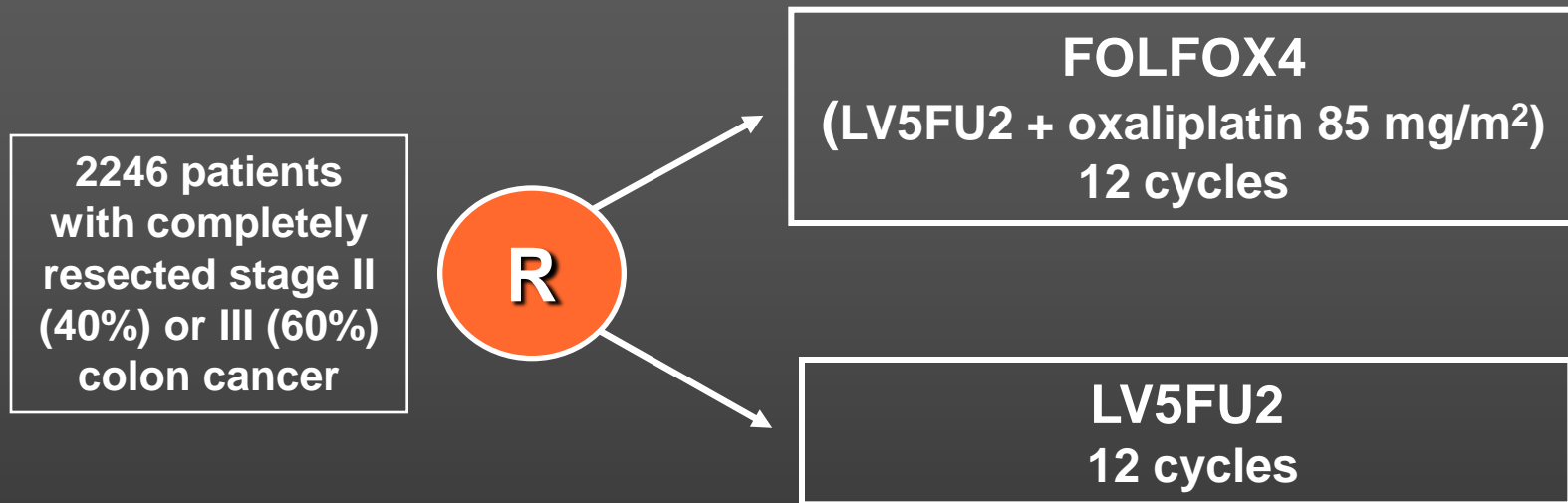
RFS: HR = 0.86 (p = 0.045)

- Adjusting for imbalances in T and N stage (post hoc):

3 yr DFS: 65.2% vs 60.4%, HR = 0.85 (p = 0.021)

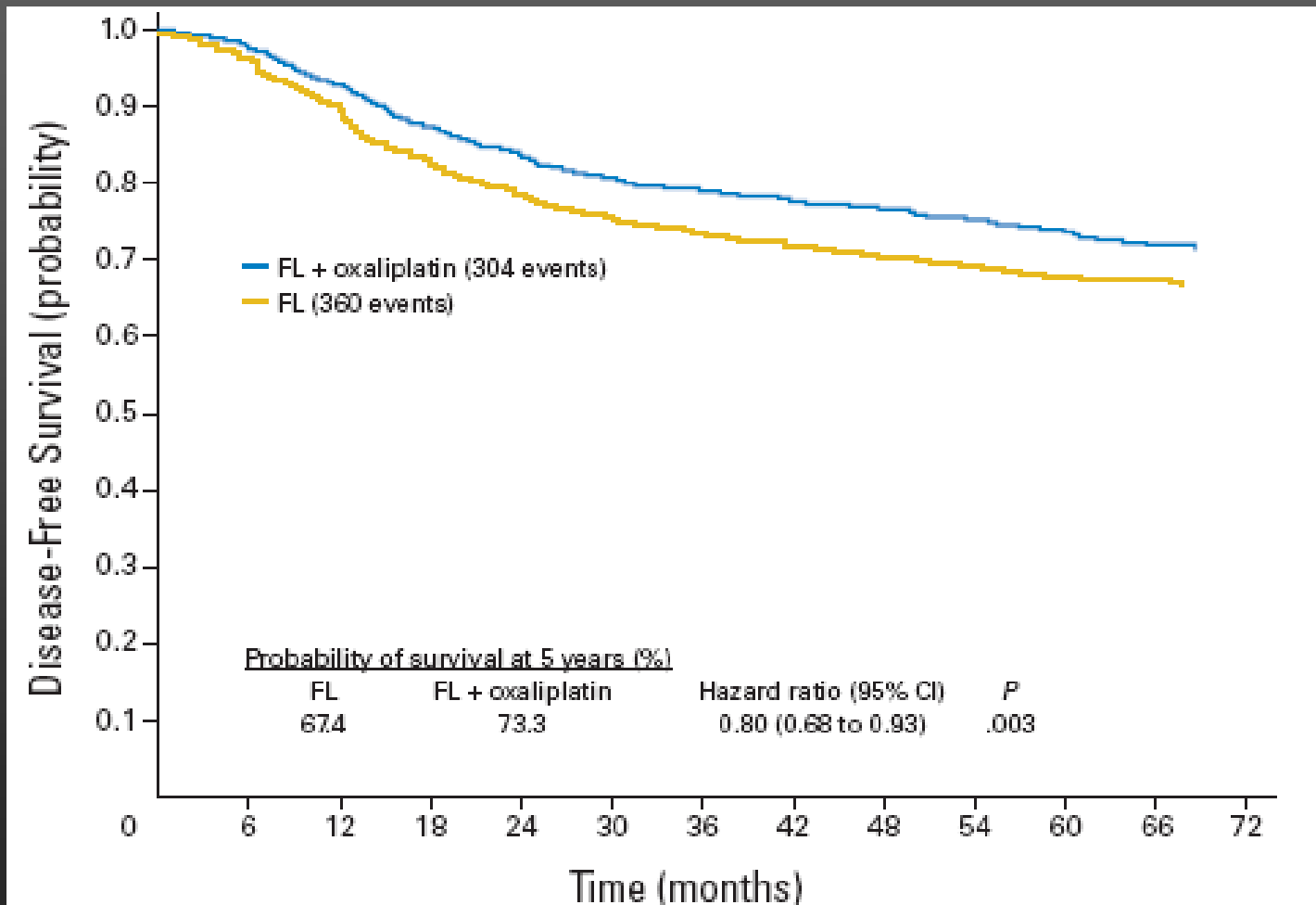
3 yr RFS: 67.9% vs 62.5%, HR = 0.82 (p = 0.009)

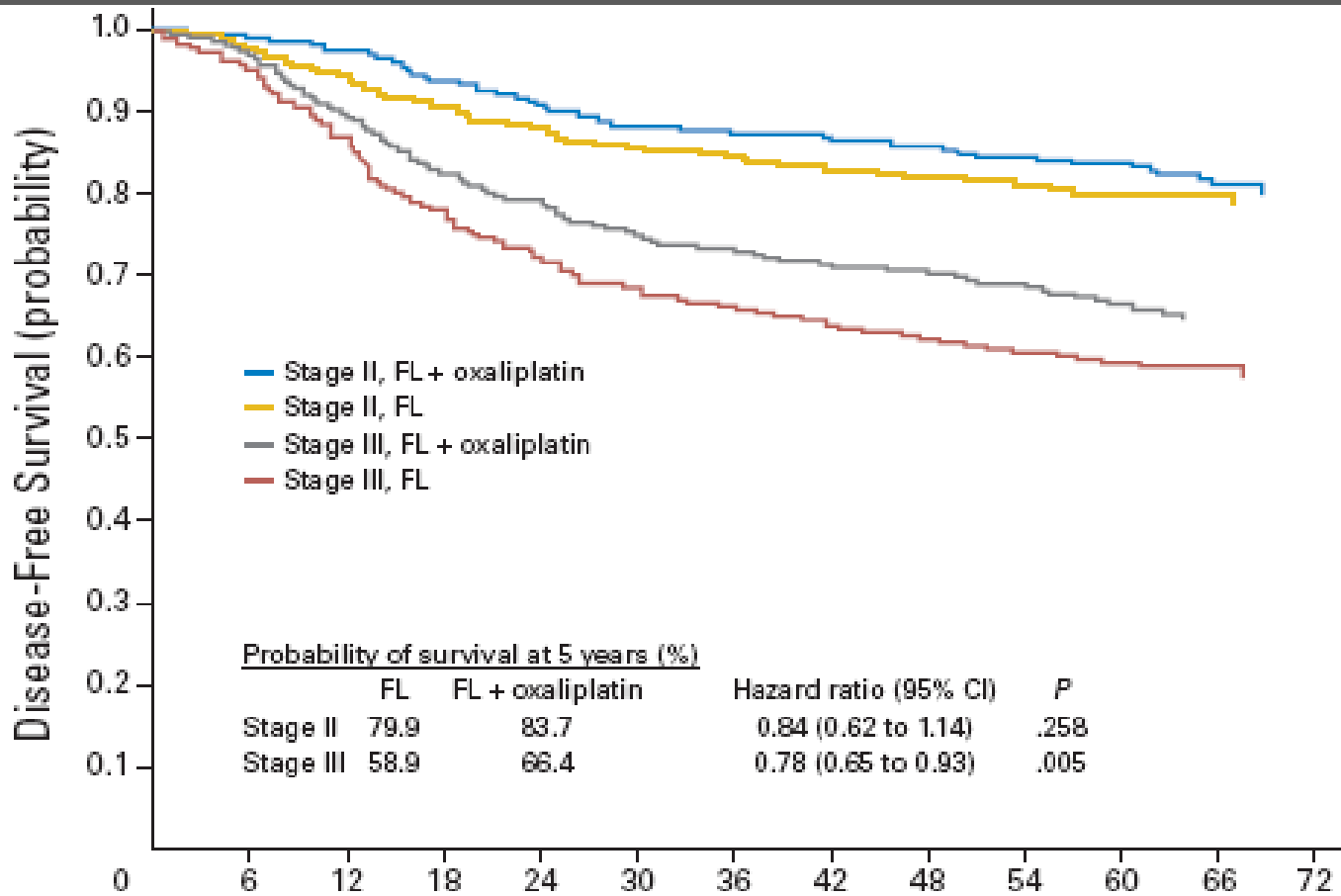
Oxaliplatin combinations: MOSAIC



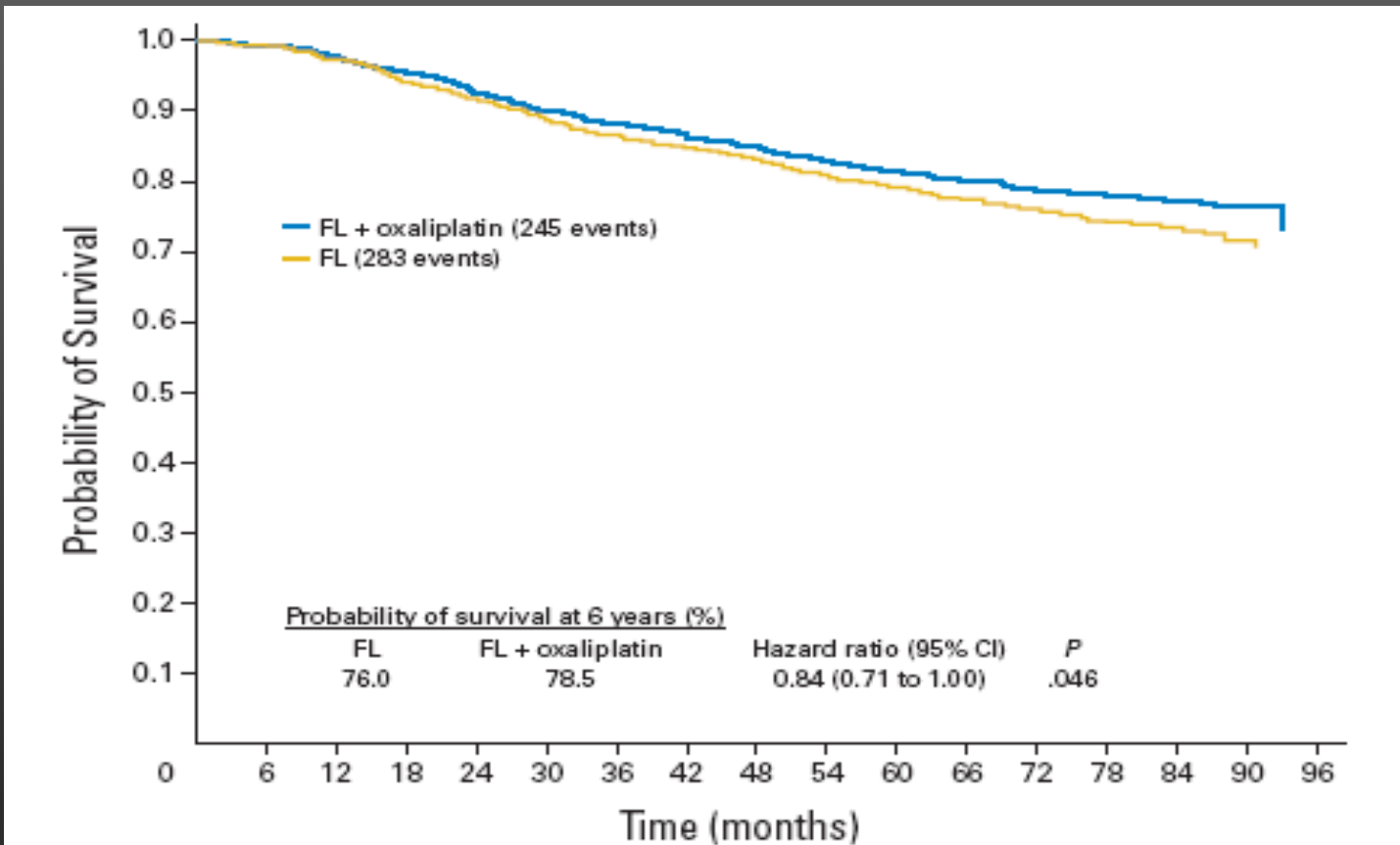
- **Primary endpoint: DFS**
- **Secondary endpoints: safety, OS**

5-Y DFS MOSAIC

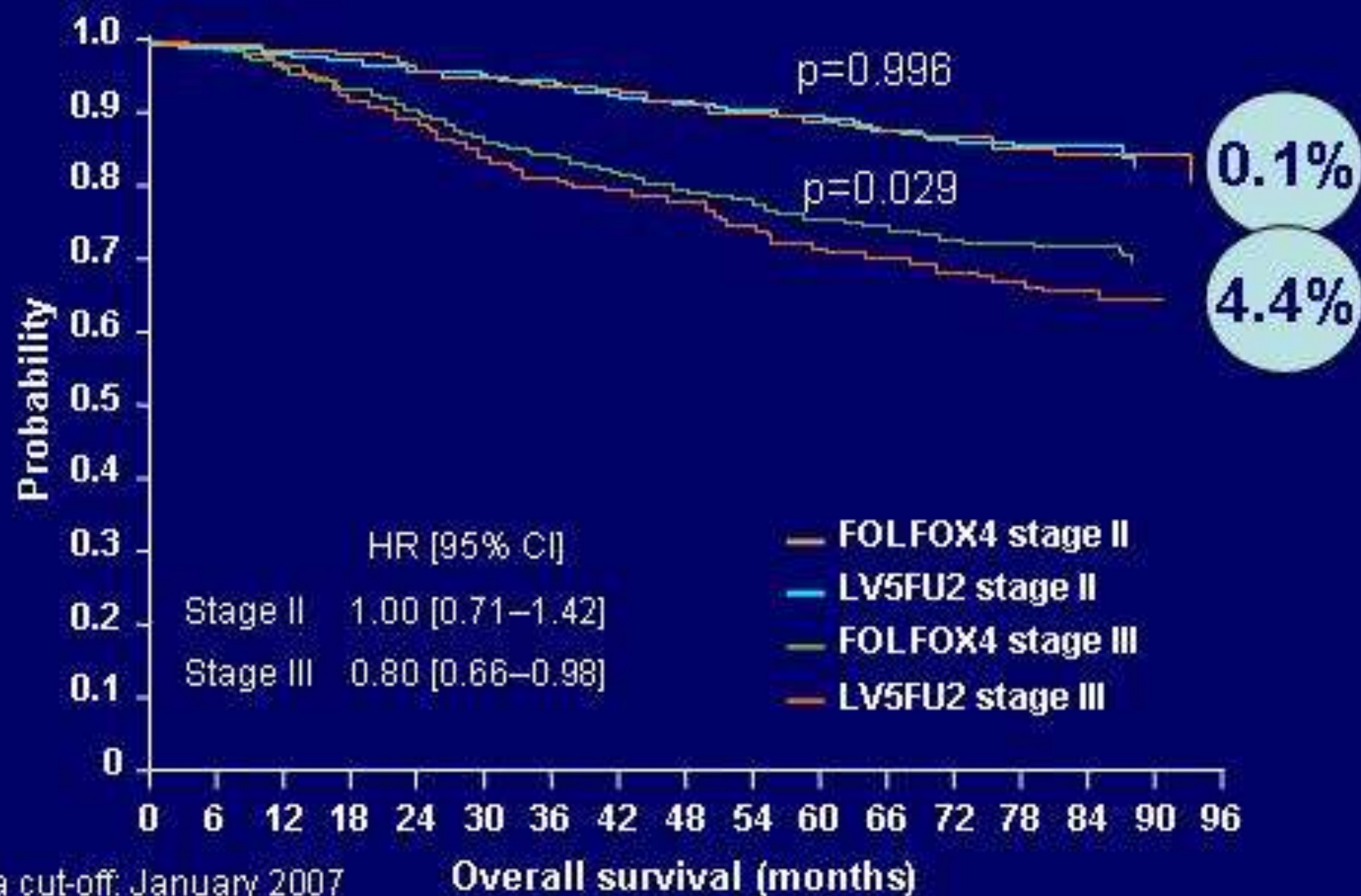




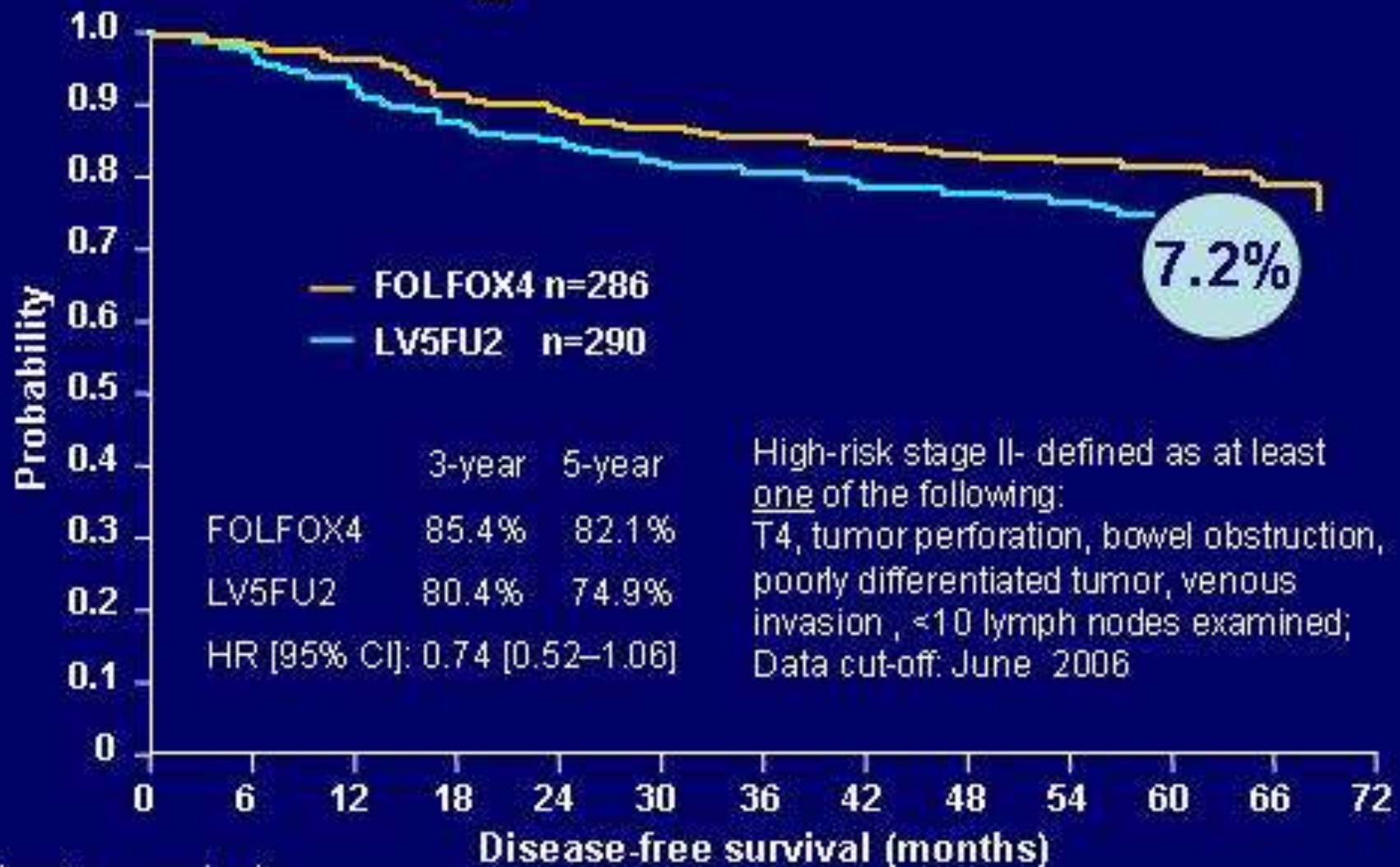
6-y OS MOSAIC



Overall Survival: Stage II and Stage III

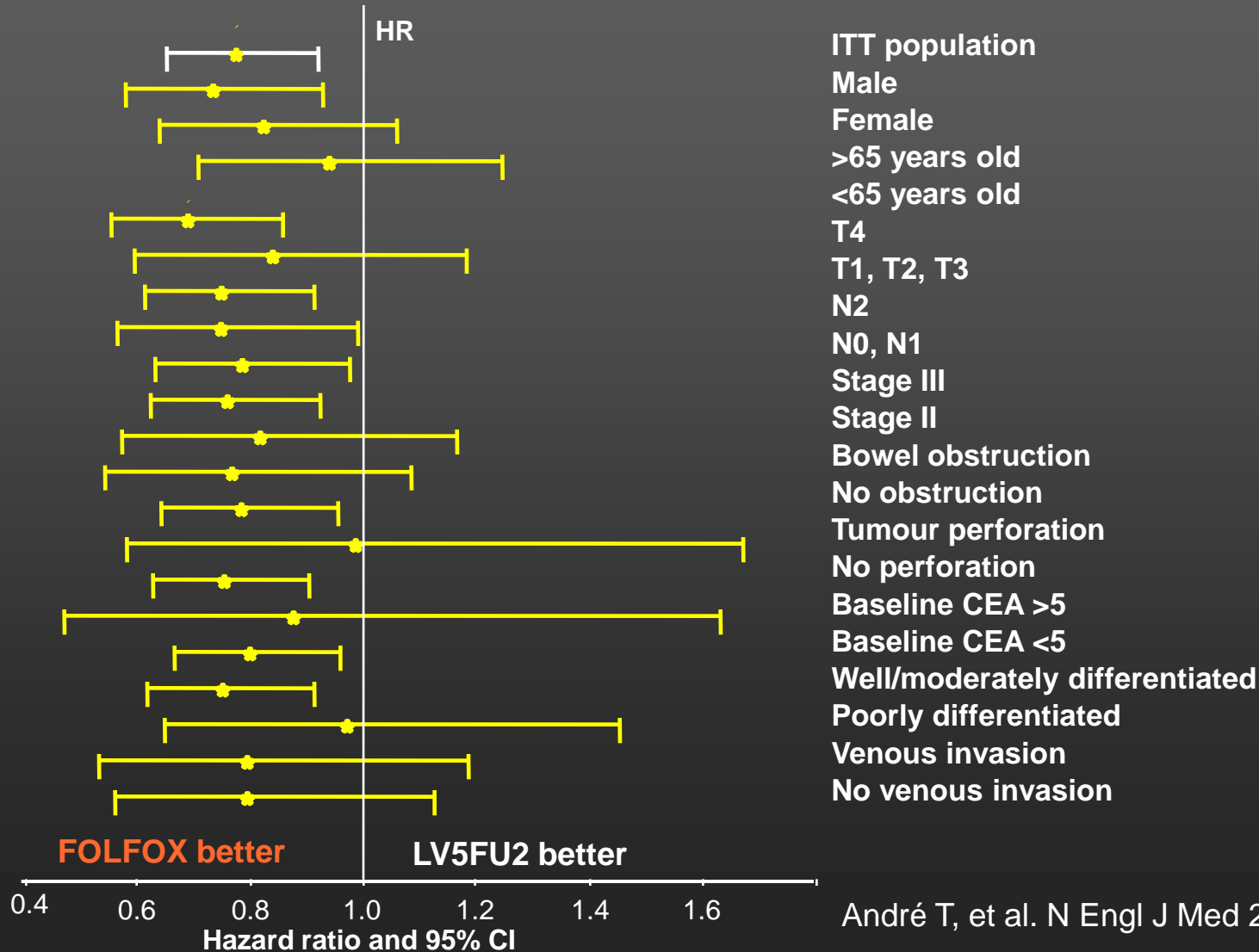


Disease-free Survival: High-risk Stage II Patients



Exploratory analysis

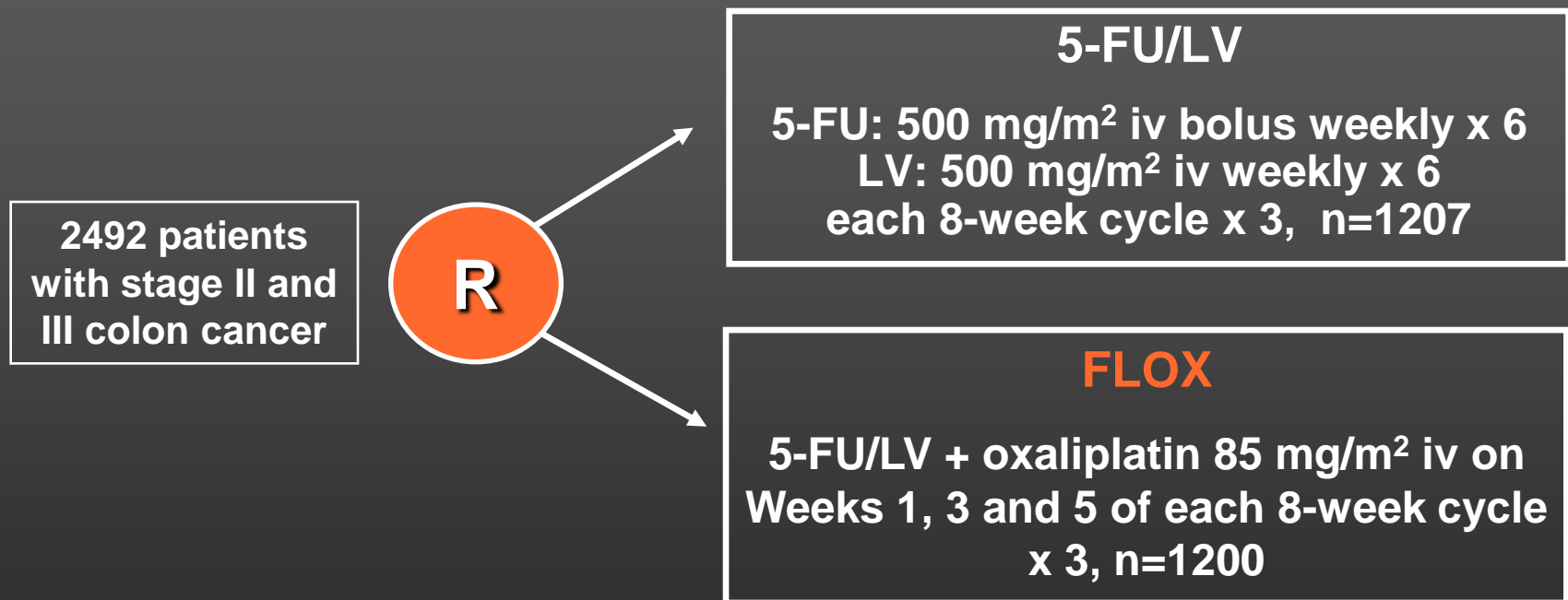
Oxaliplatin combinations MOSAIC: all patient subgroups benefit from FOLFOX



Oxaliplatin combinations: MOSAIC safety

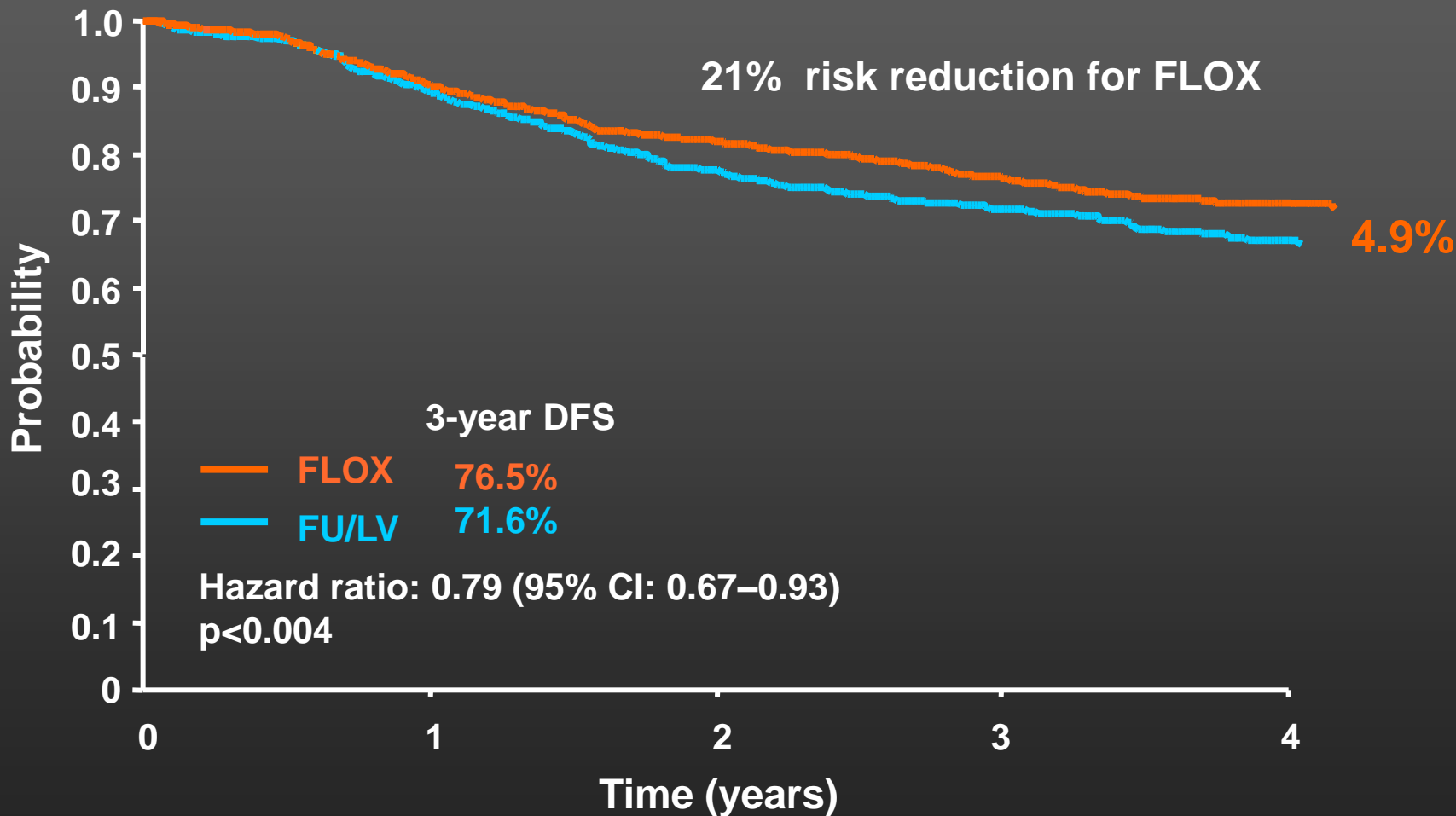
NCI-CTC \geq grade 3	FOLFOX4	LV5FU2
Neutropenia	41.0% (gr 4, 12.2%)	4.7%
Neutropenia with fever or infection	1.8%	0.2%
Diarrhoea	10.8%	6.7%
Stomatitis	2.7%	2.2%
Vomiting	5.9%	1.4%
Allergy	3.0%	0.2%
Alopecia (grade 2)	5.0%	5.0%
All cause mortality	0.5%	0.5%
Second cancer	4.0%	3.6%

Oxaliplatin combinations: NSABP C-07

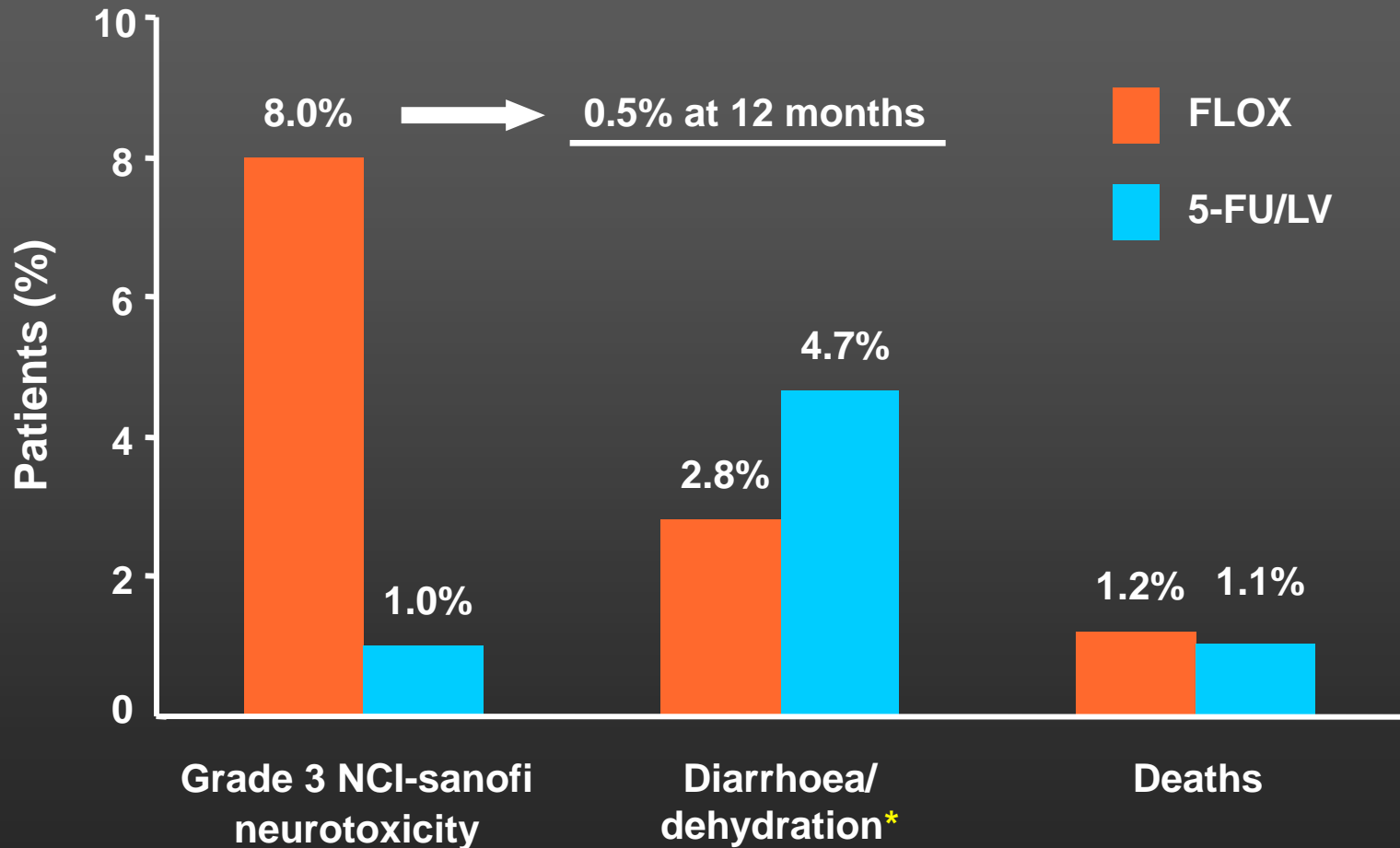


■ Primary endpoint: 3-year DFS

Oxaliplatin combinations: NSABP C-07 3-year DFS



Oxaliplatin combinations: NSABP C-07 safety

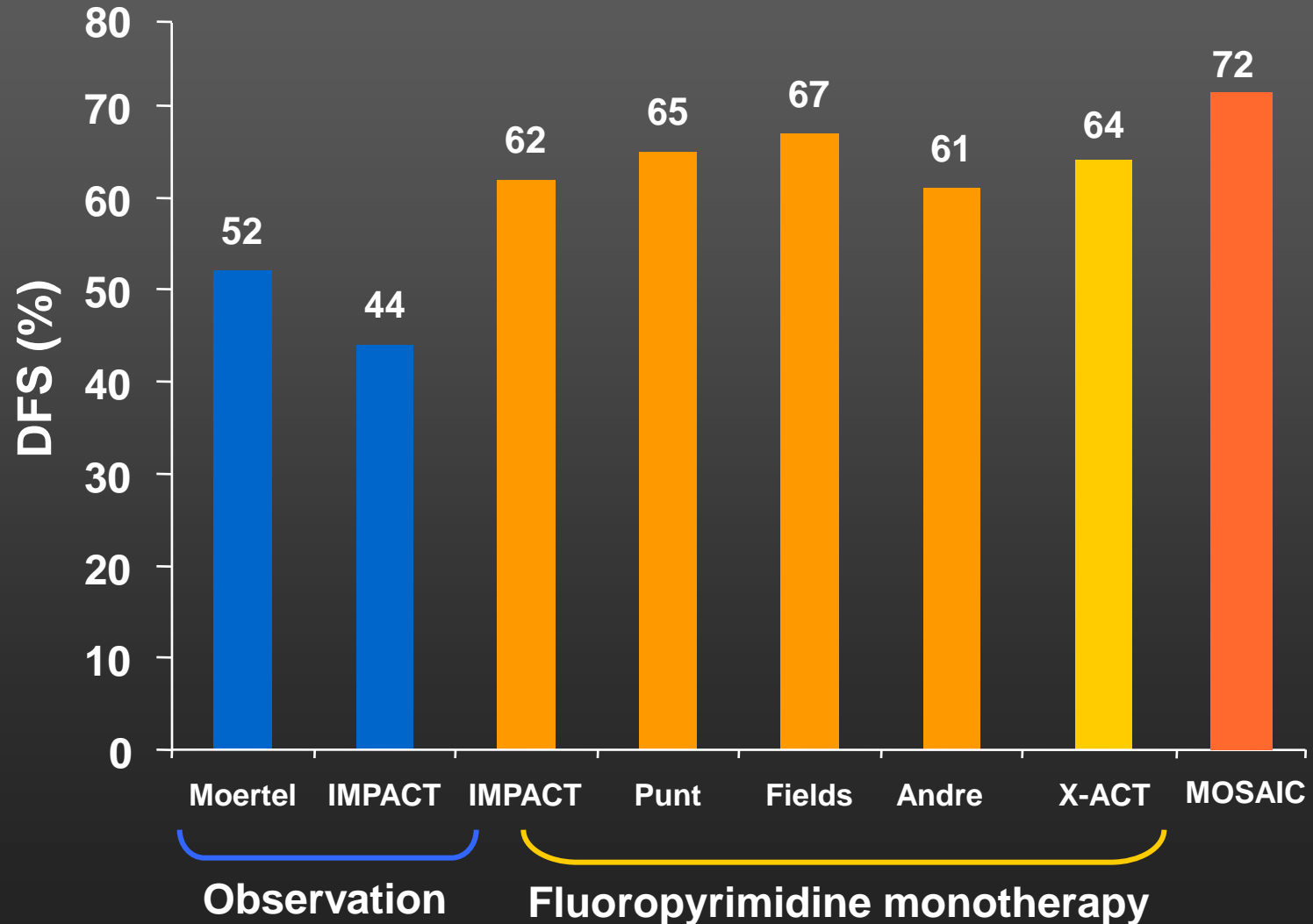


*Diarrhoea requiring hospitalisation and dehydration due to bowel thickening

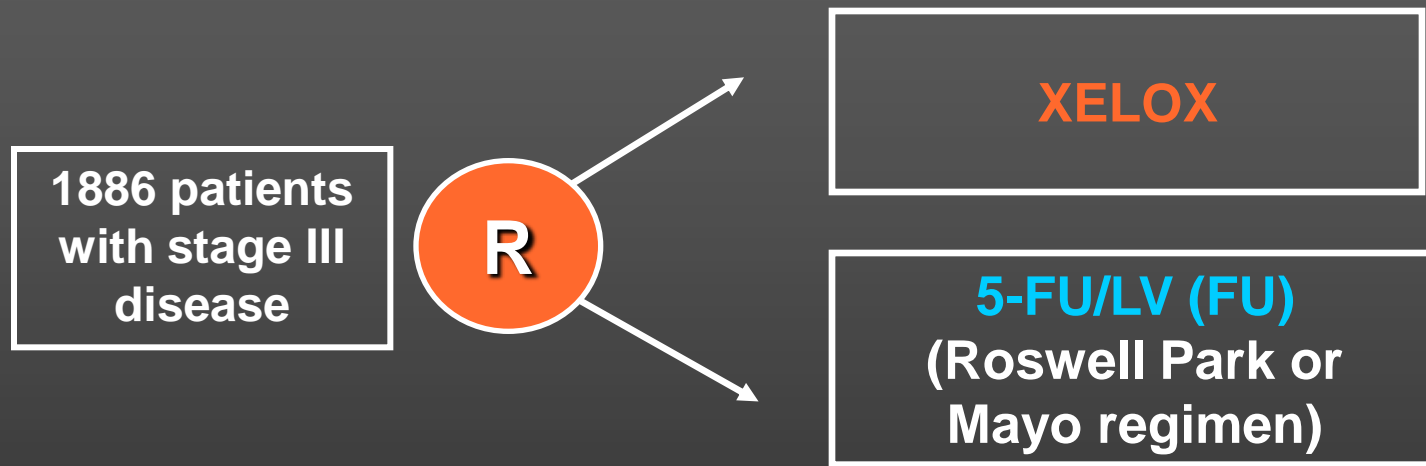
C-07 and MOSAIC: 3-year DFS (stage II and III)

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

3-year DFS in stage III CRC



Oral fluoropyrimidines: XELOX vs bolus 5-FU/LV



- **Primary endpoint: 3-year DFS**
- **Secondary endpoints: toxicity, OS, patient satisfaction, treatment convenience**

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 -

New standards in adjuvant colon cancer: which combination?

- **MOSAIC**: significant DFS benefit from the addition of oxaliplatin to 5-FU/LV
- **C-07**: confirmed efficacy of oxaliplatin in the adjuvant setting
- **CALGB C89803/PETACC-3/ACCORD-02**: no DFS benefit from the addition of irinotecan to 5-FU/LV
- Oxaliplatin-based regimens combine high efficacy with acceptable toxicity:



**standard in clinical practice
benchmark for new clinical
trials in adjuvant colon cancer**

Future directions: PETACC-8

Phase III trial

Fully resected stage III
colon cancer

Planned n=2000

Primary endpoint: DFS



FOLFOX4 + cetuximab

Treatment will be
administered
for 6 months

FOLFOX4

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

Stage II and III
colon cancer
n=3450 patients



FOLFOX4

FOLFOX4 + bevacizumab

XELOX + bevacizumab

Primary endpoint: DFS

NSABP Protocol C-08: mFOLFOX ± Bevacizumab in Stage II/III CRC

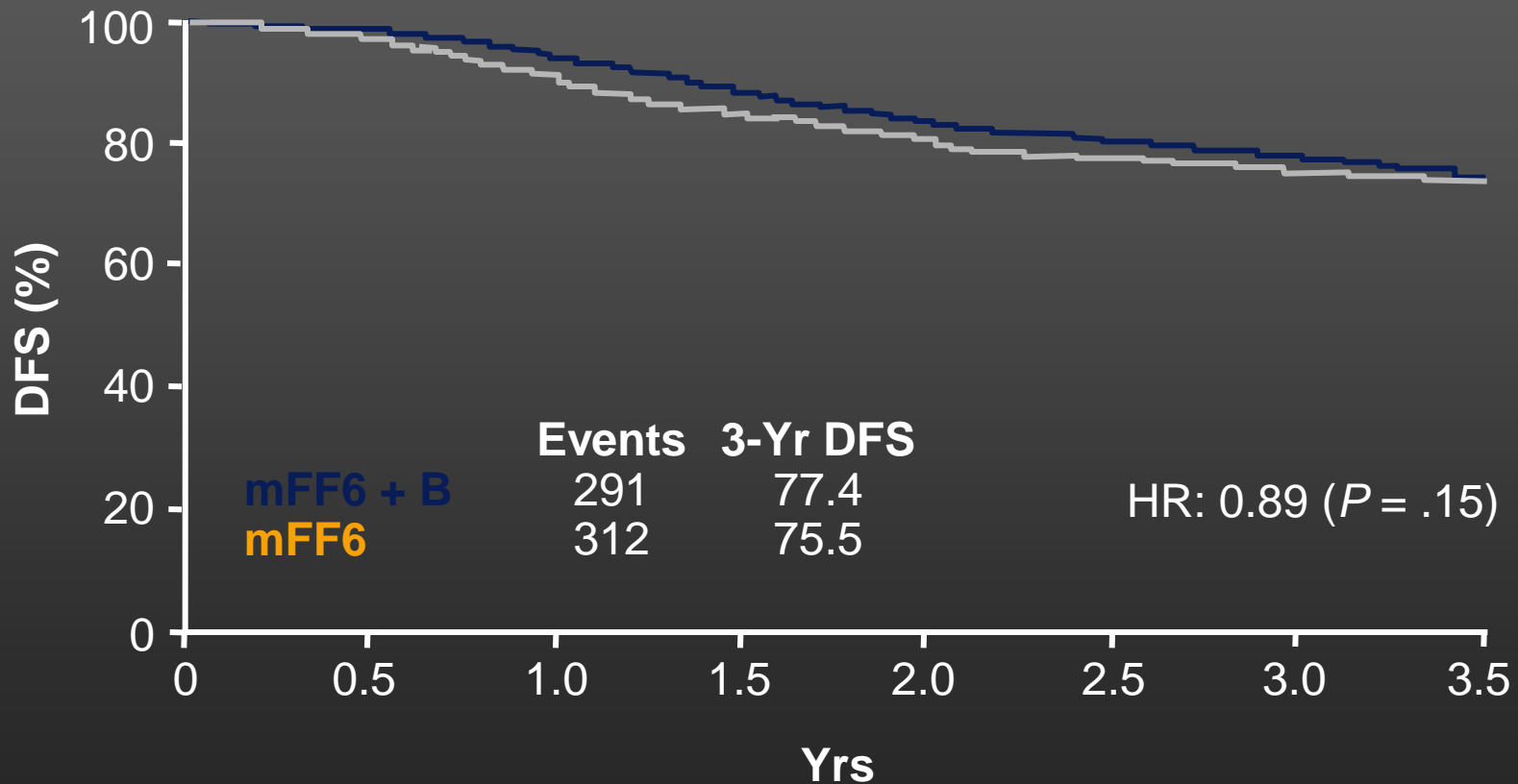
Pts with stage II or III
colon adenocarcinoma
with ECOG PS of 0/11
(N = 2710)

Arm A: mFOLFOX6 Q2W x 26
(n = 1356)

Arm B: mFOLFOX6 +
Bevacizumab 5 mg/kg Q2W x 26
(n = 1354)

- Pts stratified by number of positive lymph nodes and randomized between Days 29 and 50 postoperatively
- mFOLFOX6 regimen: LV 400 mg/m² IV, 5-FU 400 mg/m² IV, 5-FU 2400 mg/m² over 46 hours; oxaliplatin 85 mg/m² IV
- Primary endpoint: DFS

NSABP Protocol C-08: 3-Yr DFS Results



NSABP Protocol C-08: Safety Results

- Increased incidence of grade ≥ 3 adverse events, including hypertension, pain, proteinuria, wound complications, among pts receiving bevacizumab

- Bevacizumab generally well tolerated

No increase in gastrointestinal perforations, bleeding events, or thrombosis

Adverse Event, %	mFOLFOX6 + Bevacizumab (n = 1334)	mFOLFOX6 (n = 1338)
Hypertension	12.0	1.8*
Pain	11.1	6.3*
Proteinuria	2.7	0.8†
Wound complications	1.7	0.3†

* $P < .0001$; † $P < .001$

NSABP Protocol C-08: DFS Results

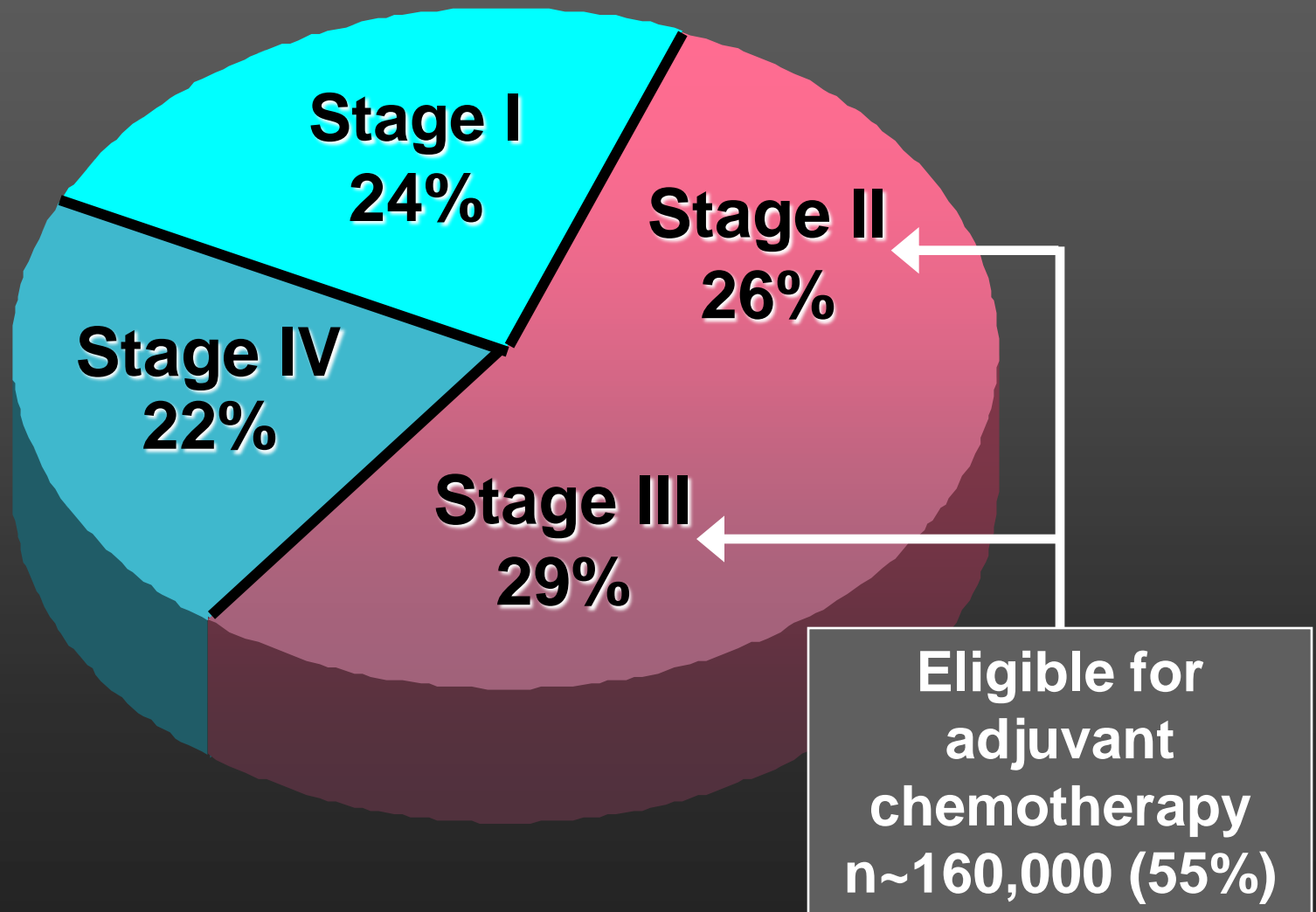
- Analysis of earlier time points (< 3 yrs) showed an improved DFS suggesting a benefit with bevacizumab in the first 2 yrs of the trial, although timing of assessment not mandated
 - DFS initially significantly improved but lost significance over time

Time Point	HR for DFS Benefit With Bevacizumab	P Value
1.0 yr	0.60	.0004
1.5 yrs	0.74	.004
2.0 yrs	0.81	.02
2.5 yrs	0.85	.05
3.0 yrs	0.89	NS

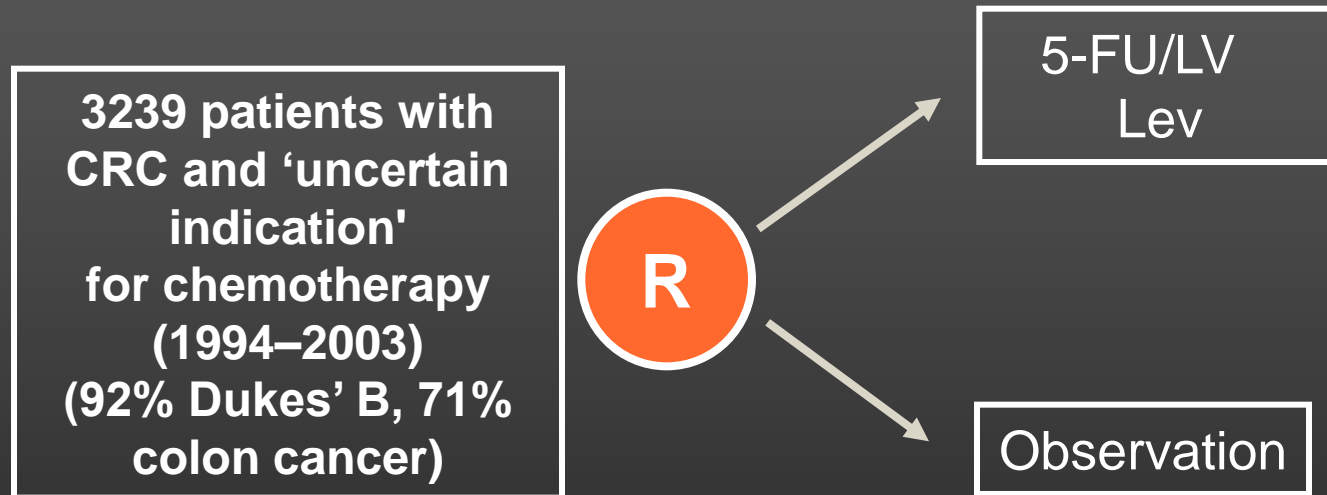
NSABP Protocol C-08: DFS Results

- Improvement in DFS conferred by bevacizumab limited to Yr 1
 - After completion of 1 yr of bevacizumab, pts in both arms had similar EFS over the subsequent 2 yrs (HR: 1.07; $P = \text{NS}$)
 - Interaction between treatment and time highly significant ($P = .001$)
- Tumor stage did not significantly affect DFS at 3 yrs
 - Stage II (HR: 0.82; $P = \text{NS}$)– Stage III (HR 0.90; $P = \text{NS}$)
- Lack of DFS benefit not due to harmful effect of bevacizumab
 - No significant difference among any parameters of patient outcome at median 36-mo follow-up

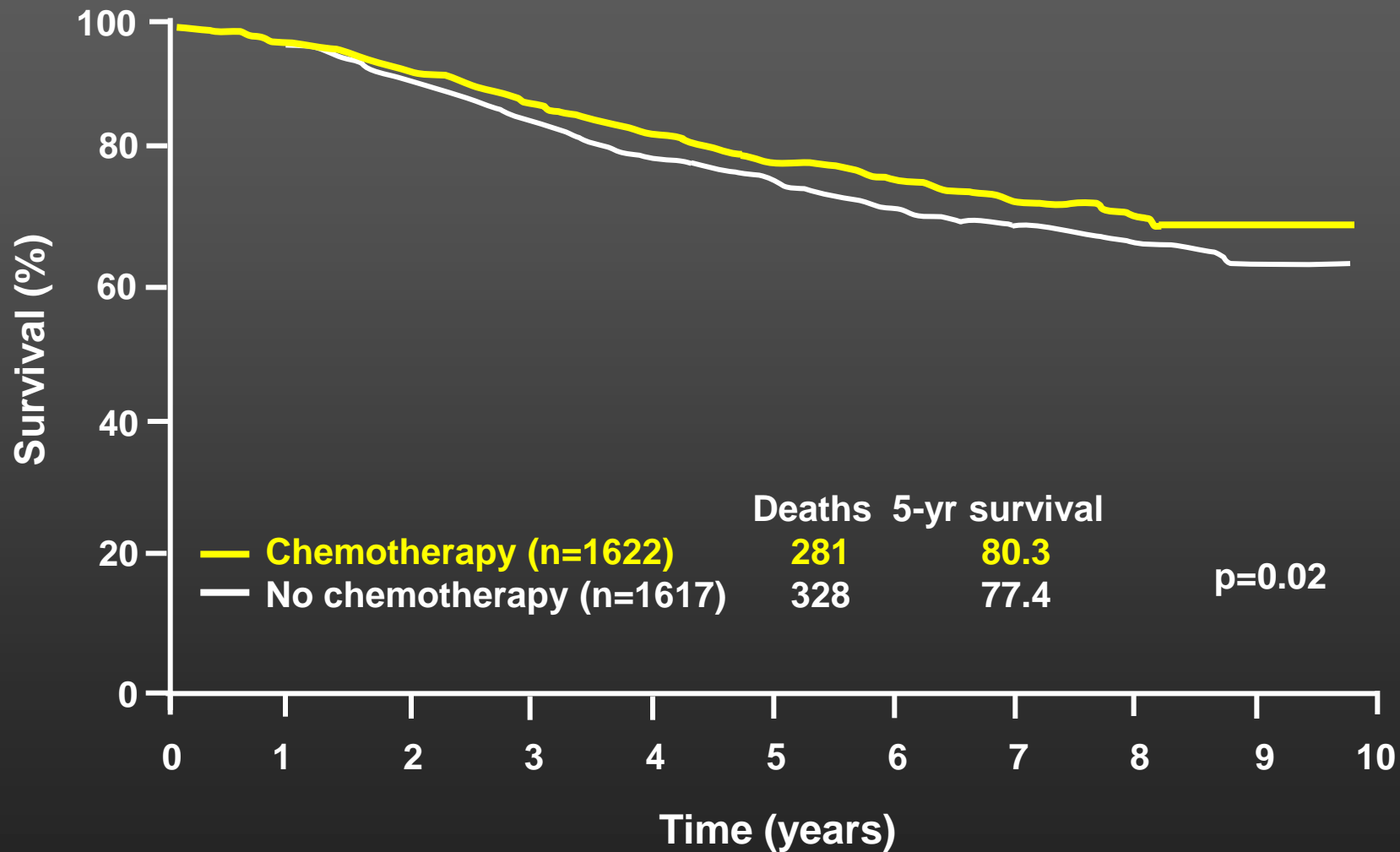
Incidence of colorectal cancer in the U.S. and Western Europe 2006 (n~300,000)



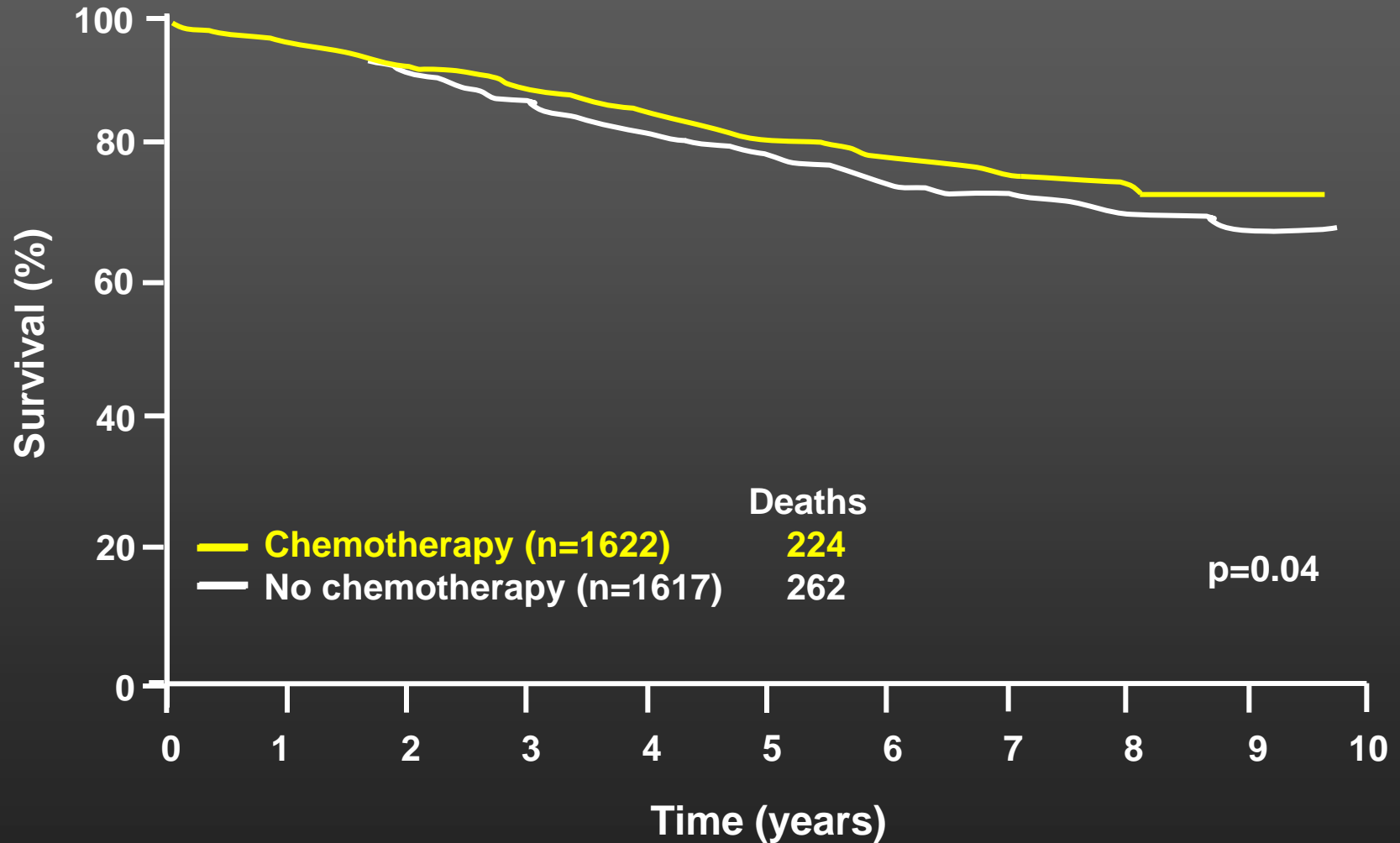
QUASAR



QUASAR: survival in ITT population



QUASAR: survival in stage II patients



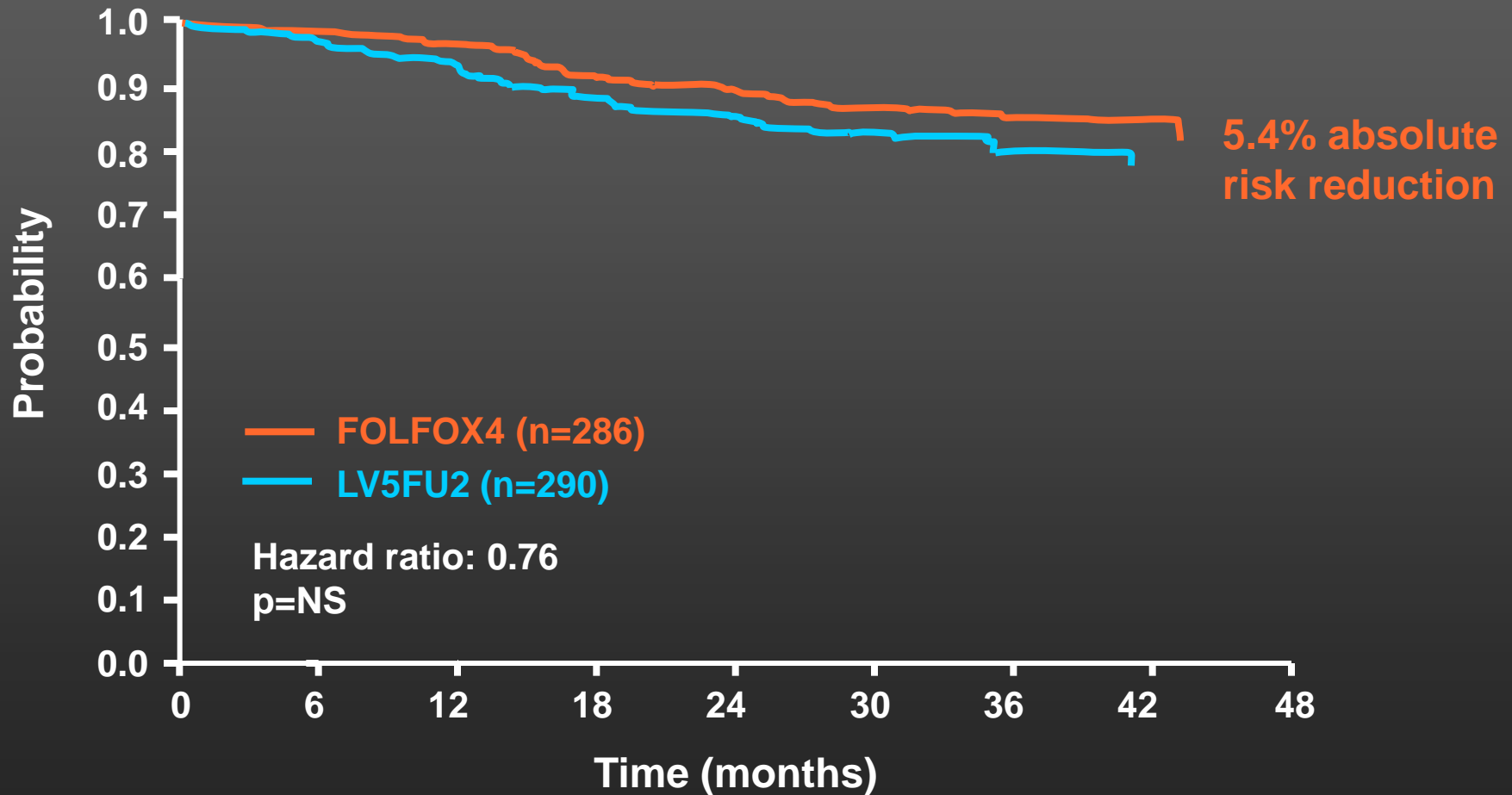
Adjuvant therapy for stage II colon cancer: Cancer Care Ontario metaanalysis

- Data: 62 randomised trials; 11 meta-analysis
- Primary analysis based on subset of 3586 patients in whom deaths in patients with stage II disease were provided
 - OR: 0.82 (95% CI 0.67–1.01; $p=0.07$)
 - Absolute survival benefit: ~4–6%

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

MOSAIC: 4-year DFS in high-risk stage II patients



New guidelines for adjuvant treatment of colon cancer: NCCN 2009

- 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
 - clinical trial
 - observation

Risk stratification in stage II colon cancer

- Conventional high-risk factors:
 - T4 invasion
 - bowel obstruction
 - tumour perforation
 - poorly differentiated tumour
 - venous invasion
 - <10 lymph nodes examined
- Emerging molecular risk factors...

Prognostic and predictive markers

- In the future, accurate prognostic and predictive markers will help to identify:
 - prognostic markers: select treatment according to patient's prognosis
 - predictive markers: select patients most likely to benefit from adjuvant chemotherapy

QUASAR Validation Study of Multigene RT-PCR Assay for Recurrence Prediction

- New clinical tools needed for better risk assessment and treatment decision-making in pts with stage II colon cancer
- Current study designed to develop and validate multigene expression assay to
 - Assess recurrence risk after surgery for individual pts
 - Identify pts with differential response to 5-FU/LV
 - Maintain independent clinical value among existing measures (tumor stage, microsatellite instability)
- Development of gene set from 761 candidate genes
 - 48 genes associated with recurrence and 66 genes associated with treatment benefit observed significant across 4 independent clinical trials (n = 1851)
 - Surgery alone: NSABP C-01/C-02 (n = 270) and Cleveland Clinic study (n = 765)
 - Surgery + 5-FU/LV: NSABP C-04 (n = 308) and NSABP C-06 (n = 508)

QUASAR Validation Study: Study Design

- After additional modeling and analysis, final gene set generated
 - 7 recurrence genes to yield recurrence score (0-100)
 - 6 treatment benefit genes to yield treatment score (0-100)
 - 5 reference genes: *ATP5E*, *GPX1*, *PGK1*, *UBB*, *VDAC2*
- Recurrence score calculated from expression of 7 tumor genes
 - Stromal : *FAP*, *INHBA*, *BG*
 - Cell cycle: *Ki-67* , *C-Myc* , *MYBL2*
 - *GADD45B*
- Validation based on pts from QUASAR study with stage II colon cancer and tissue blocks obtained for gene expression analysis (n = 1436)
 - QUASAR trial: 3239 pts with resected CRC randomized to 5-FU/LV or observation only^[2]
 - Prespecified primary endpoint for gene expression validation study
 - Prognostic value of treatment score for 5-FU/LV benefit also assessed

QUASAR Validation Study: Results

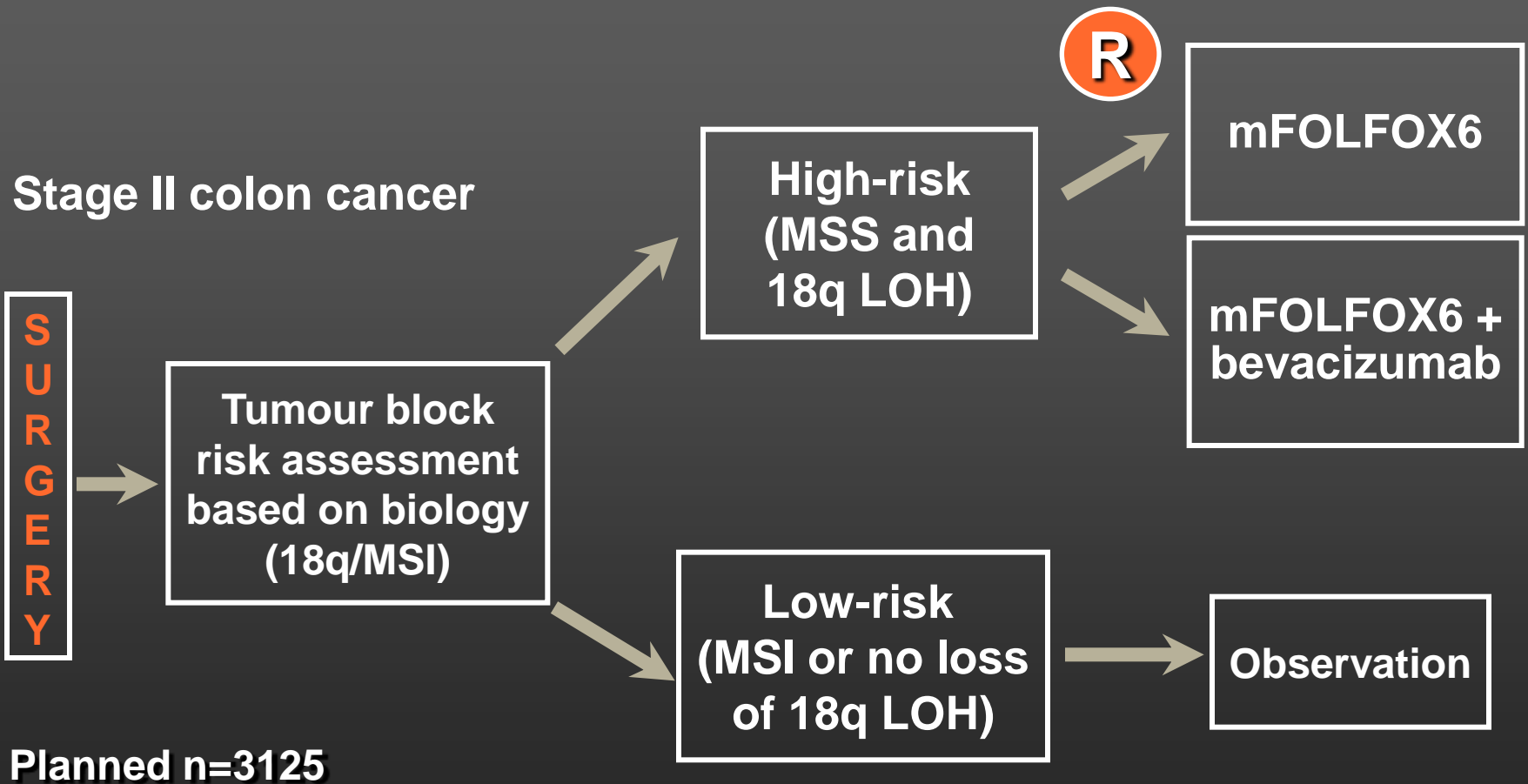
- Significant association between recurrence score and risk of recurrence at 3 yrs following surgery in pts receiving surgery alone (n = 711; $P = .004$)
 - Comparison of recurrence risk in high vs low recurrence score risk groups also significant (HR: 1.47; $P = .046$)
 - Prespecified clinical and pathologic covariates also significant in multivariate analysis in pts receiving surgery alone (n = 605)

Clinical or Pathologic Variable	HR (95% CI)	P Value
MMR (deficient vs proficient)	0.32 (0.15-0.69)	< .001
Tumor stage (T4 vs T3)	1.83 (1.23-2.75)	.005
Tumor grade (high vs low)	0.62 (0.40-0.96)	.026
Number of nodes examined (< vs \geq 12)	1.47 (1.01-2.14)	.040
LVI (present vs absent)	1.40 (0.88-2.23)	.175
Recurrence score (continuous, per 25 units)	1.61 (1.13-2.29)	.008

QUASAR Validation Study: Results

- Recurrence score (per 25 units) predictive of DFS and OS
 - DFS HR: 1.42 (95% CI: 1.09-1.84; $P = .010$)
 - OS HR: 1.33 (95% CI: 1.01-1.76; $P = .041$)
- MMR deficiency, recurrence score, and tumor stage identified as key independent disease recurrence indicators in stage II pts
 - T4 stage: 13%
 - T3 and MMR proficient: 76%
 - MMR deficient: 11%
- No significant differences in treatment score by treatment interaction in OS, DFS, or relapse-free interval

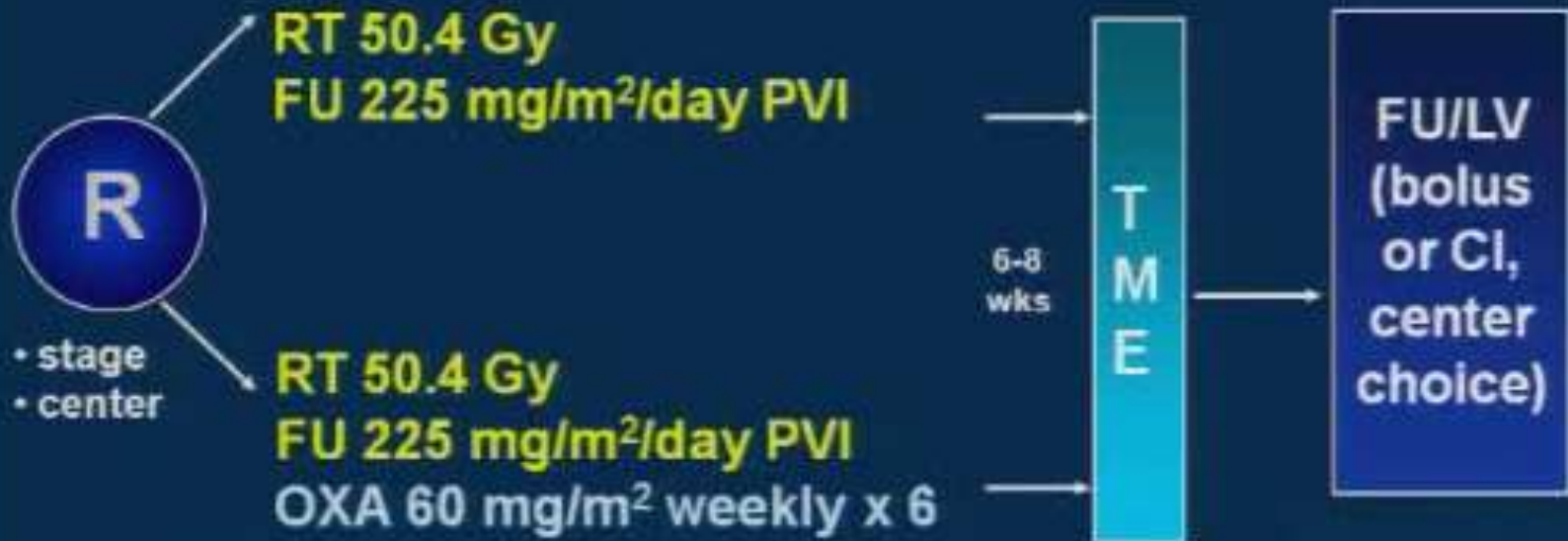
Future directions: E5202



New randomized trials

Author	N	Chemo	RT	Grade 3-4 Toxicity	Pathologic CR rate
Gerard et al # 4007	295	Capecitabine 800 mg/m bid	45 Gy in 25 fractions	11%	13.8%
	292	Capecitabine 800 mg/m bid 5 of 7 d Oxaliplatin 50 mg/m/wk	50 Gy in 25 fractions	25%	18.8%
Aschele et al # 4008	379	5-FU 225 mg/m/d	50.4 Gy in 28 fractions	8%	16%
	368	5-FU 225 mg/m/d Oxaliplatin 60 mg/m/wk x 6	50.4 Gy in 28 fractions	24%	15%

STUDY OUTLINE



STUDY END-POINTS

primary: overall survival

- 30% RR in mortality rates (3-y S: 75 --> 82%)
- 80% power - alpha error: 0.05

secondaries:

• pathologic complete response (pCR):

- all path reports available (cut-off data 01/03/09)
- 12% --> 25%; 90% power

• disease-free survival

• safety

STUDY POPULATION

747: randomized
response/survival analyses

379
FU/RT

5 never started
- consent withdrawal (2)
- squamous histology (1)
- immediate surgery (2)

379

ASCO Annual '09 Meeting

5 received FU alone

732: treated
safety/compliance analyses

368
FU/OXA/RT

10 never started
(3) consent withdrawal
(2) squamous /melanoma
(1) immediate surgery
(2) only RT
(2) different chemo

353

TOXICITY

	% of patients		p
	FU/RT (n=379)	FU/OXA/RT (n=353)	
grade III-IV			
any type	8	24	<.0001
diarrhea	4	15	<.0001
radiation dermatitis	2	5	0.038
grade II-III			
neurosensory	0.5/0	36/1	<.0001
Tx related deaths	0.3 (1)	0.6 (2)	

pathologic CR

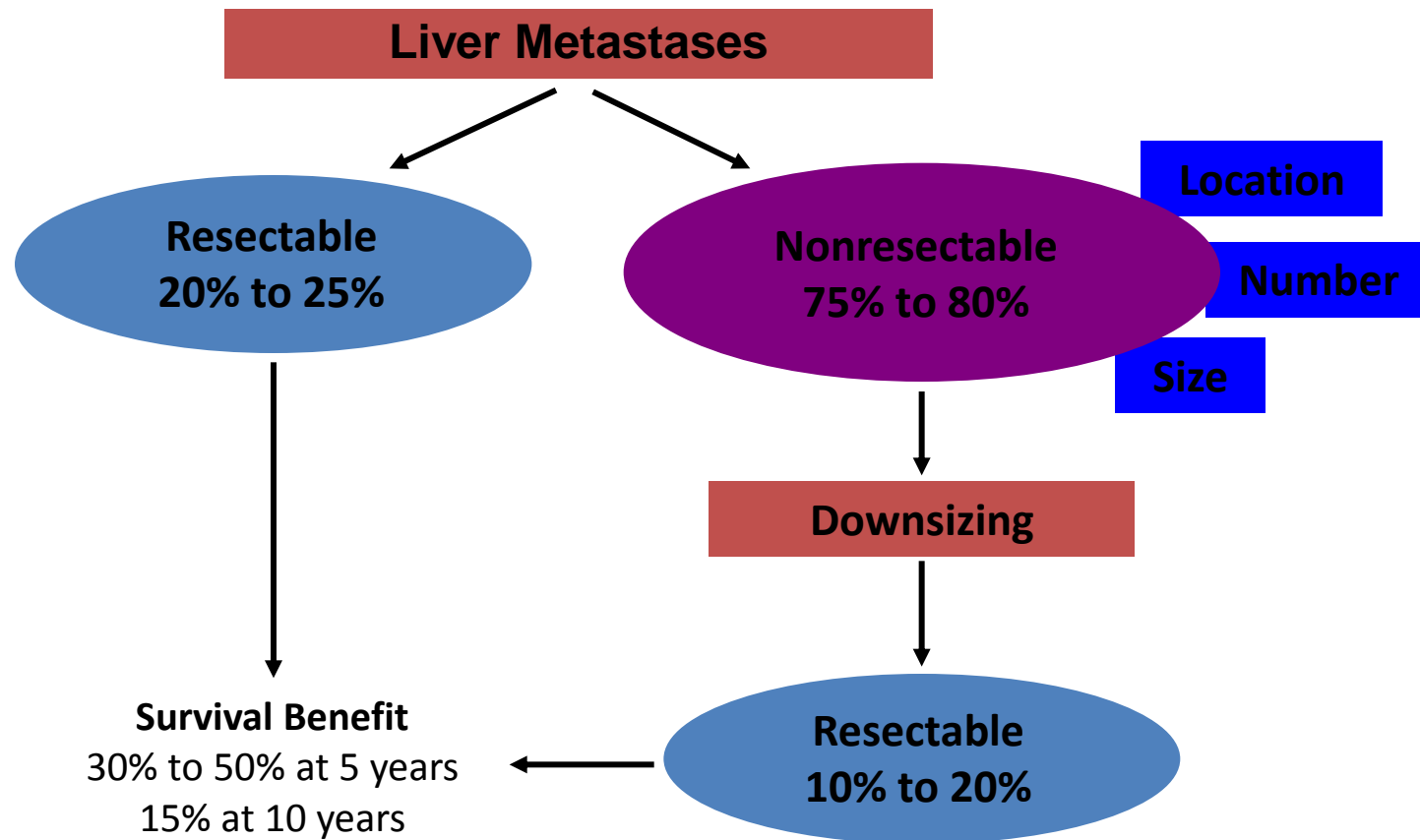
	patients, %		
	FU/RT (n= 379)	FU/OXA/RT (n= 368)	p
ypT0N0 (95% ci)	16 (13-20)	16 (13-20)	0.94

**Treatment of CRC metastases
Which strategy ? Which patients?**



- FACTORS

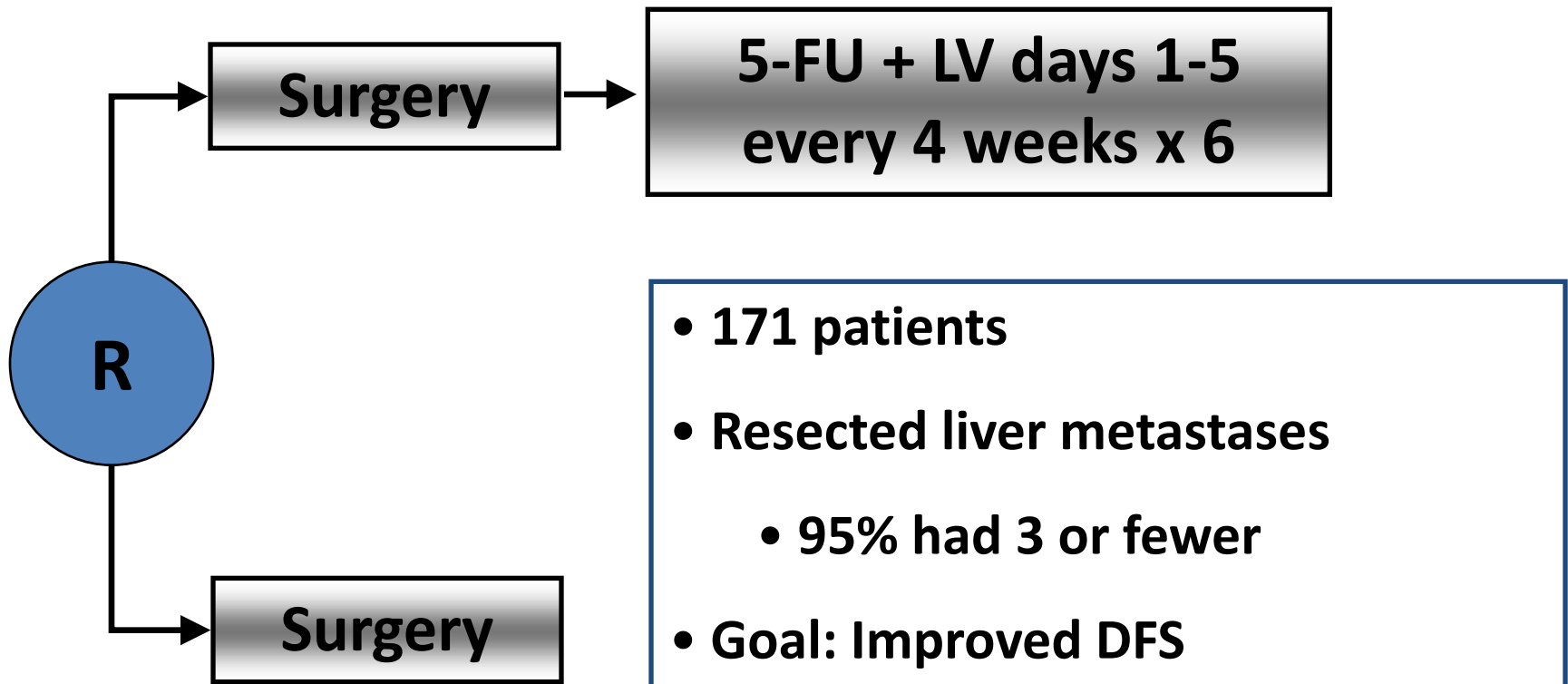
Hepatic Metastases From Colorectal Carcinoma



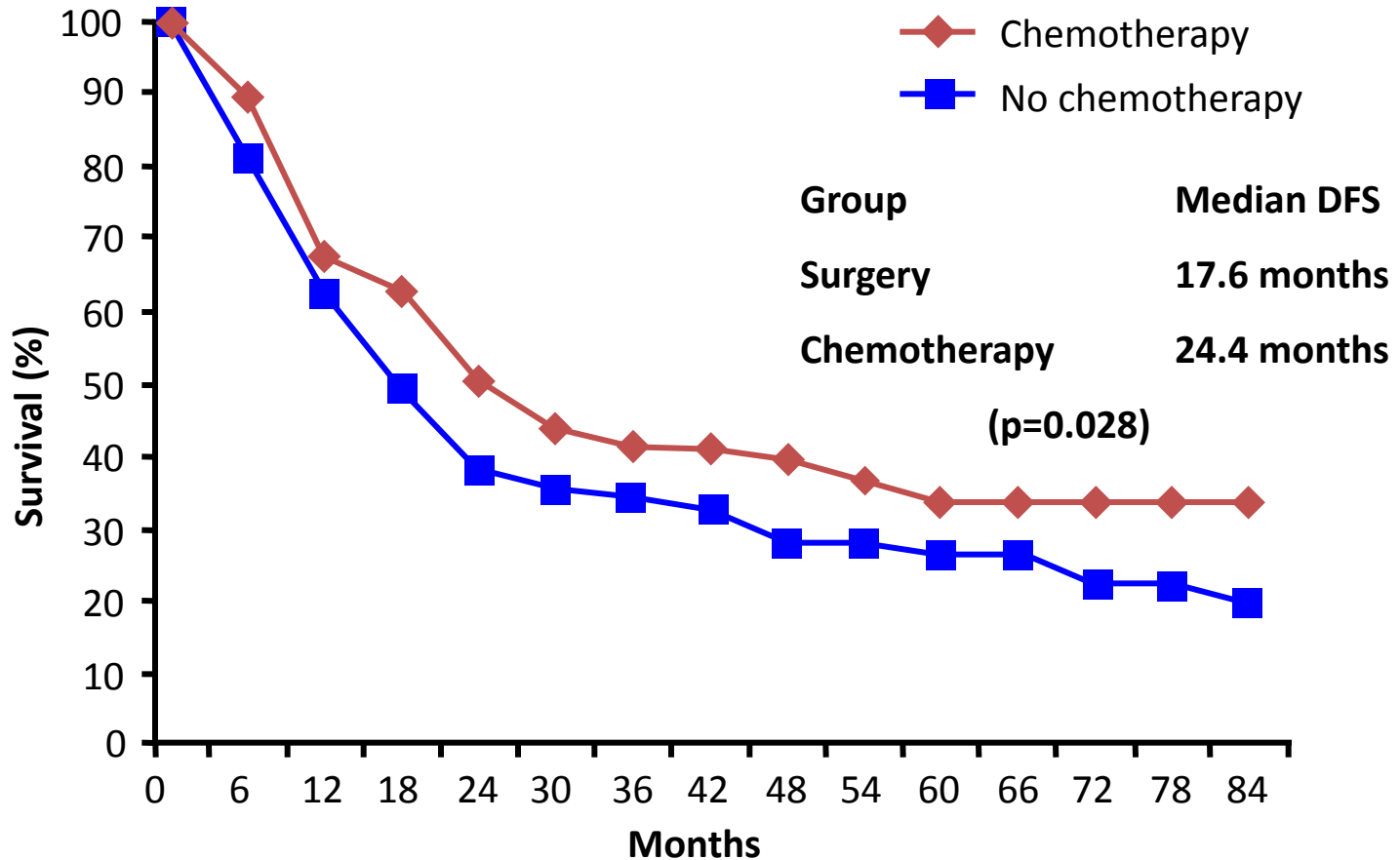
Role of Chemotherapy for Resectable Disease

- One adjuvant systemic chemotherapy versus surgery alone
- One peri-operative trial
- One Adjuvant hepatic artery infusion chemotherapy combined with systemic chemotherapy

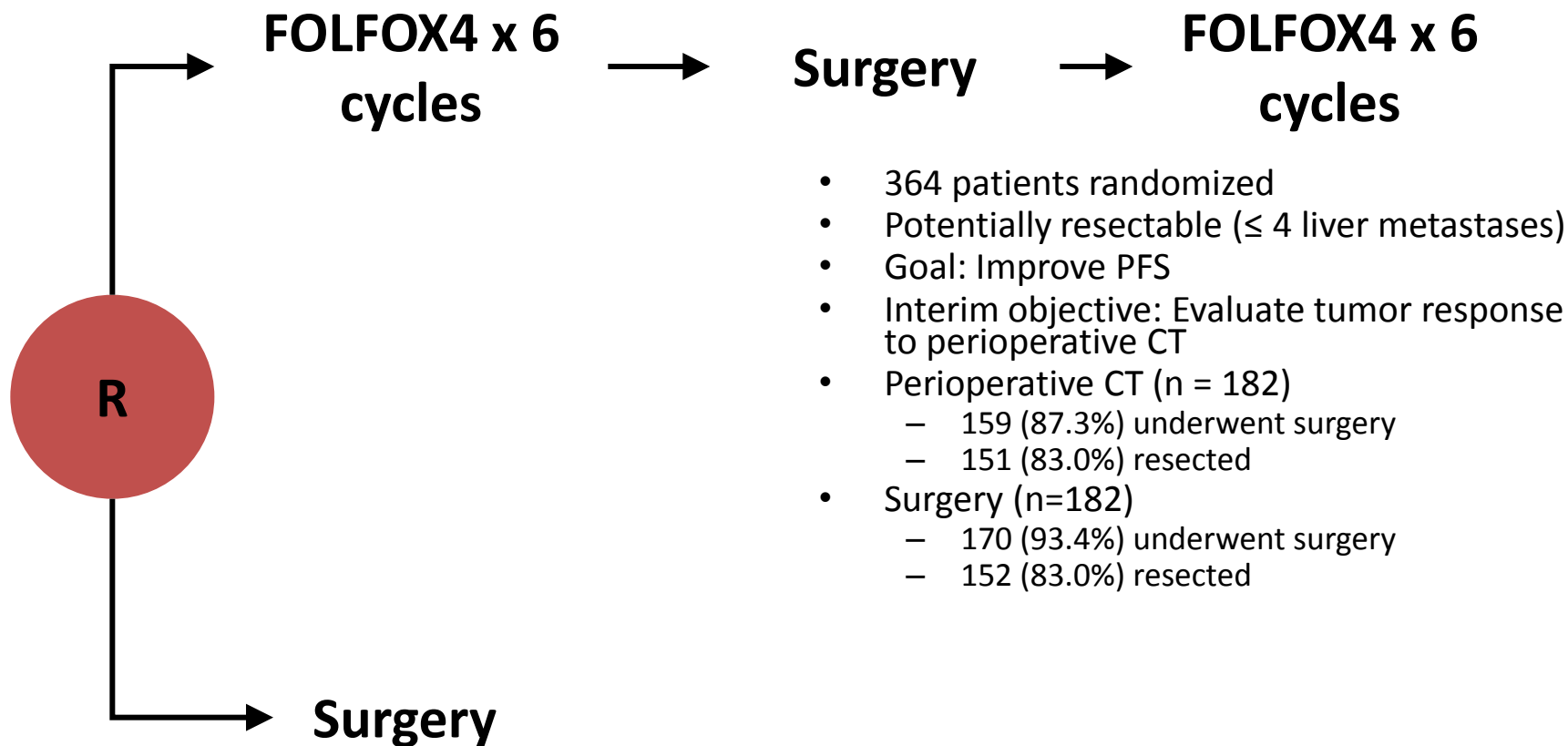
Adjuvant Therapy: AURC 9002



Disease-free Survival After Liver Resection



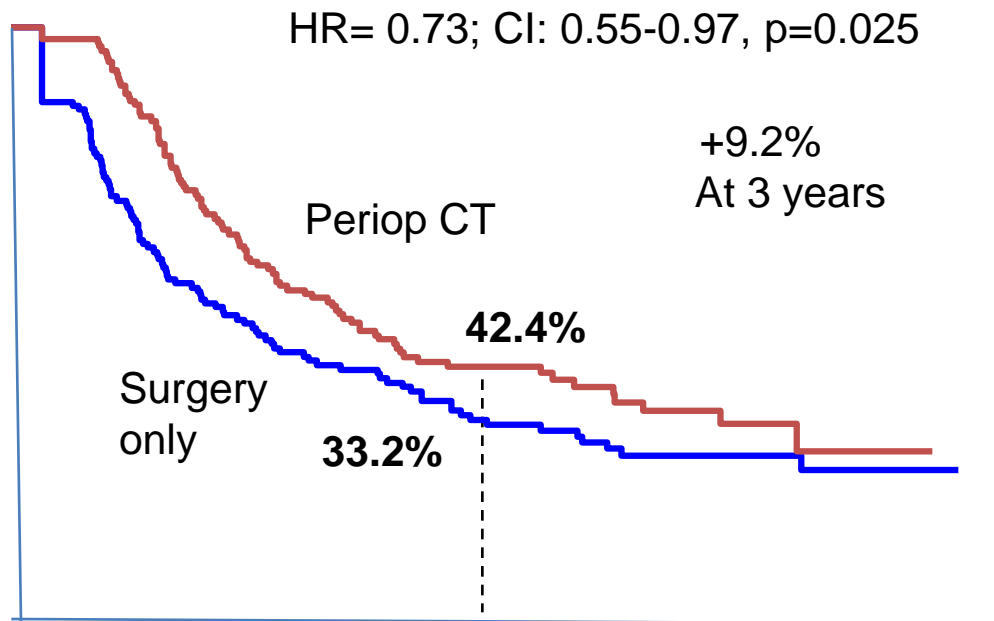
EORTC 40983 (EPOC Trial)



EORTC 40983: RECIST Response After Pre-operative CT

Complete response:	7 (3.8%)
Partial response:	73 (40.1%)
Stable disease:	64 (35.2%)
Progressive disease:	12 (6.6%)
8 progressed after 3-4 cycles, 3 were resected 4 progressed after 6 cycles, 1 was resected	
Not evaluable	26 (14.3%)
Ineligible	7
Benign lesion	3
<3 cycles	12
No follow-up measures	4

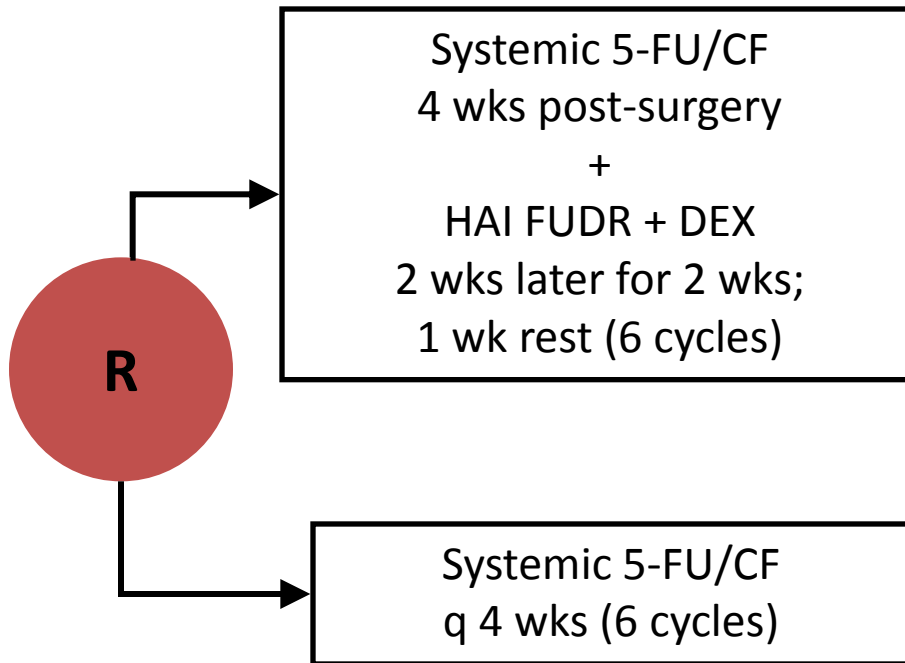
EORTC 40983: Progression-Free Survival in Resected Patients



Surgery only
Periop CT

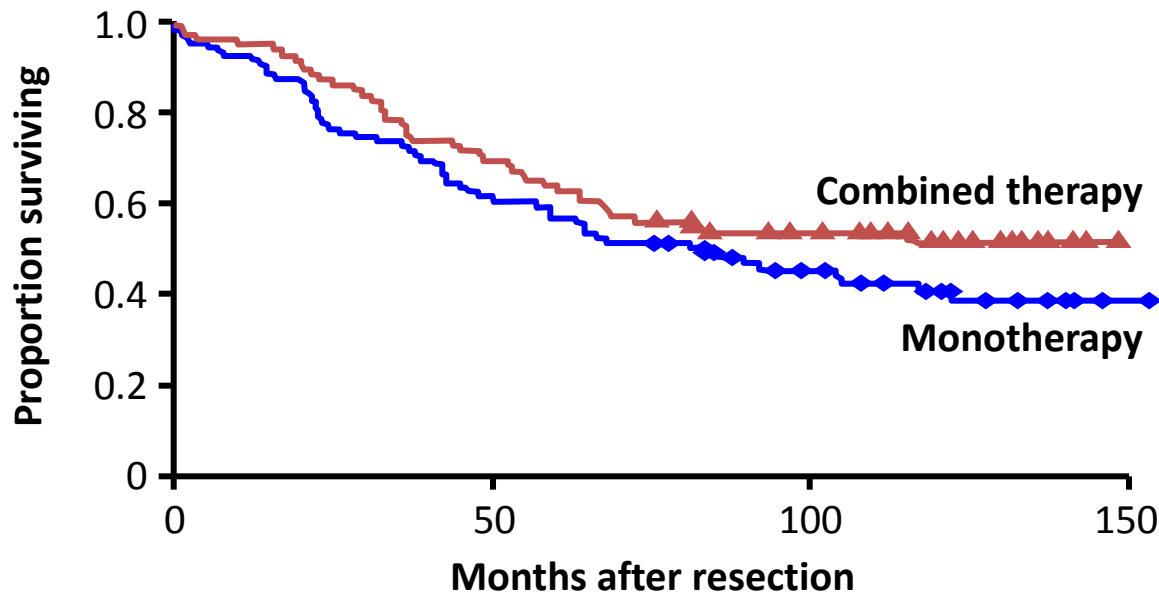
Hepatic Artery Infusion

Memorial Sloan-Kettering Randomized Study



- 156 patients randomized
- Initial resection of liver metastases

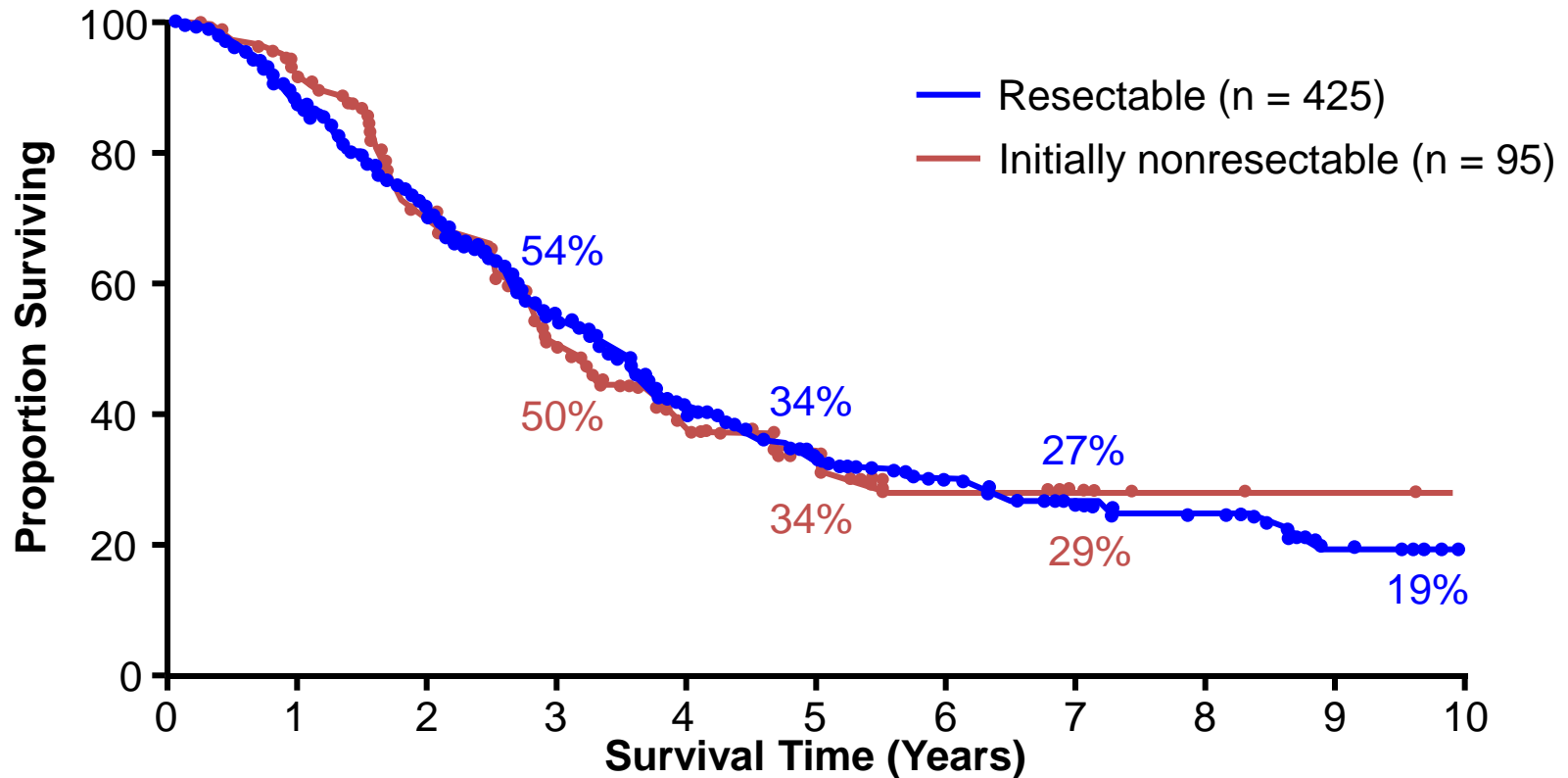
HAI Versus Systemic Therapy Alone: Long-term Follow-up*



	Combination Therapy	5-FU/LV	P Value
10-y OS (%)	41.1	27.2	Not reported
mOS (mo)	68.4	58.8	NS
PFS (mo)	31.3	17.2	0.02

*All patients followed for a minimum of 6 y, with a median follow-up of 10.3 y.

Survival After Primary or Secondary Resection of Liver Metastases



Adam R, et al. Chemotherapy and surgery: new perspectives on the treatment of unresectable liver metastases, *Annals of Oncology*, 2003, Vol. 14, supplement 2, pp.ii13-ii16, by permission of Oxford University Press.

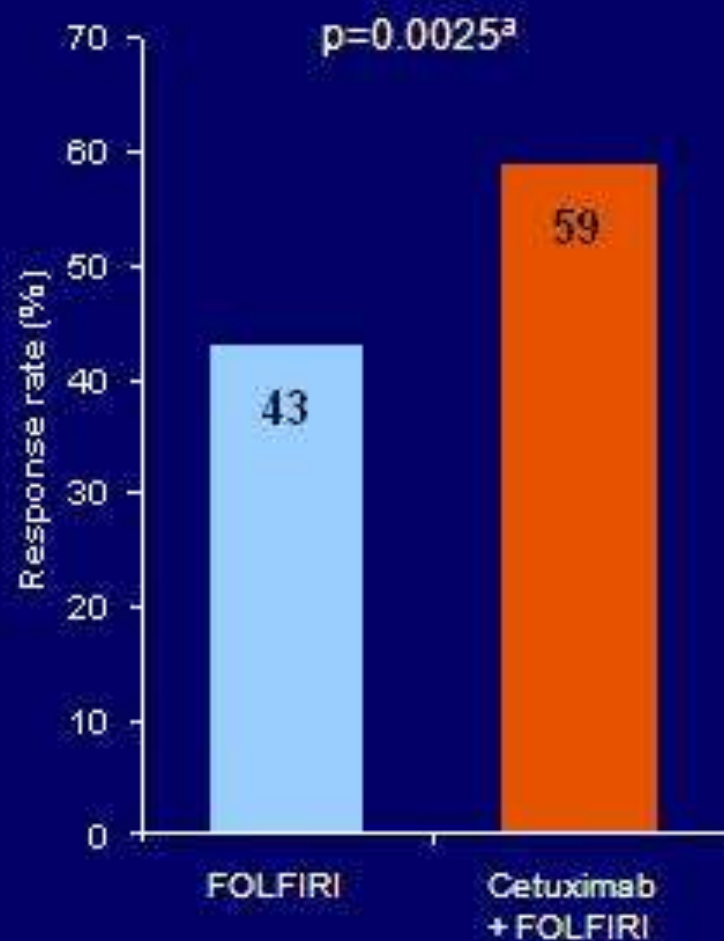
Adam R. *Ann Oncol*. 2003;14(suppl 2):ii13-iii16.

3 cytotoxics vs 2 cytotoxics + 1 biologic

<i>Trial</i>	AVF2107 IFL + BV <i>NEJM '04</i>	NO16966 FOLFOX/XELOX + BV <i>JCO '08</i>	CRYSTAL FOLFIRI + CETUX <i>ESMO 2008</i>	GONO FOLFOXIRI <i>JCO '07</i>
<i>N. Pts</i>	402	700	599	122
<i>RR (%)</i>	45%	38%	47%	60%
<i>R0 surgery</i> <i>(Liver only)</i>	< 2% NA	6% 12%	4% 10%	19% 36%
<i>PFS (mos)</i>	10.6	9.4	8.9	9.9
<i>OS (mos)</i>	20.3	21.3	19.9	23.6

Relating KRAS status to efficacy

Secondary endpoint: Response – KRAS wild-type

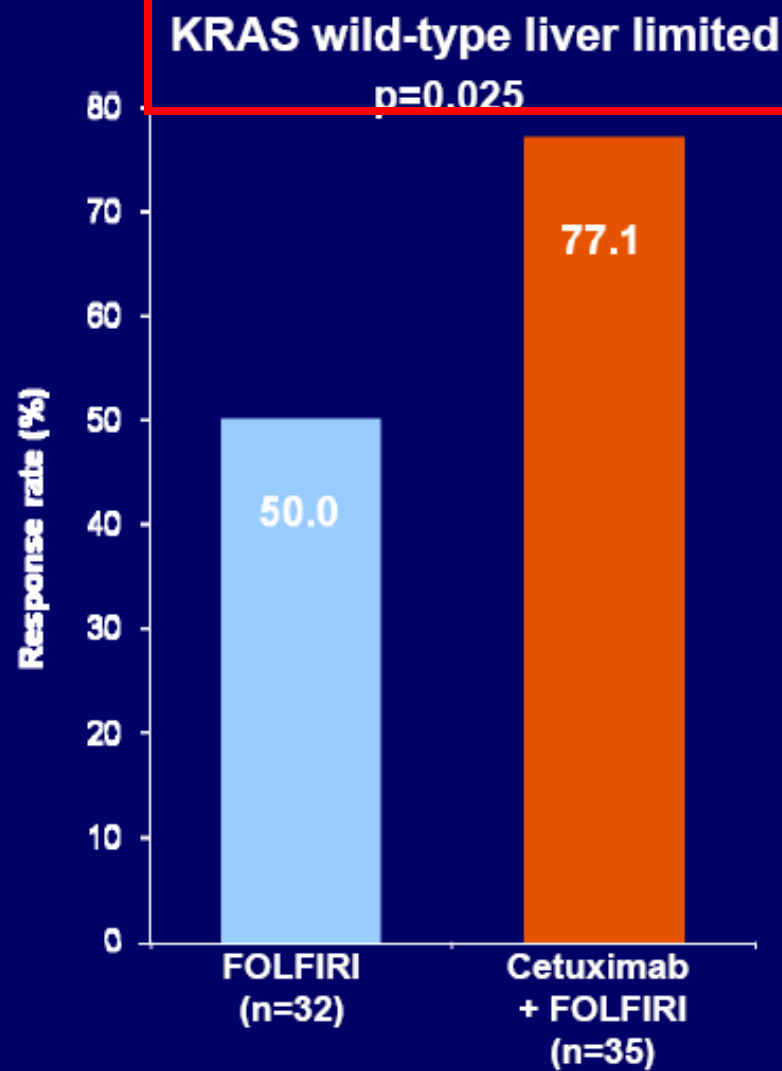
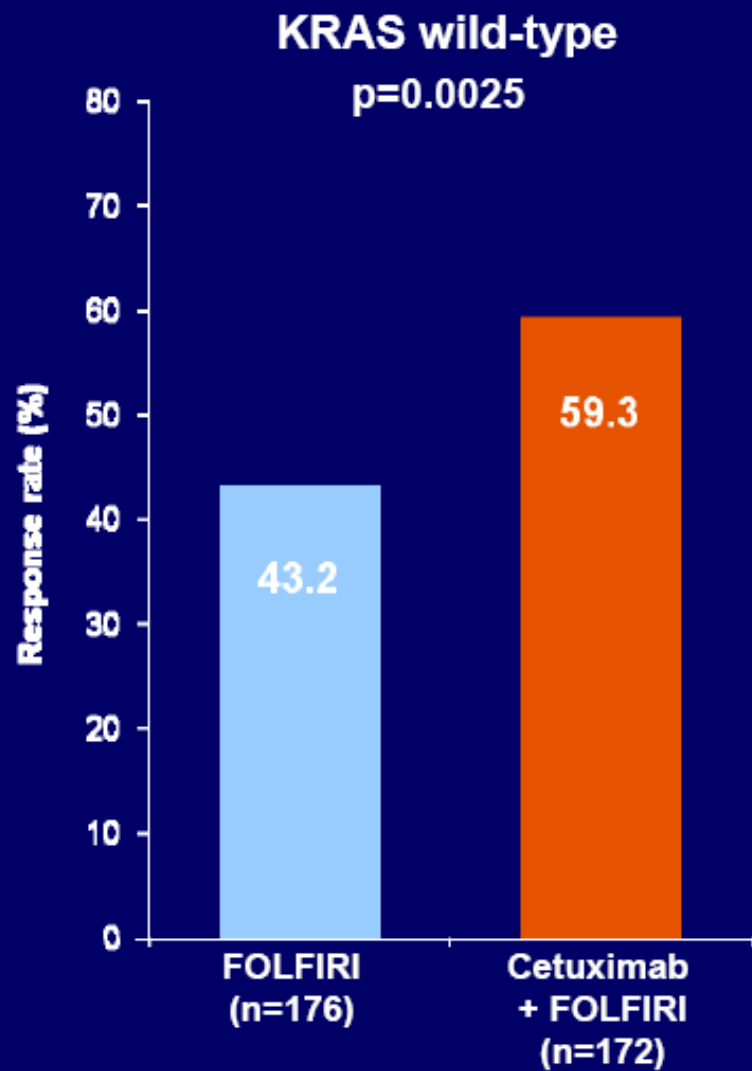


	FOLFIRI n=176 %	Cetuximab + FOLFIRI n=172 %
CR	0	1.2
PR	43.2	58.1
SD	43.8	30.8
PD	9.1	5.2
RR (CR+PR)	43.2	59.3
95% CI	[35.8%, 50.9%]	[51.6%, 66.7%]

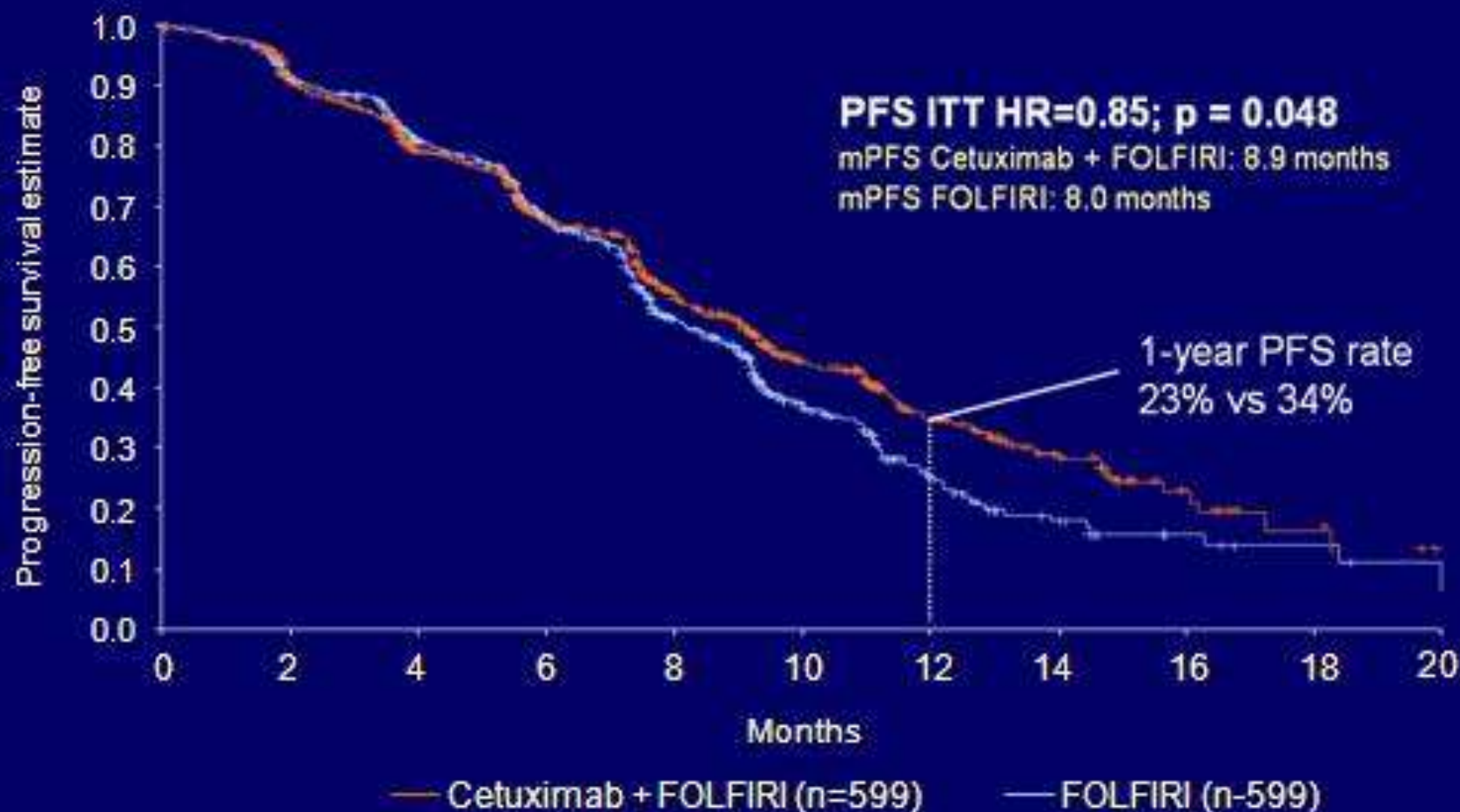
^aCochran-Mantel-Haenszel (CMH) test

Relating KRAS status to efficacy

Secondary endpoint: Response rate



CRYSTAL trial – Primary endpoint PFS ITT population independent review



Relating KRAS status to efficacy: PFS

Cetuximab + FOLFIRI HR=0.63; p=0.007

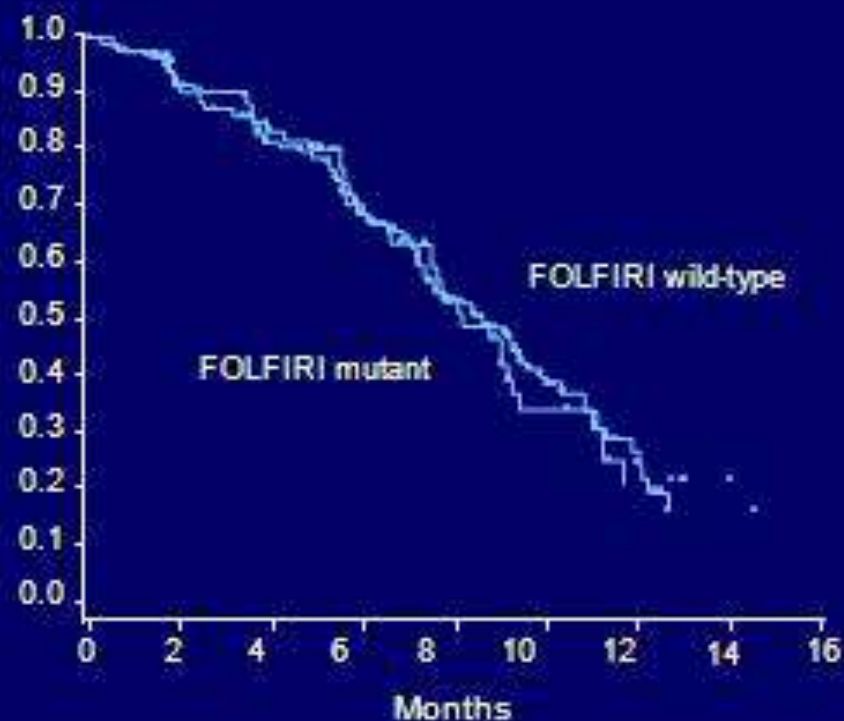
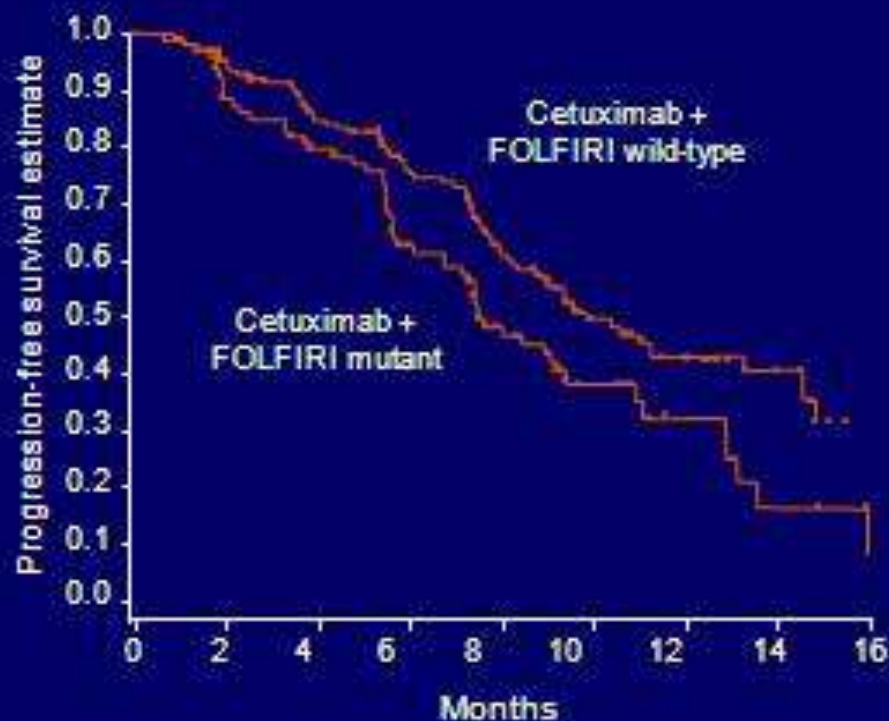
mPFS wild-type (n=172): 9.9 months

mPFS mutant (n=105): 7.6 months

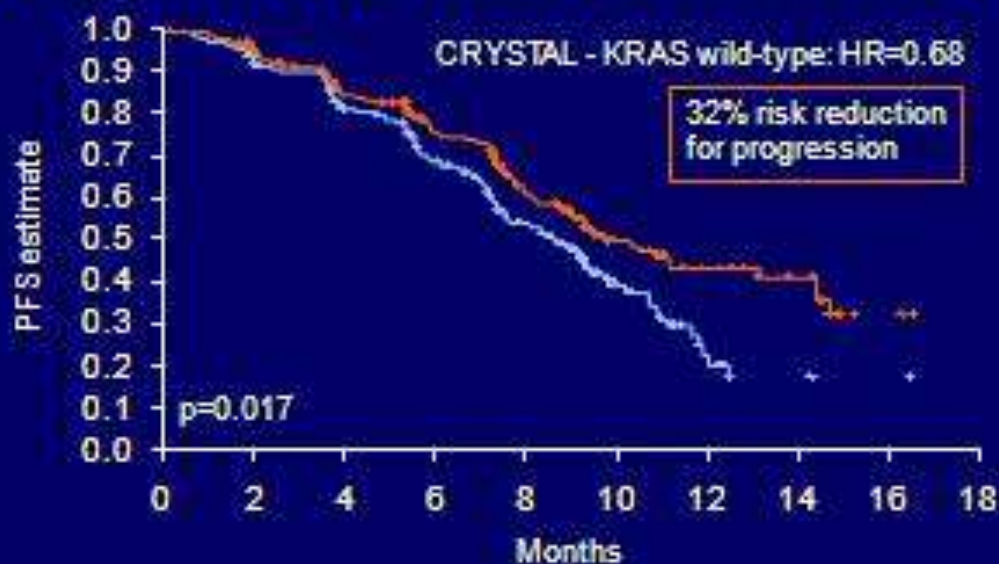
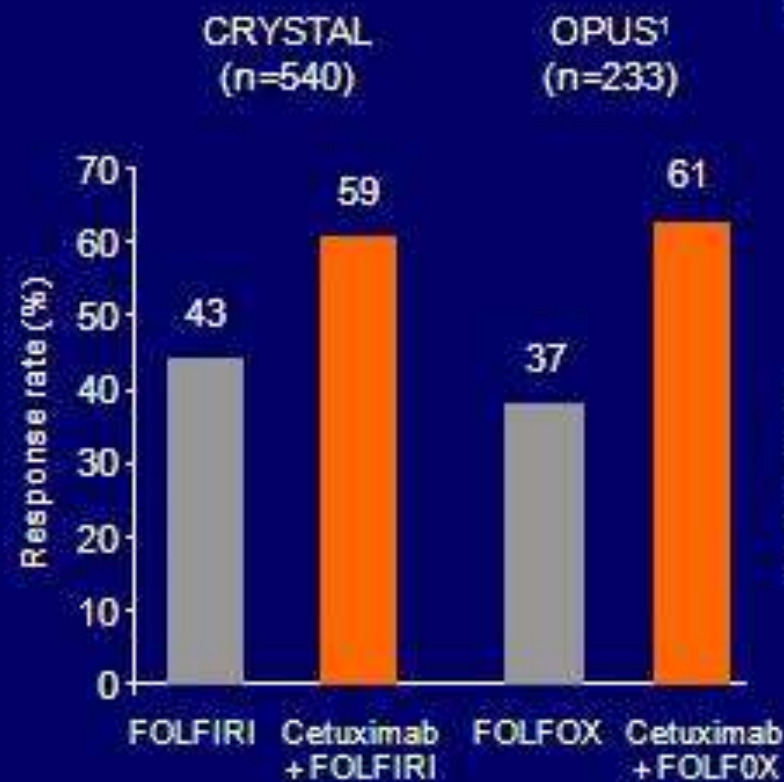
FOLFIRI HR=0.97; p=0.87

mPFS wild-type (n=176): 8.1 months

mPFS mutant (n=87): 8.7 months

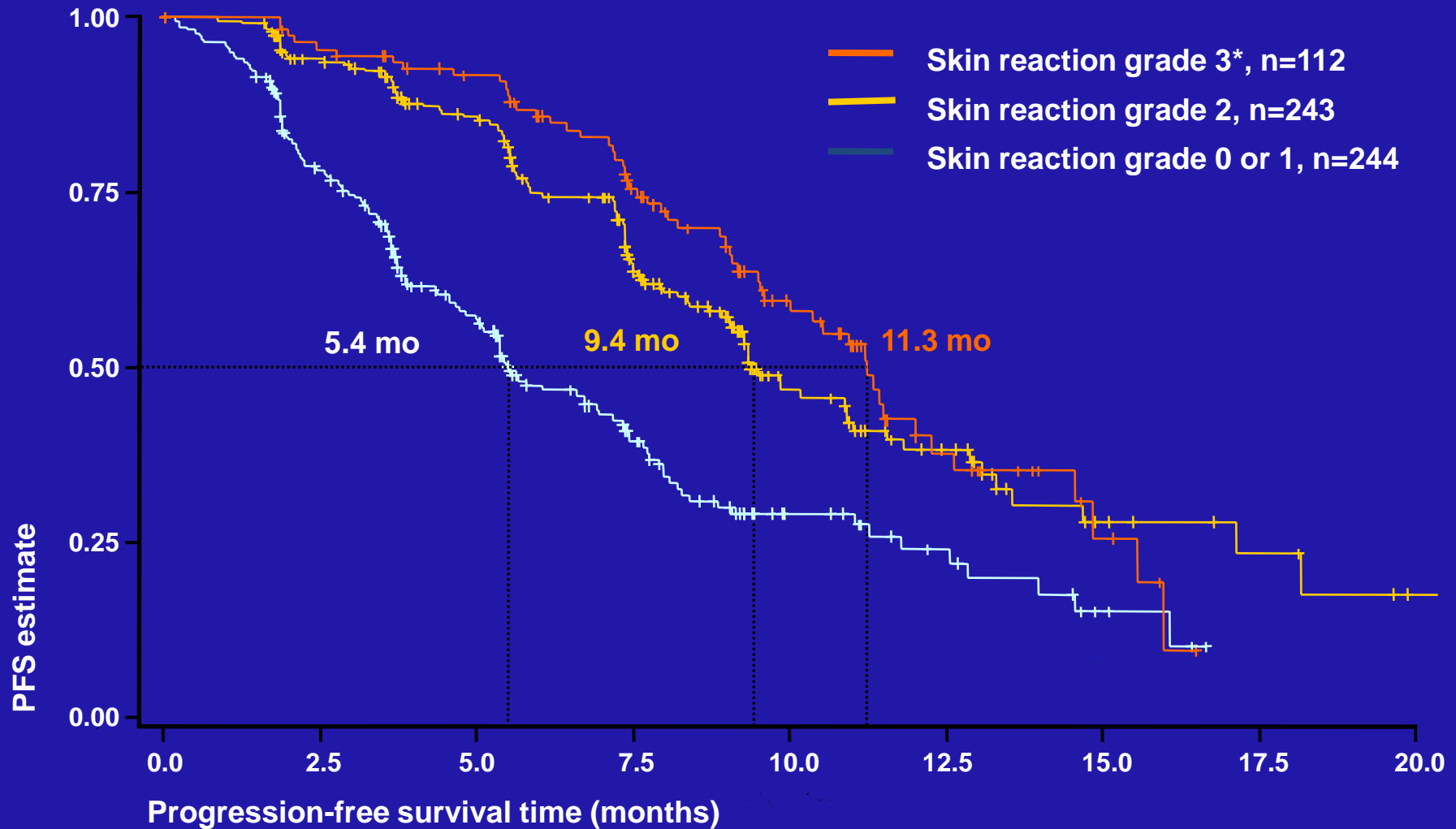


Cetuximab + CT in KRAS wild-type: Data consistency



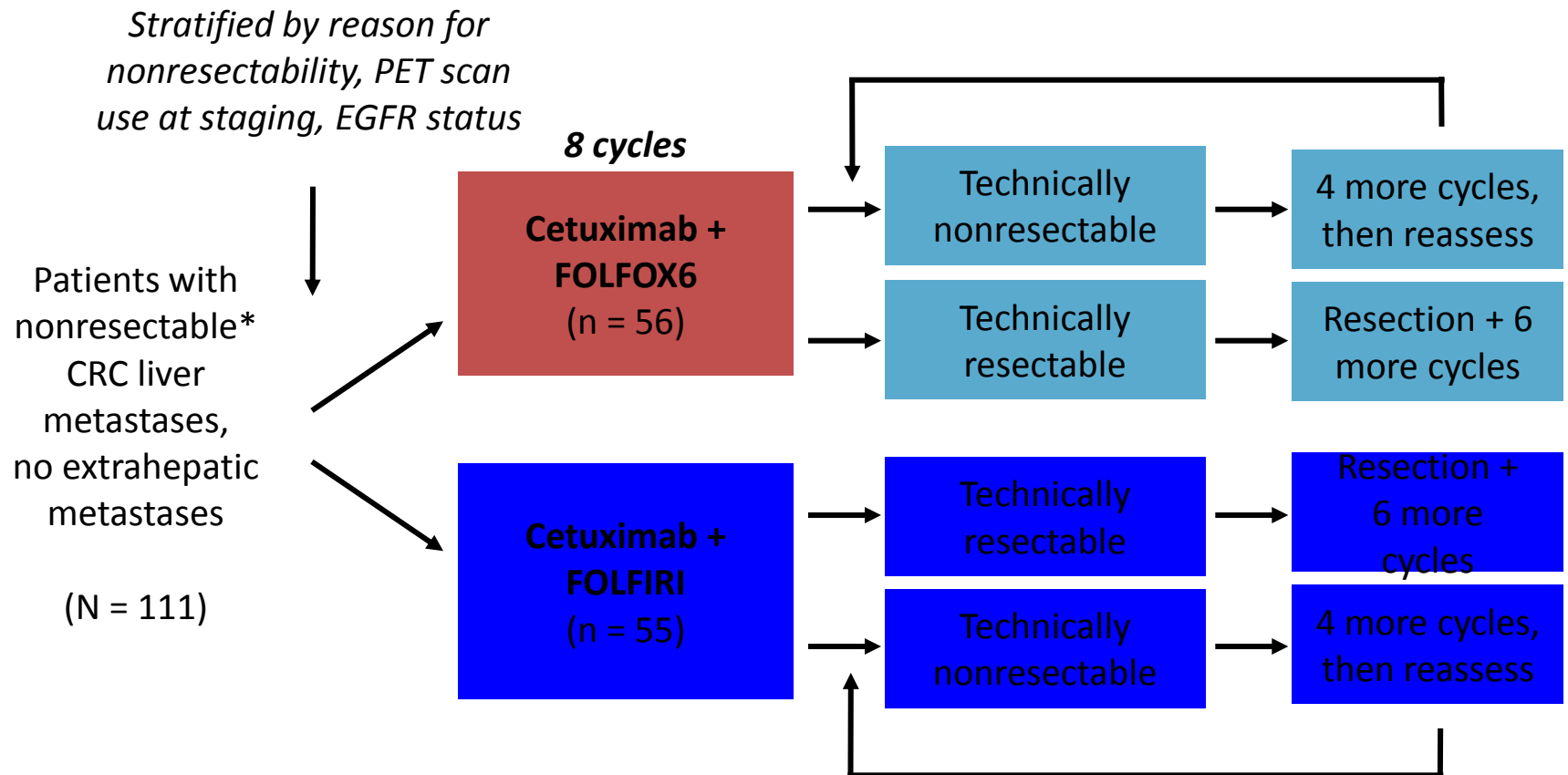
CRYSTAL trial:

Subgroup analysis of PFS time by
on-study skin reactions: cetuximab + FOLFIRI



*There were no grade 4 skin reactions

CELIM: Neoadjuvant Cetuximab and FOLFOX 6 or FOLFIRI for CLM



*Nonresectable at BL defined as due to technical limitations or ≥ 5 liver metastases.

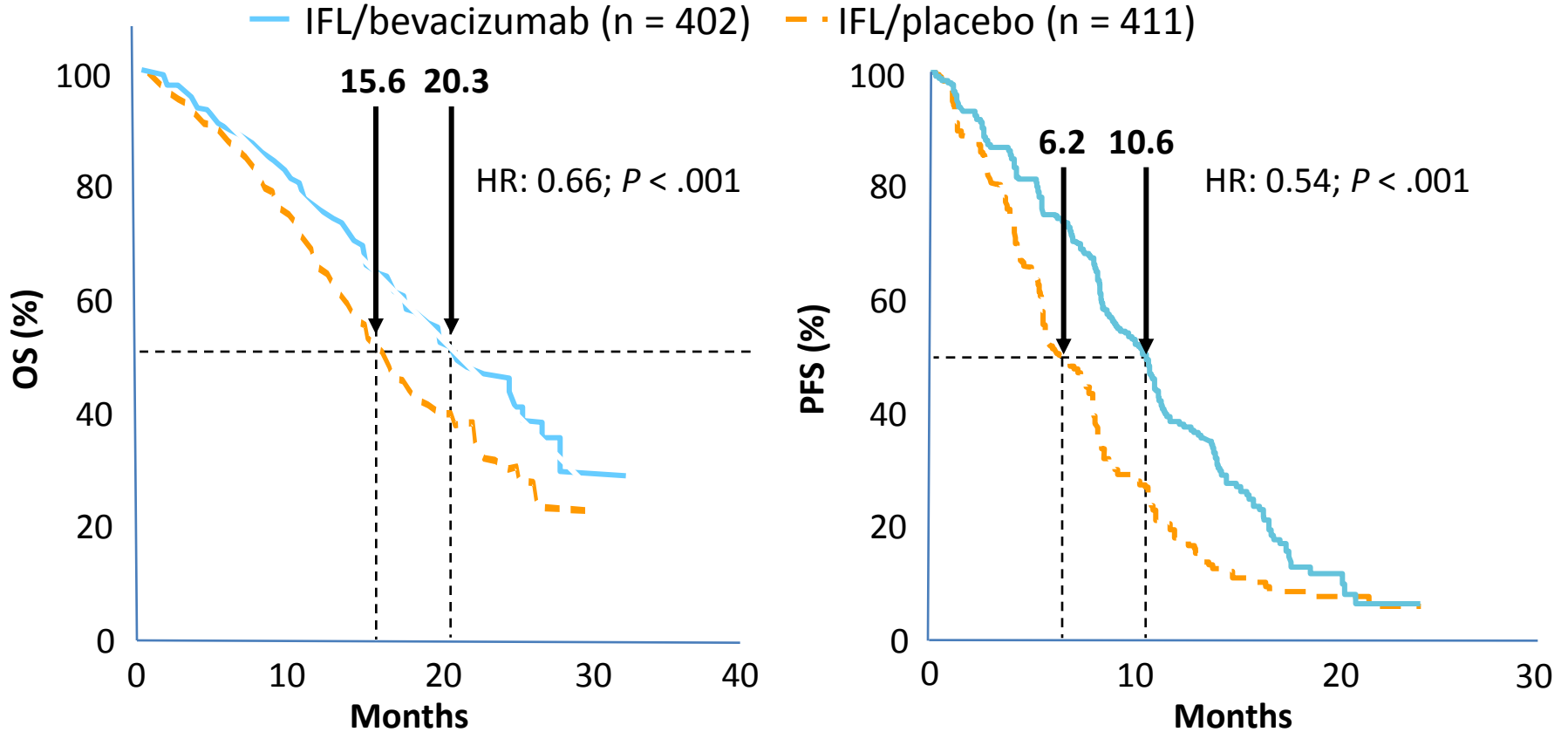
Folprecht G, et al. GI Cancers Symposium 2009. Abstract 296.

CELIM: Neoadjuvant Cetuximab and FOLFOX 6 or FOLFIRI for CLM

Response, %	FOLFOX 6 + Cetuximab (n = 53)	FOLFIRI + Cetuximab (n = 53)
Best OR (CR + PR)	81	66
Confirmed OR (CR + PR)	68	57
Confirmed SD	28	30
Confirmed PD	4	13

- Overall 34% of patients underwent R0 resection
- 25% of patients converted from unresectable to resectable
- Both regimens effective neoadjuvant treatments for patients with K-ras^{wt} tumors
 - 70% confirmed OR

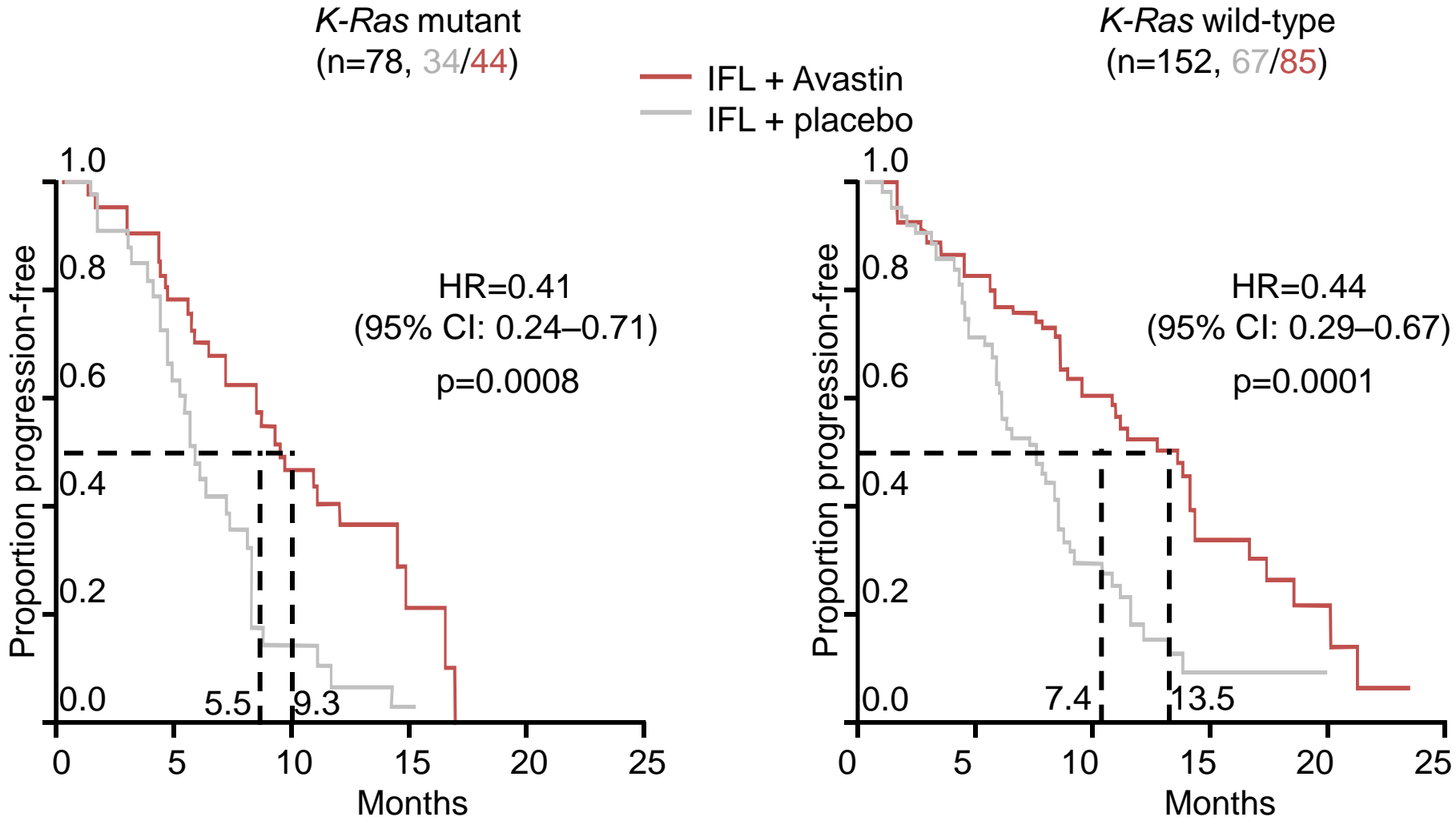
First-Line Irinotecan/5-FU/LV + Bevacizumab



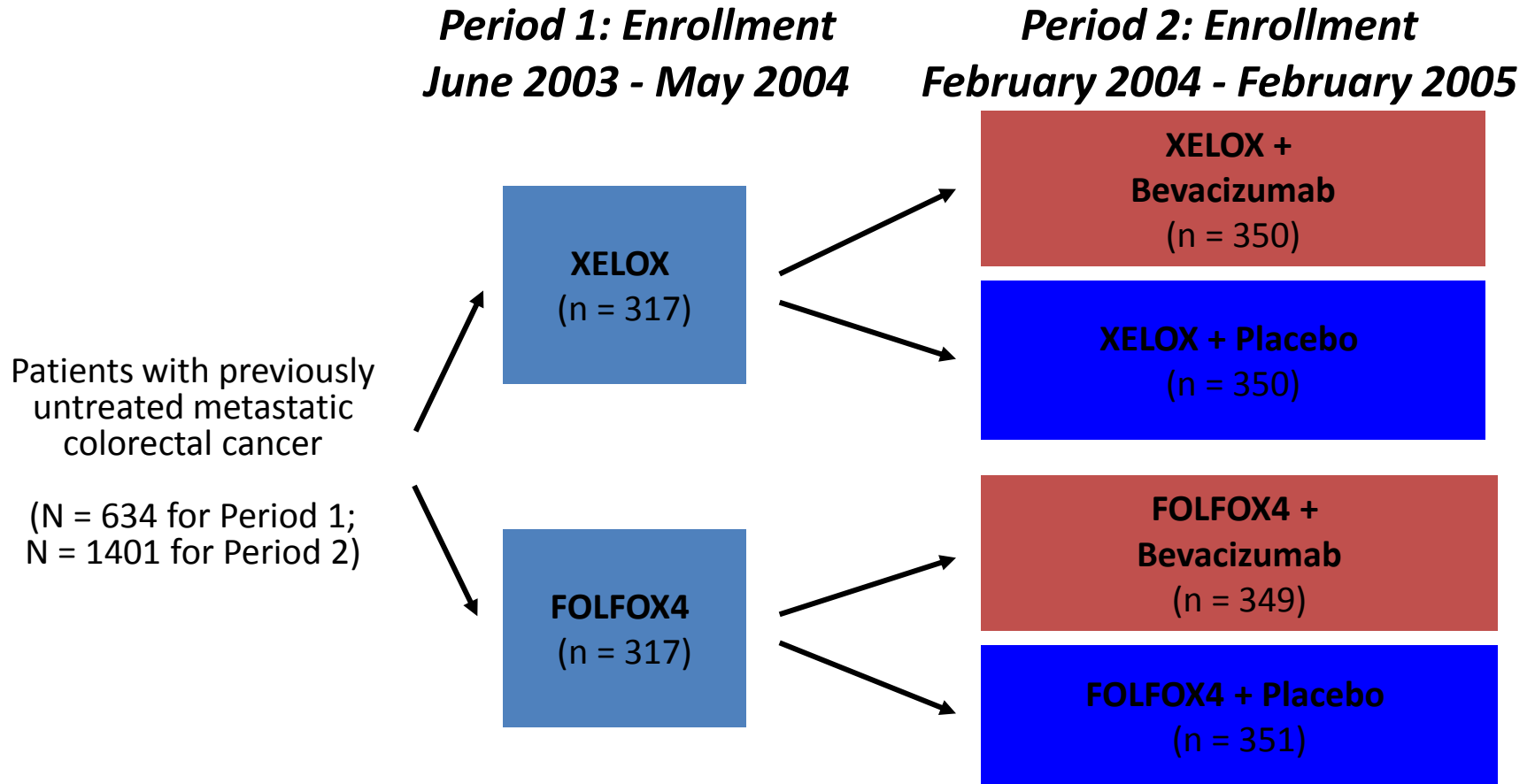
Copyright © 2004 Massachusetts Medical Society. All rights reserved.

Hurwitz H, et al. N Engl J Med. 2004;350:2335-2342.

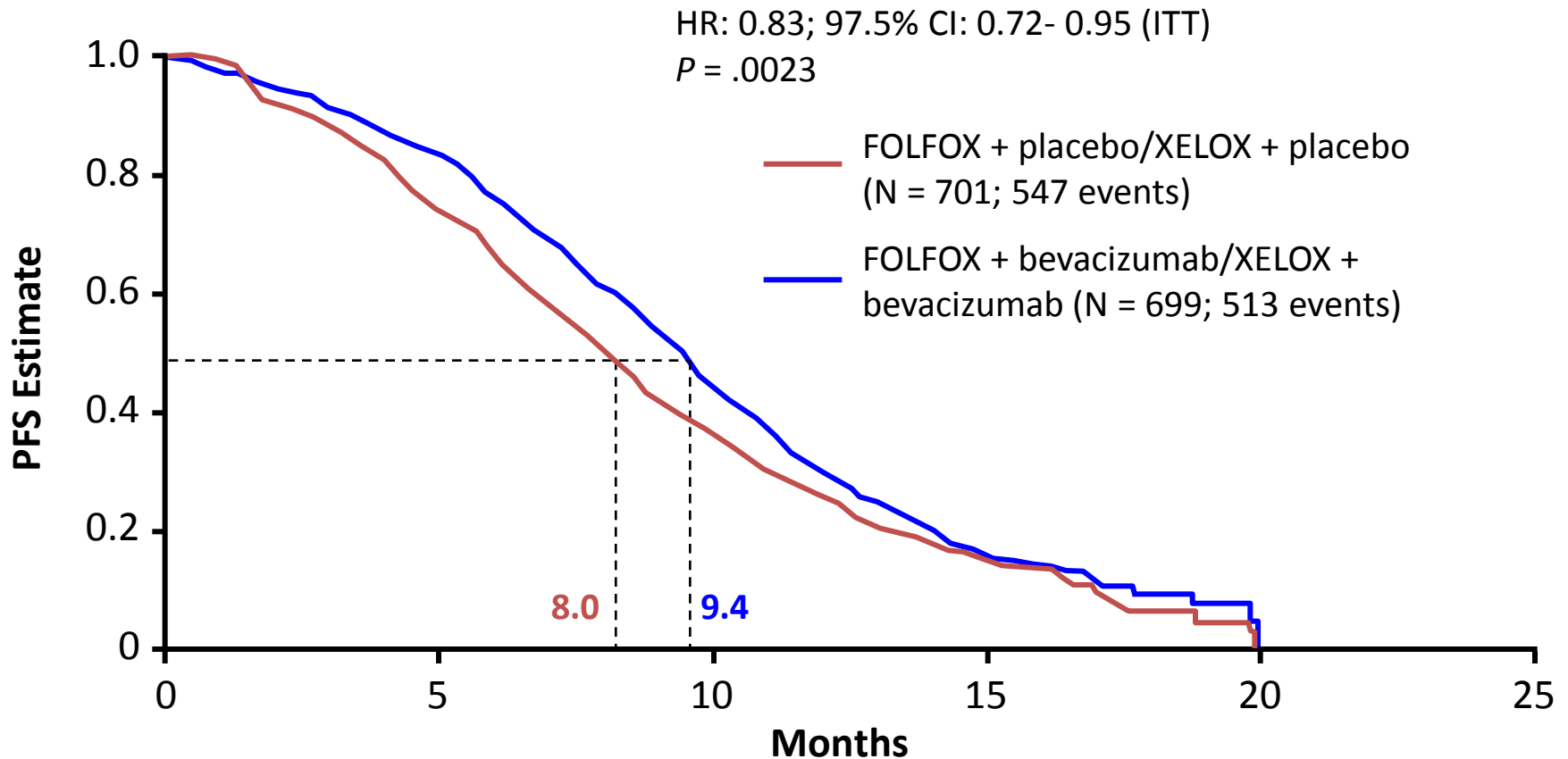
Avastin demonstrates PFS benefit regardless of *K-Ras* mutation status



NO16966 Study Design

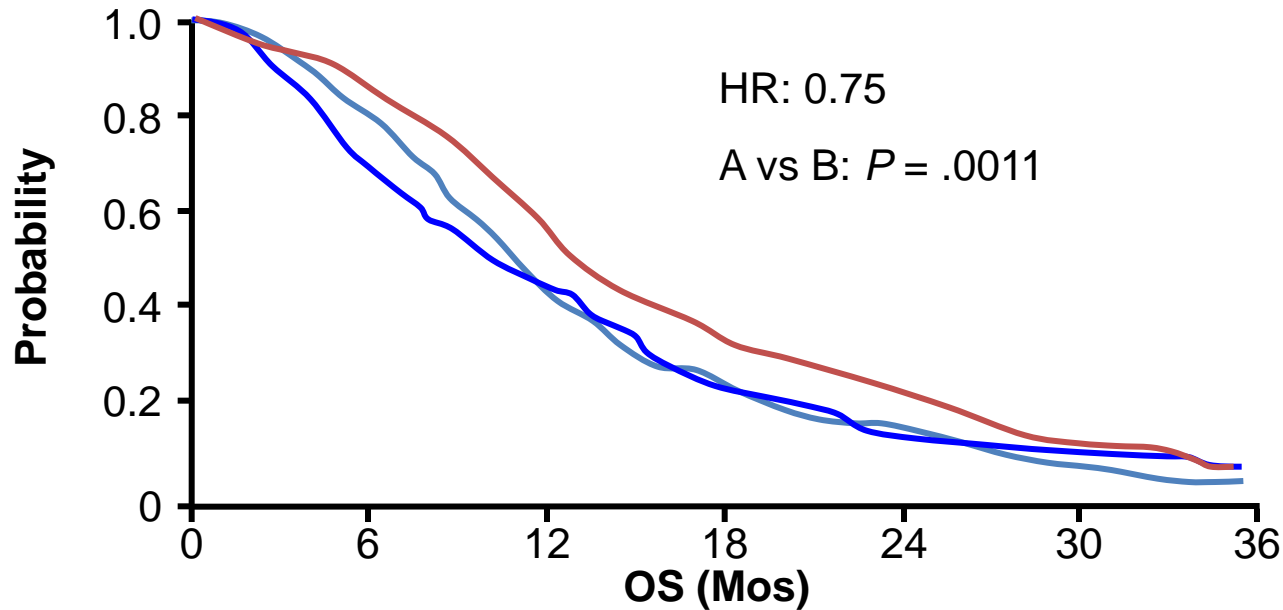


NO16966: PFS



no significant differences were seen in terms of OS **BUT** 71% of pts discontinued treatment due to non-progression events

E3200: Overall Survival



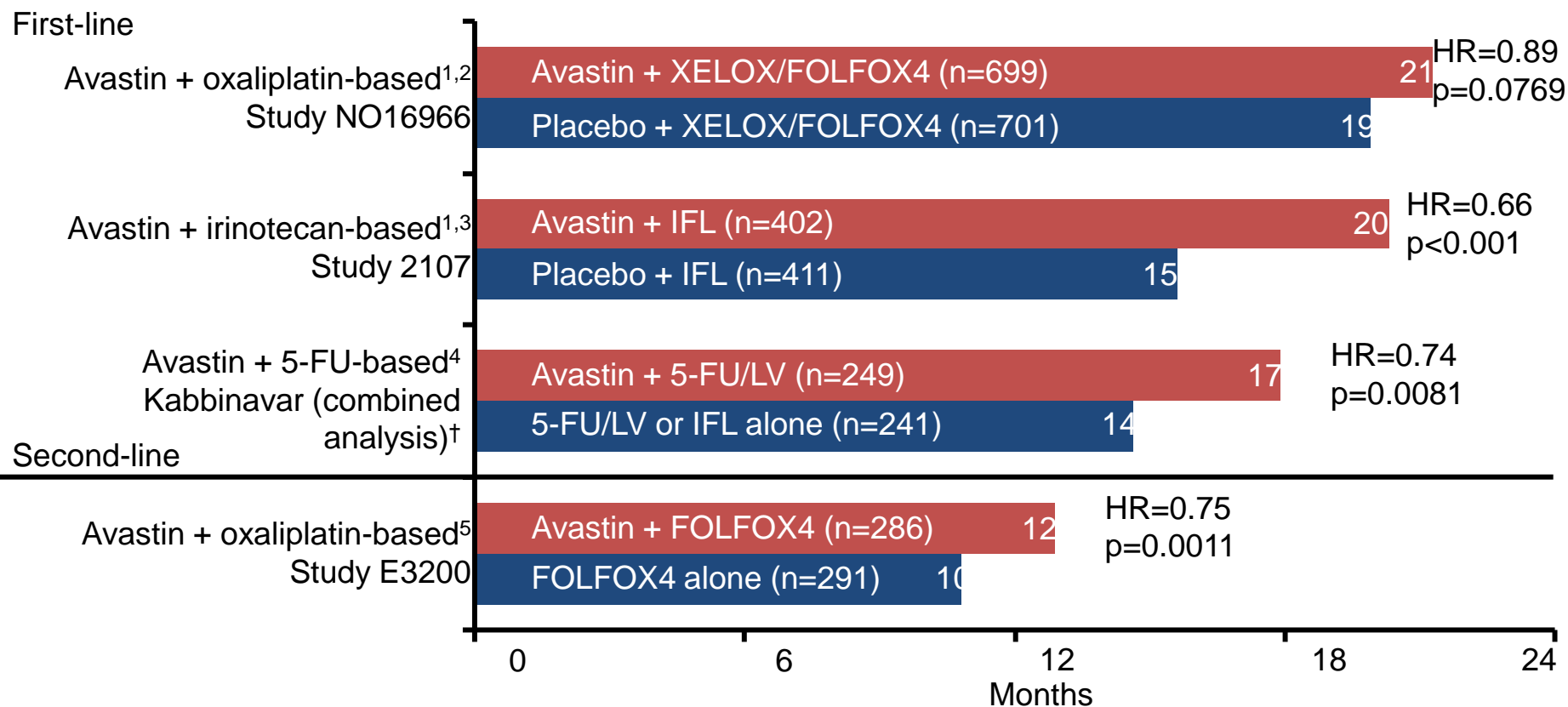
	Total, n	Dead, n	Alive, n	Median, mos
— A: FOLFOX4 + Bevacizumab	286	254	32	12.9
— B: FOLFOX4	291	264	27	10.8
— C: Bevacizumab	243	219	24	10.2

Giantonio BJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol.* 2007;25(12):1539-1544. Reprinted with permission from the American Society of Clinical Oncology.

Giantonio BJ, et al. *J Clin Oncol.* 2007; 25:1539-1544.

Avastin increases OS in first- and second-line mCRC with all major chemotherapy regimens

Avastin is proven to increase OS

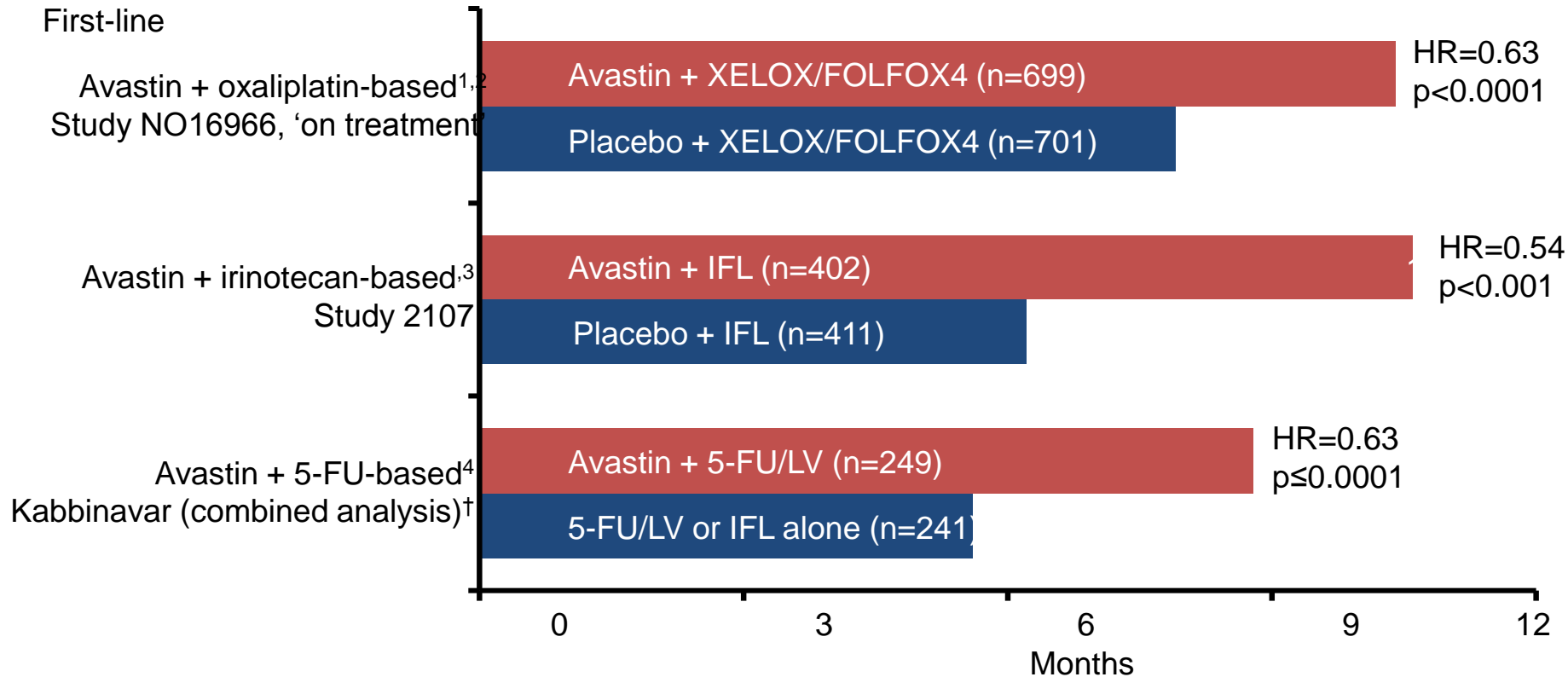


HR = hazard ratio; OS = overall survival
[†]The combined analysis included two phase II studies and one phase III study

1. Avastin Summary of Product Characteristics 2008
 2. Saltz LB, et al. J Clin Oncol 2008; 3. Hurwitz H, et al. N Engl J Med 2004
 4. Kabbinavar FF, et al. J Clin Oncol 2005; 5. Giantonio BJ, et al. J Clin Oncol 2007

Avastin provides a consistent increase in PFS with all major chemotherapy regimens

Median PFS with Avastin-based regimens in phase II/III trial



- Avastin consistently increases PFS with all major chemotherapy regimens¹⁻⁴

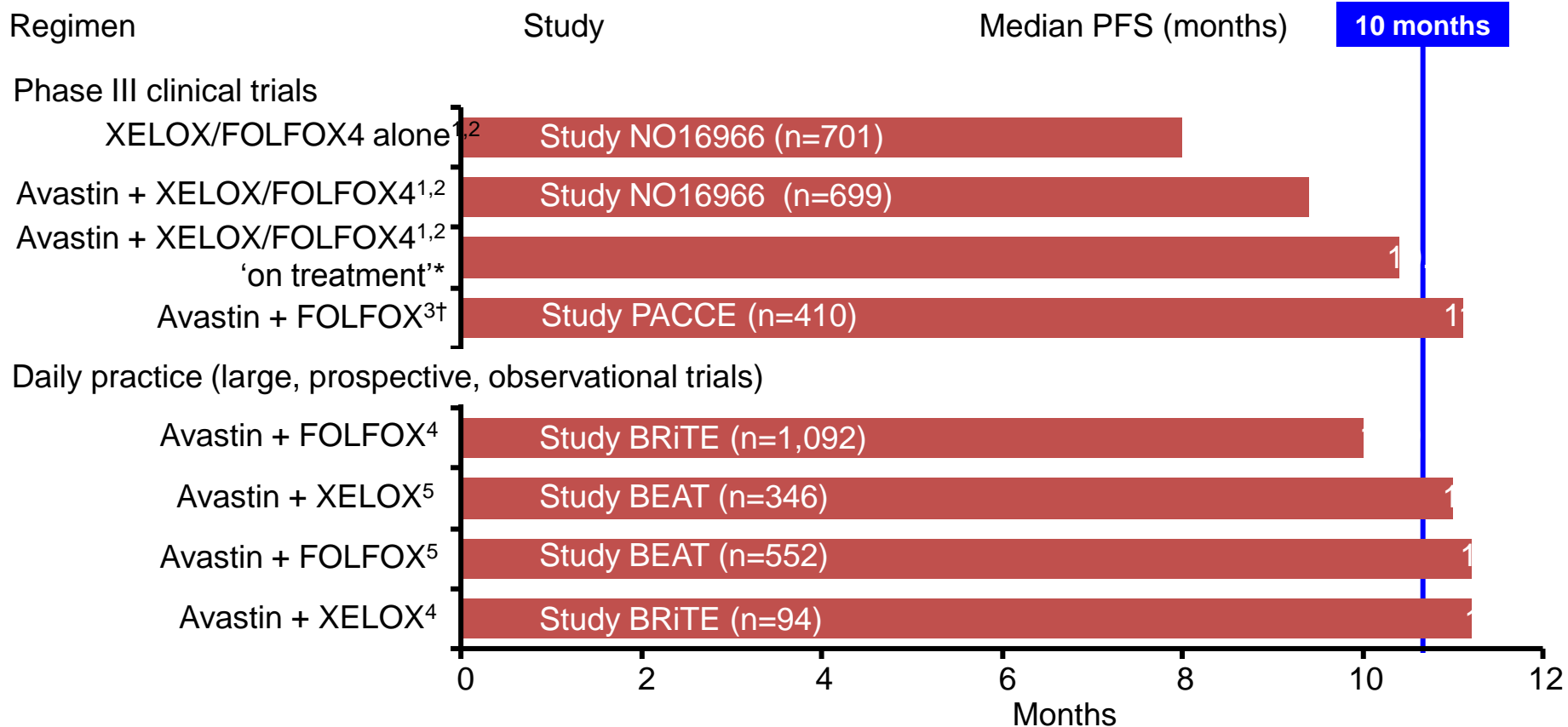
PFS = progression-free survival

†The combined analysis included two phase II studies and one phase III study

1. Avastin Summary of Product Characteristics 2008; 2. Saltz LB, et al. J Clin Oncol 2008
3. Hurwitz H, et al. N Engl J Med 2004; 4. Kabbinavar FF, et al. J Clin Oncol 2005

Proven benefits of Avastin-based therapy including FOLFOX or XELOX confirmed in daily practice

Avastin-based therapy including FOLFOX or XELOX



*Secondary endpoint

†93% of patients received FOLFOX

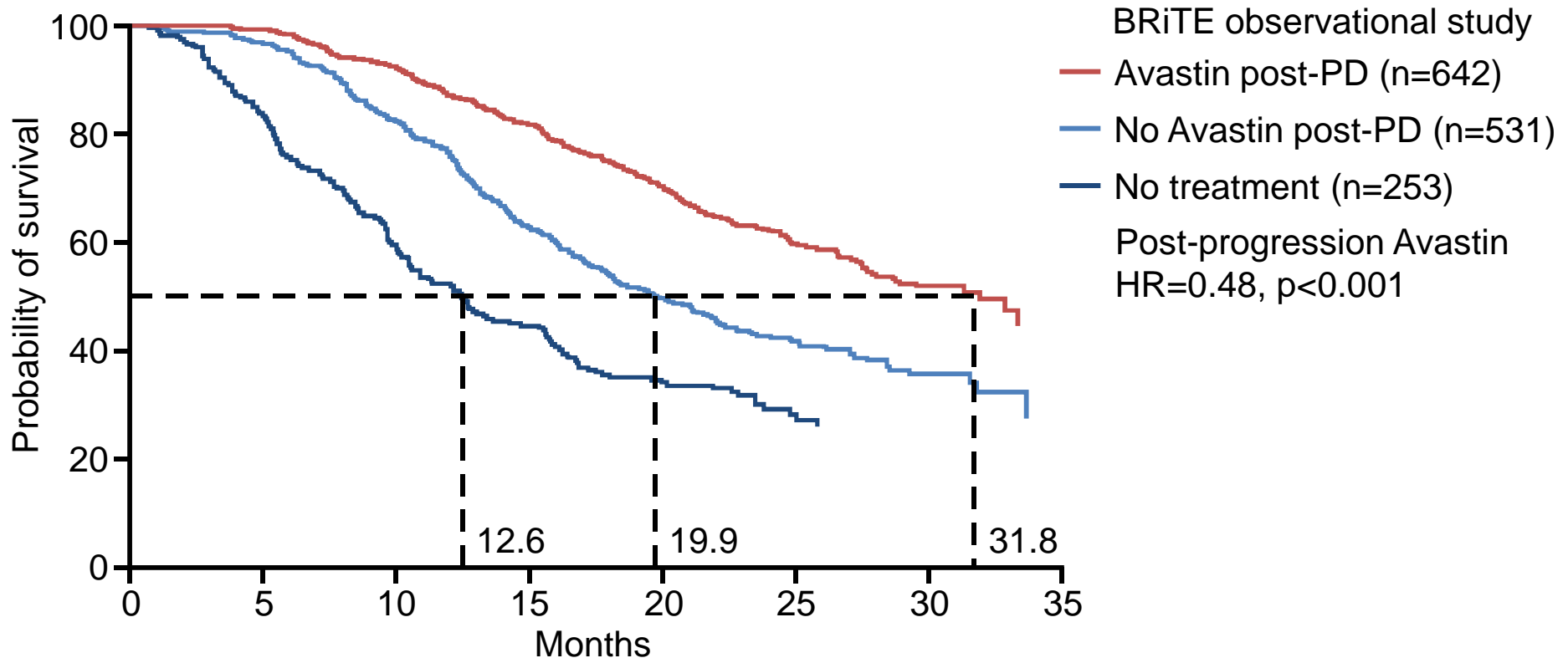
1. Avastin Summary of Product Characteristics 2008

2. Saltz LB, et al. J Clin Oncol 2008 3. Hecht J, et al. ASCO GI 2008

4. Kozloff M, et al. ASCO GI 2007; 5. Berry S, et al. ASCO 2008

Considerable survival benefit with Avastin treatment throughout course of disease

Continuous VEGF inhibition results in tumor control

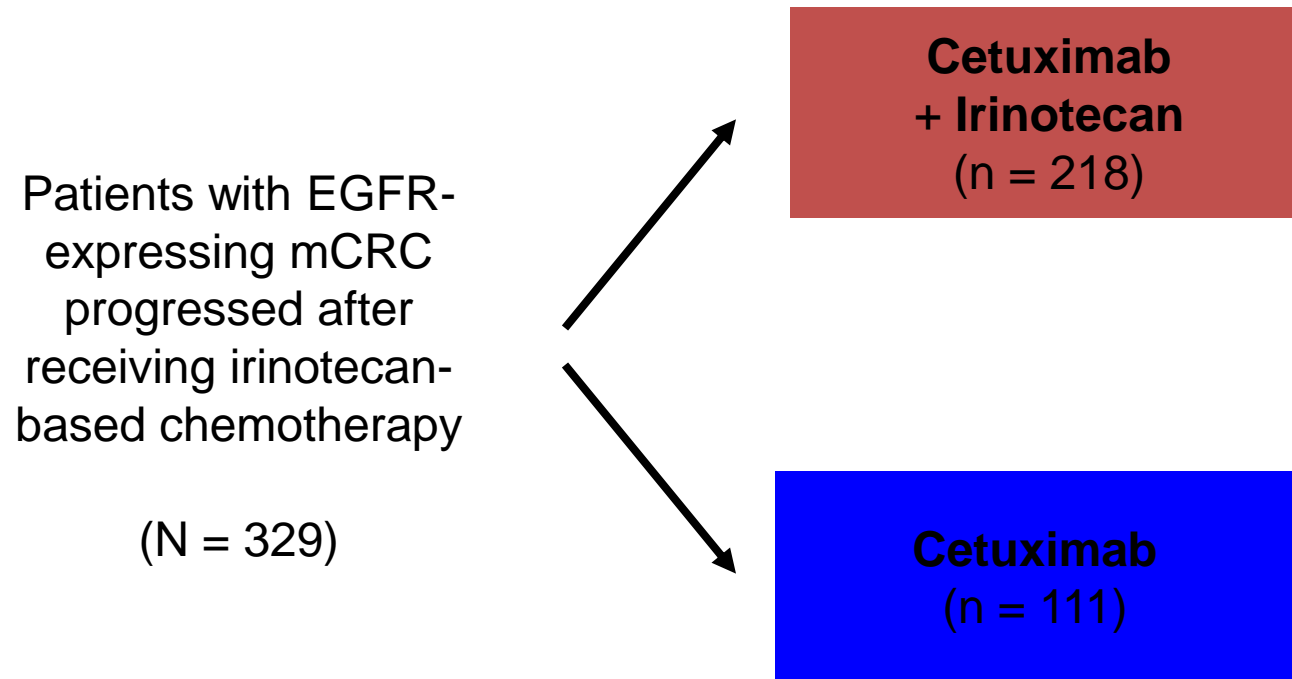


- A multivariate analysis of data from the BRiTE observational study confirmed Avastin post-progressive disease was the only variable that significantly increased survival ($p < 0.001$)

PD = progressive disease

BOND Trial: Cetuximab Trial in Metastatic Colorectal Cancer

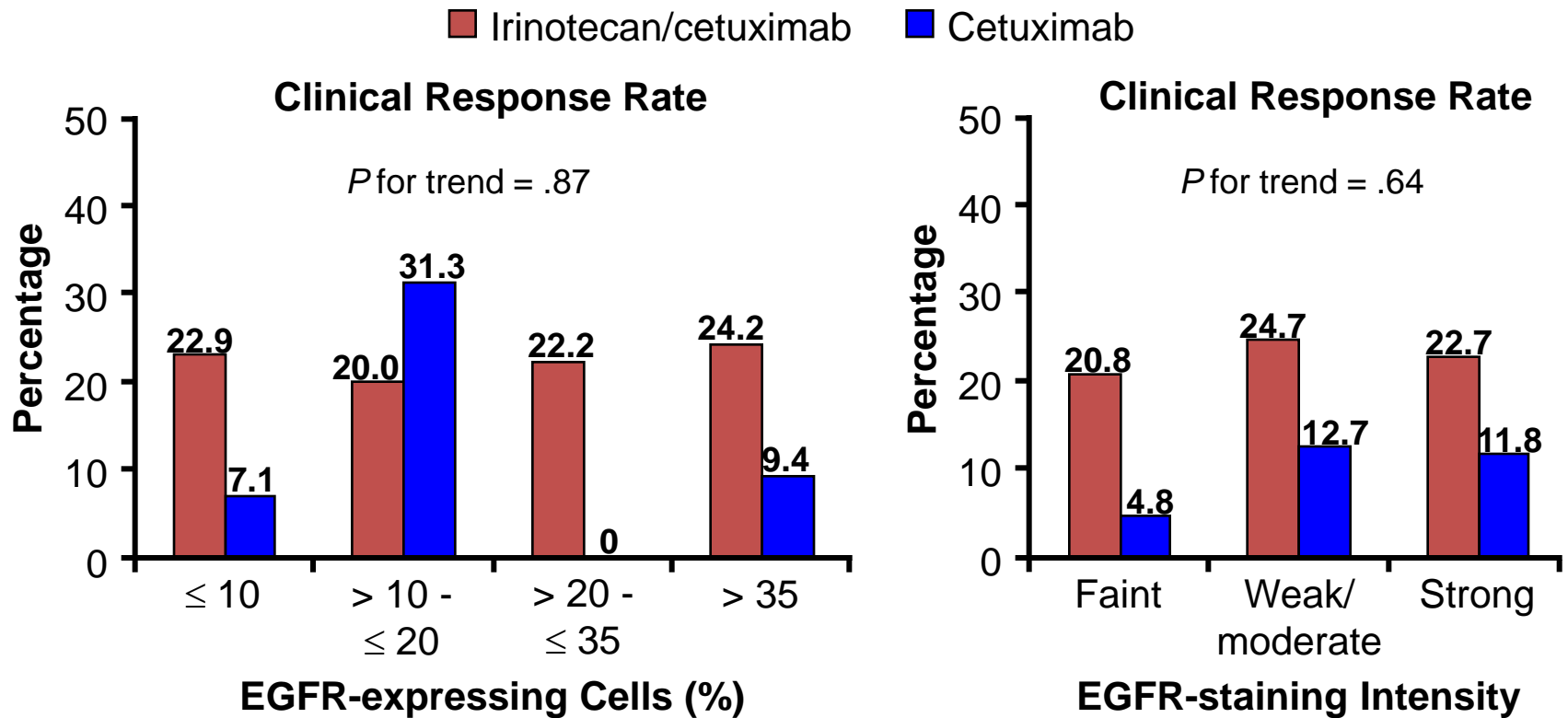
Randomized phase II study design



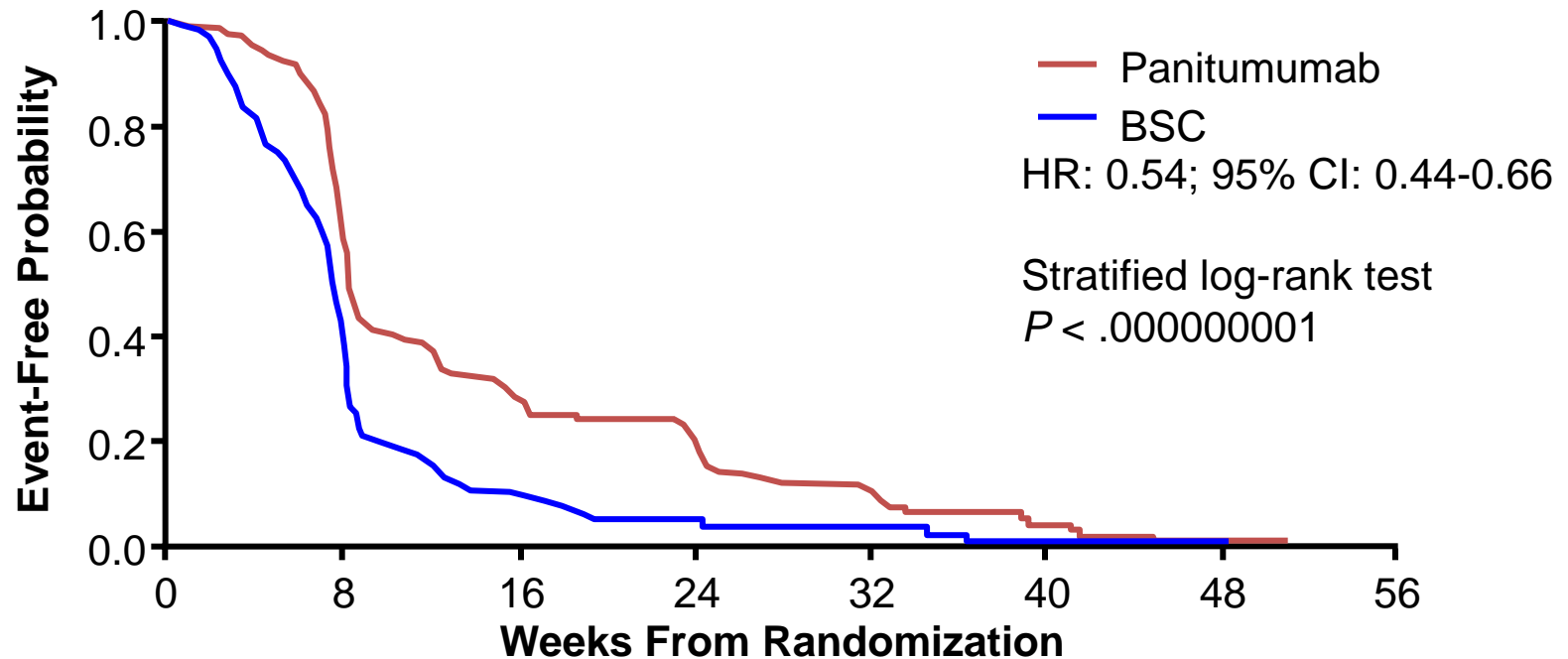
BOND Trial: Efficacy Outcomes

Treatment Group	ORR for Cetuximab, % (n)	ORR for Cetuximab + Irinotecan, % (n)	<i>P</i> Value
All patients	11 (111)	23 (218)	.007
Irinotecan- oxaliplatin failure	11 (44)	24 (80)	.09
Irinotecan refractory	15 (69)	26 (132)	.07

Correlation of Response Rate and EGFR Expression (IHC): BOND Data



Panitumumab vs Best Supportive Care: Efficacy



- Rate of disease progression was 46% lower in the panitumumab arm

Van Cutsem E, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol.* 2007;25(13):1658-1664. Reprinted with permission from the American Society of Clinical Oncology.

Van Cutsem E, et al. *J Clin Oncol.* 2007;25:1658-1664.

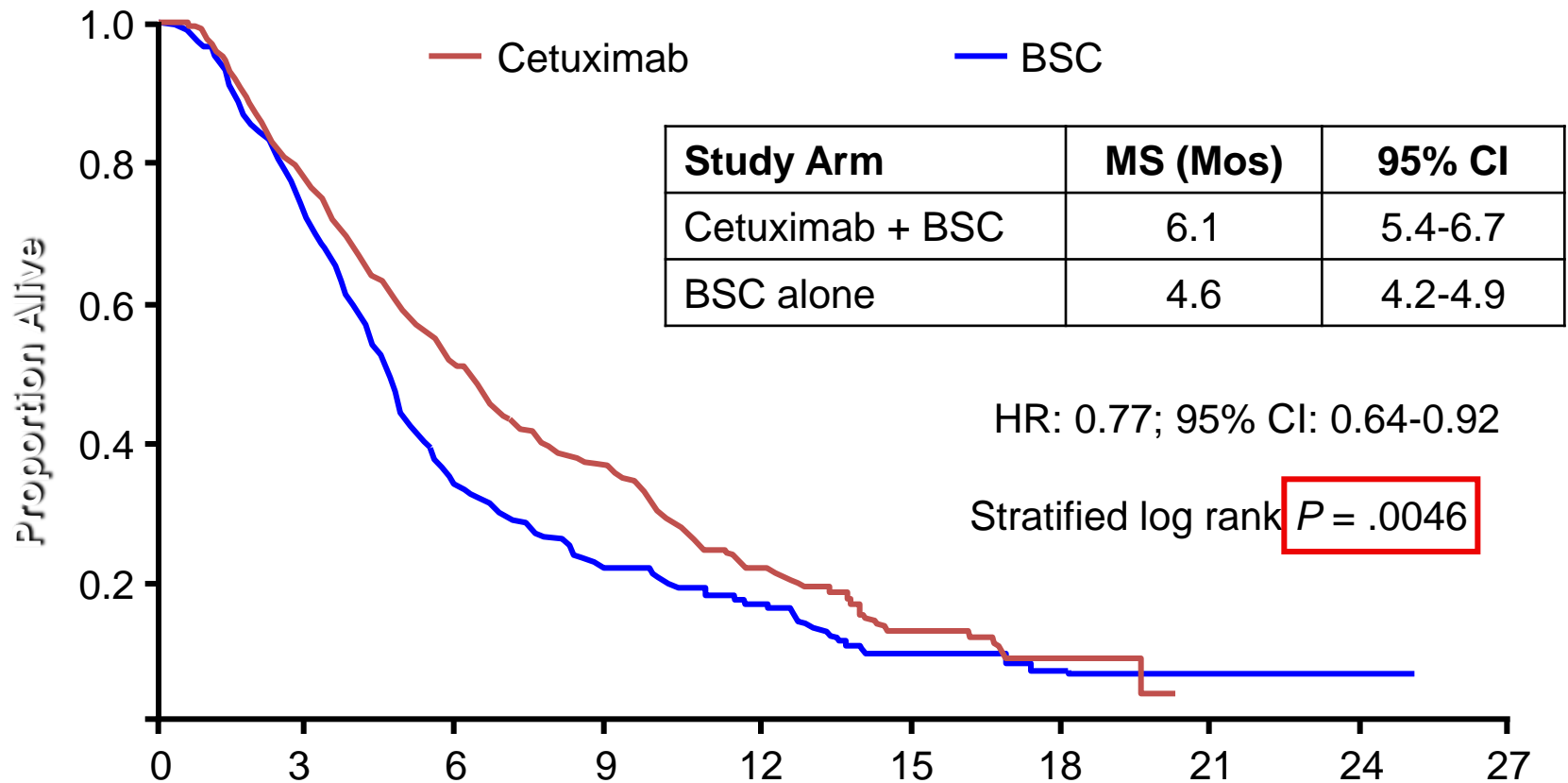
Panitumumab vs Best Supportive Care: Efficacy

KRAS Evaluable Group			
PFS	Pmab + BSC	BSC Alone	HR (95% CI)
Events/N (%)	191/208 (92)	209/219 (95)	0.59 (0.48-0.72)
Median, wks	8.0	7.3	
Mean, wks	15.4	9.6	
Wild-Type KRAS Group			
PFS	Pmab + BSC	BSC Alone	HR (95% CI)
Events/N (%)	115/124 (93)	114/119 (96)	0.45 (0.34-0.59); <i>P</i> < .0001
Median, wks	12.3	7.3	
Mean, wks	19.0	9.3	
Mutant KRAS Group			
PFS	Pmab + BSC	BSC Alone	HR (95% CI)
Events/N (%)	76/84 (90)	95/100 (95)	0.99 (0.73-1.36)
Median, wks	7.4	7.3	
Mean, wks	9.9	10.2	

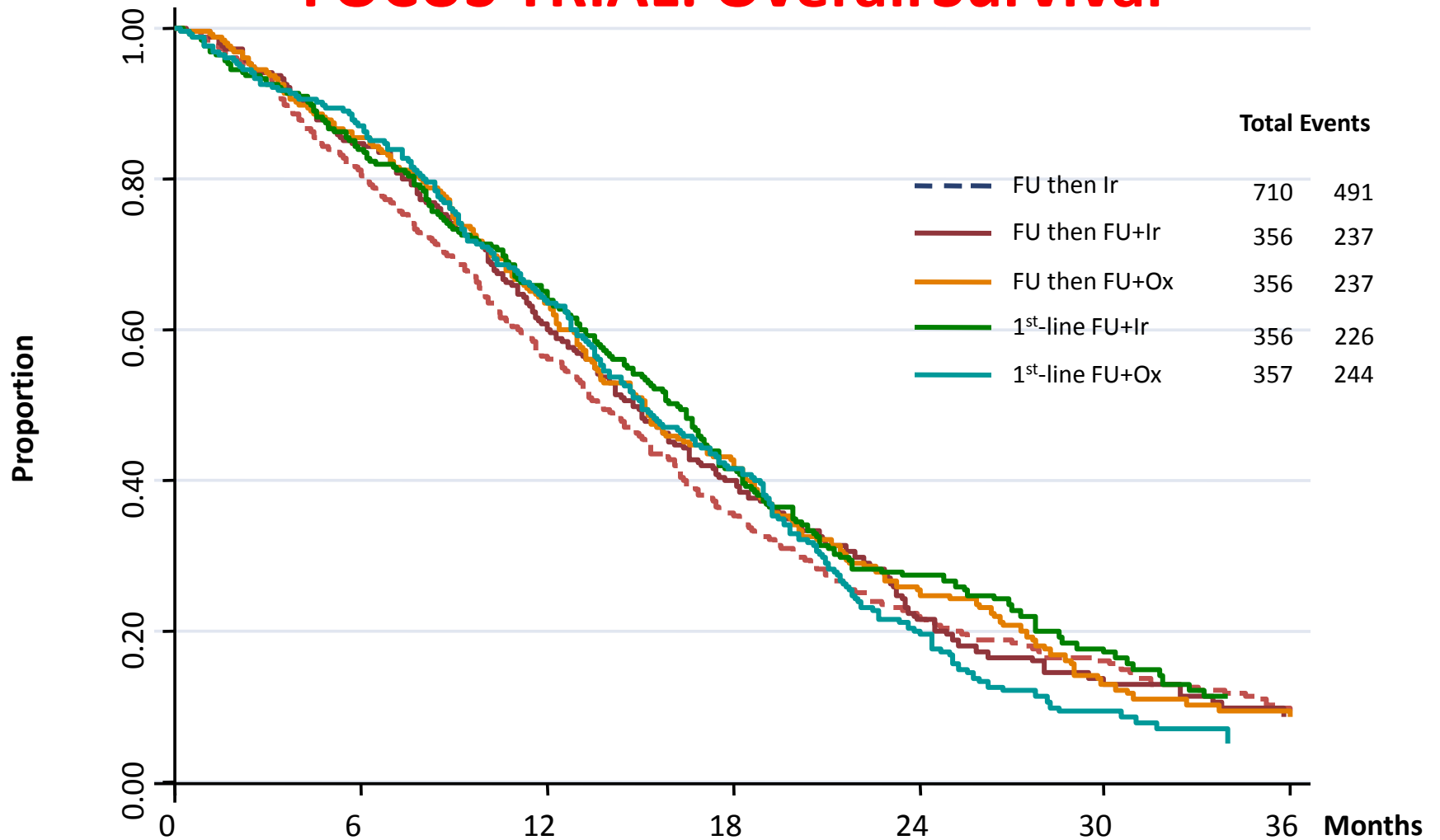
Panitumumab vs Best Supportive Care: Objective Tumor Response

KRAS						
	All Evaluable		Mutant		Wild Type	
Response, n (%)	Pmab + BSC (n = 208)	BSC (n = 219)	Pmab + BSC (n = 84)	BSC (n = 100)	Pmab + BSC (n = 124)	BSC (n = 119)
CR	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PR	21 (10)	0 (0)	0 (0)	0 (0)	21 (17)	0 (0)
SD	52 (25)	22 (10)	10 (12)	8 (8)	42 (34)	14 (12)
PD	104 (50)	149 (68)	59 (70)	60 (60)	45 (36)	89 (75)
CR, PR, SD	73 (35)	22 (10)	10 (12)	8 (8)	63 (51)	14 (12)

NCIC CTG CO.17: Overall Survival



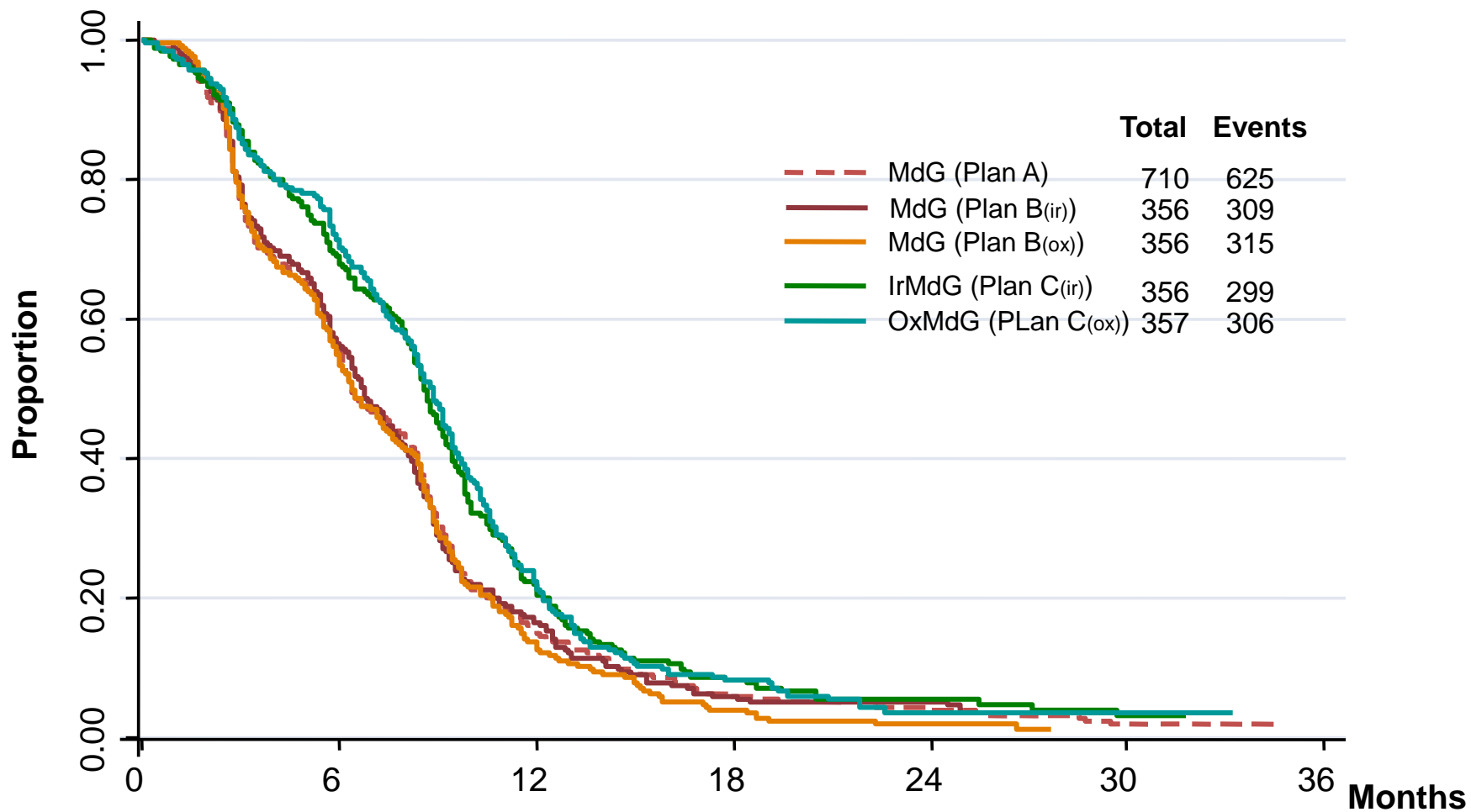
FOCUS TRIAL: Overall Survival



At risk:

	0	6	12	18	24	30	36
FU then Ir	710	547	319	166	76	45	19
FU then FU+Ir	356	285	169	90	37	17	9
FU then FU+Ox	356	286	172	96	46	20	11
1 st -line FU+Ir	356	279	183	88	47	22	11
1 st -line FU+Ox	357	298	183	94	36	12	3

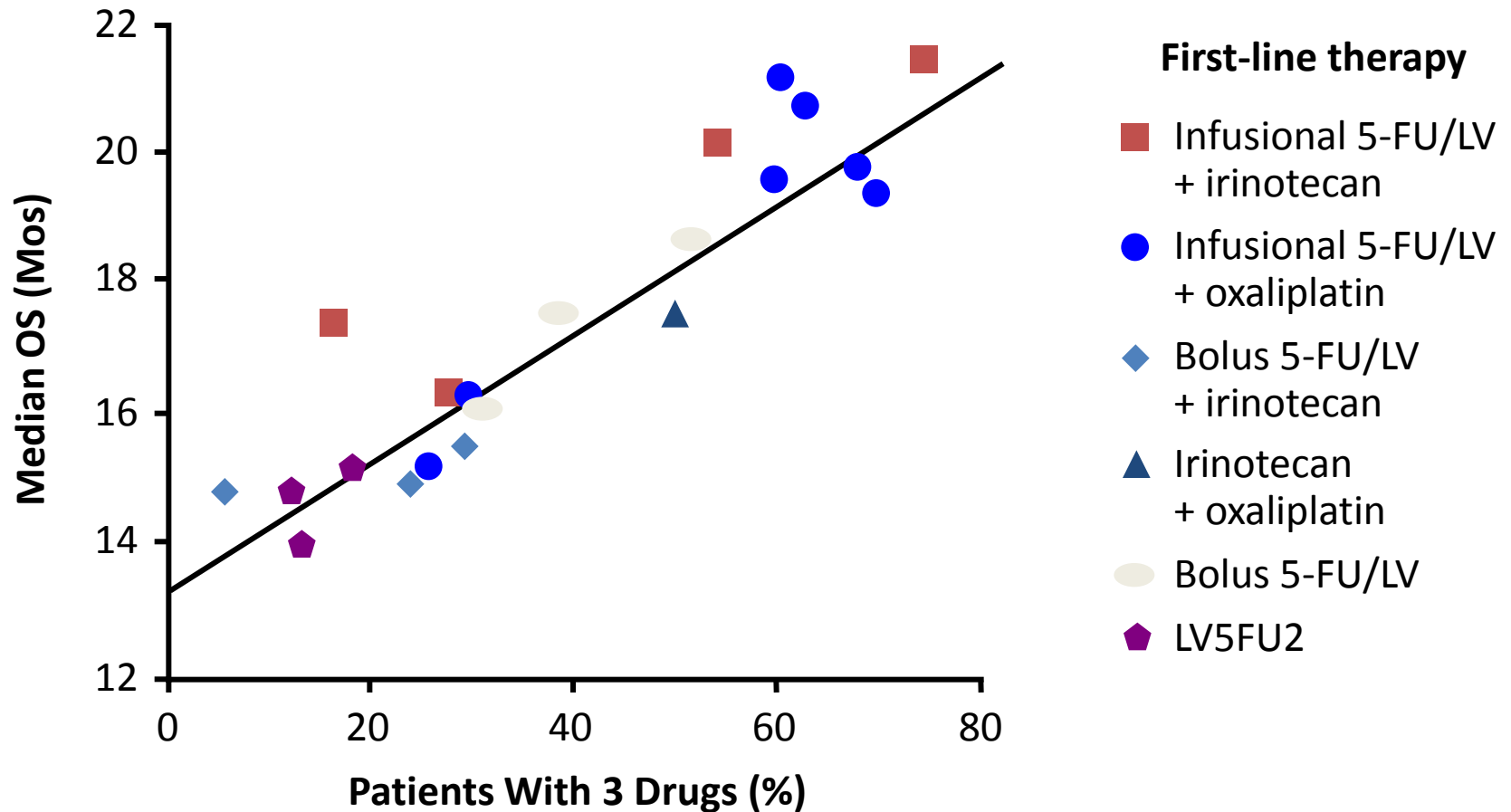
FOCUS TRIAL:PFS, 1st-line



Plan	regimen	median PFS
A	MdG	6.3 mo
B(ir)	MdG	6.7 mo
B(ox)	MdG	6.4 mo
C(ir)	IrMdG	8.6 mo
C(ox)	OxMdG	8.8 mo

Comparison	Log-rank HR	p-value
C(ir) vs A	0.77 (0.67 - 0.88)	<0.001
C(ox) vs A	0.75 (0.66 - 0.86)	<0.001

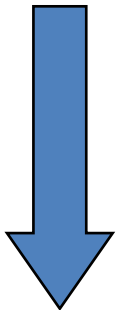
Access to Chemotherapy Improves Survival



The specific initial endpoints of the different palliative approaches

AGGRESSIVE

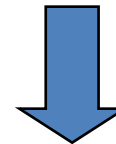
- Sx control
- RR



Shrink the tumor

NON AGGRESSIVE

- QOL
- TT sx deterioration
- TT PS deterioration
- OS



delay progression

State of the art first line strategy

Does the patient need aggressive treatment?

