What is the best cytotoxic backbone for biologics?

Outcomes more than the sum of the parts

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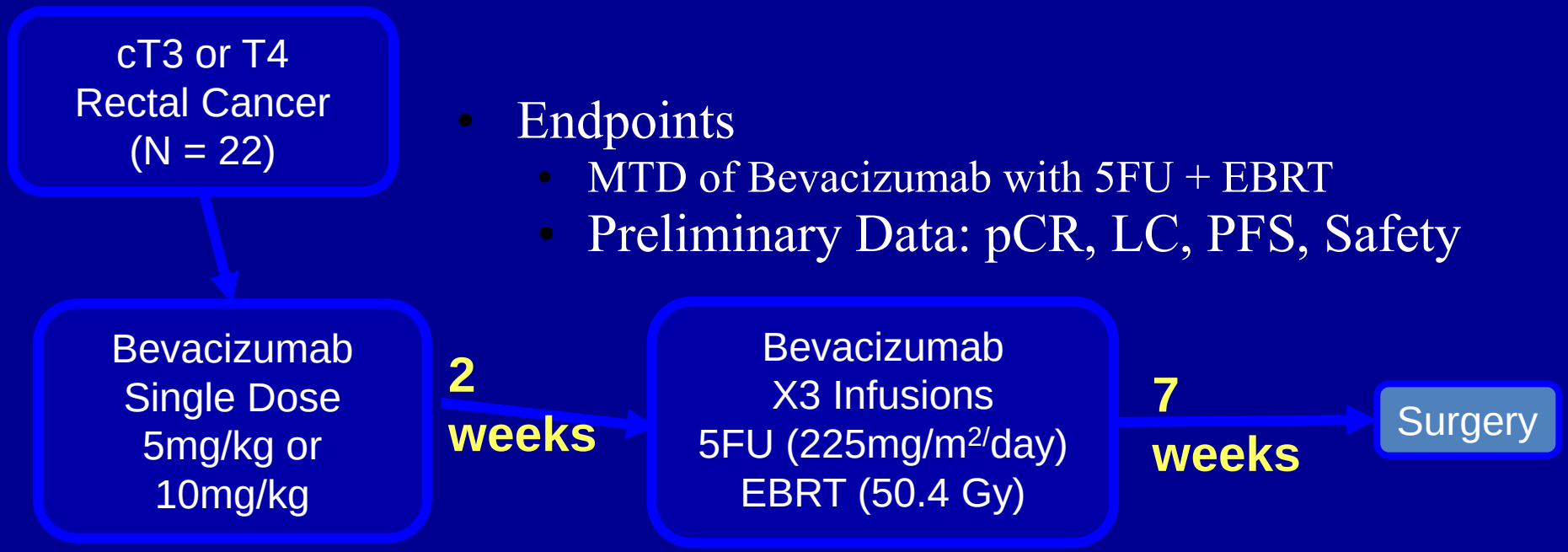
What is the best cytotoxic backbone
Assumptions

- Biologics increase efficacy cytotoxics OR
- Cytotoxics augment efficacy of biologics

- Combination cytotoxics superior efficacy
- Chemotherapy / biologic interaction favorable
- Toxicities not overlapping
- Dosing not compromised

Mechanism of Action Study
Neoadjuvant Rectal Cancer

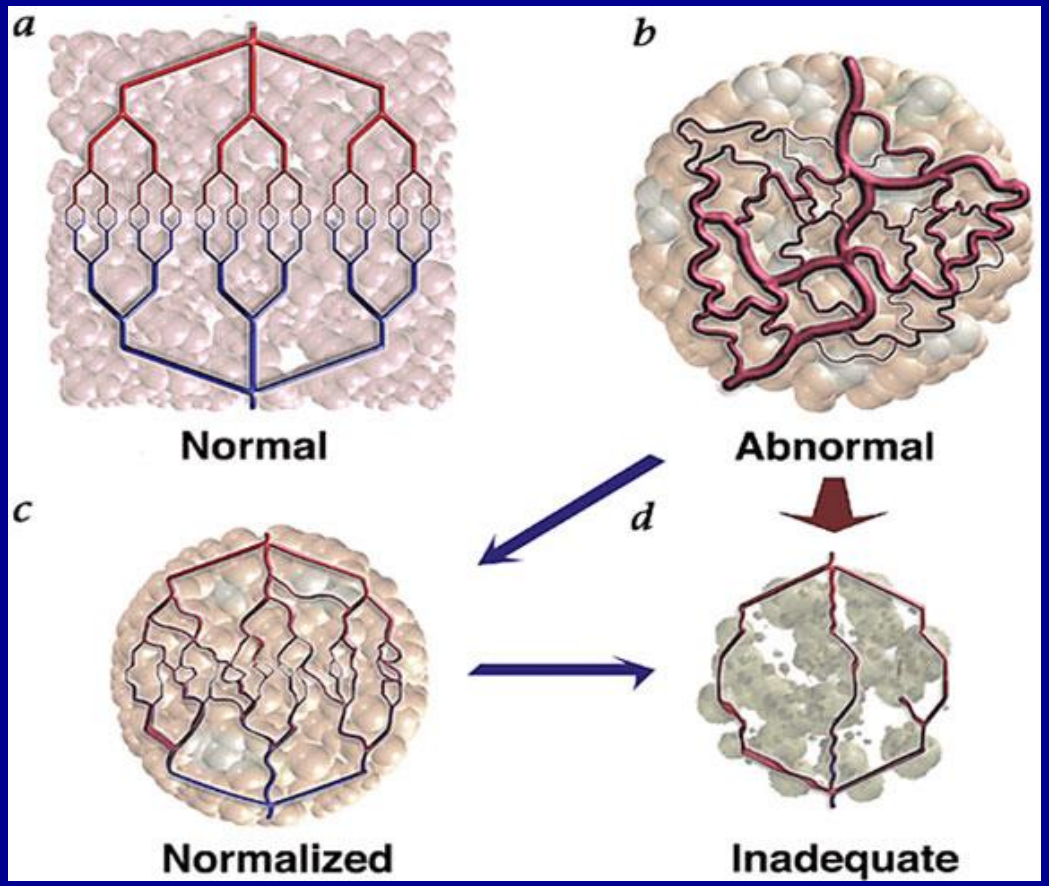


- Endpoints
  - MTD of Bevacizumab with 5FU + EBRT
  - Preliminary Data: pCR, LC, PFS, Safety

- Correlative studies
  - Functional imaging (PET, CT perfusion studies)
  - Interstitial Pressure Measurement
  - Circulating Endothelial Cells and Precursors
  - Tissue
  - Serum and Urine

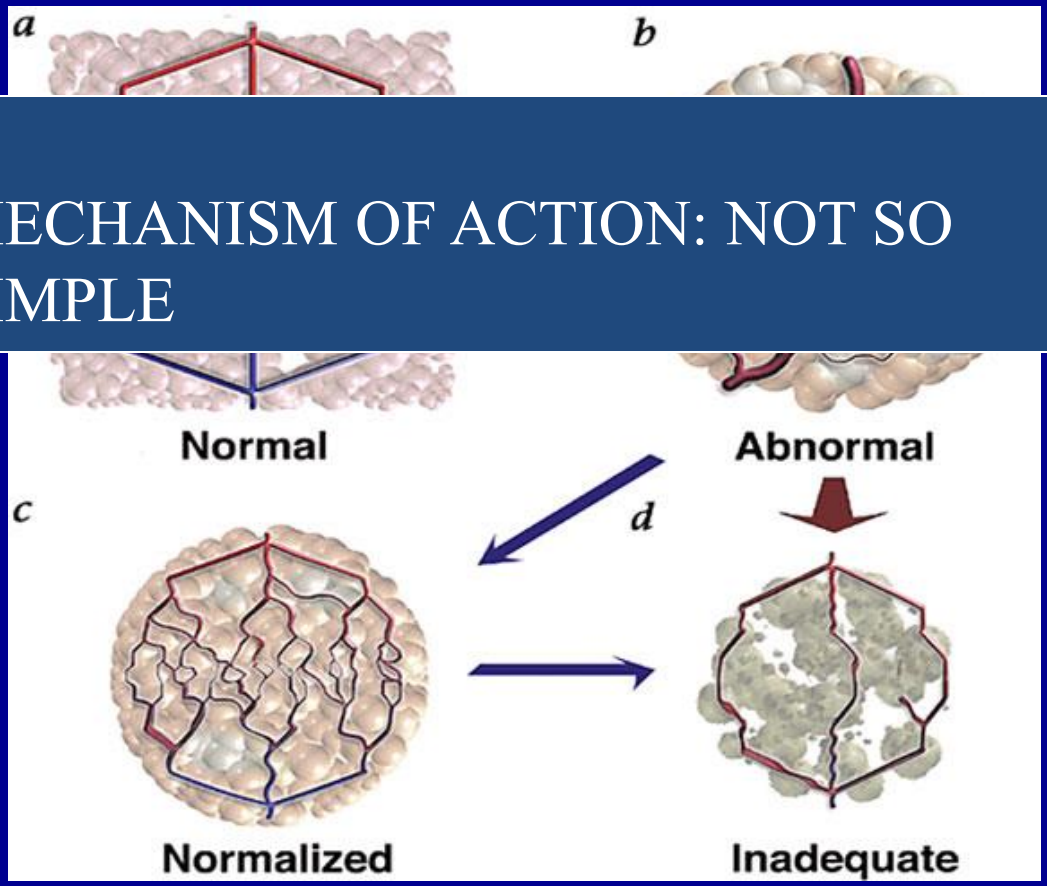
Willett et al. *Nat Med*. 2004;10:145.

Antiangiogenic Therapy and Vascular Normalization



Jain. *Nat Med.* 2001;7:987.

Antiangiogenic Therapy and Vascular Normalization



MECHANISM OF ACTION: NOT SO SIMPLE

Jain. *Nat Med.* 2001;7:987.

What is the best cytotoxic backbone
Facts

- Cytotoxics have toxicity and limits
- Chemotherapy / biologic interaction not necessarily favorable
- Less chemotherapy may be better
- Sequence may matter

What is the best cytotoxic backbone?

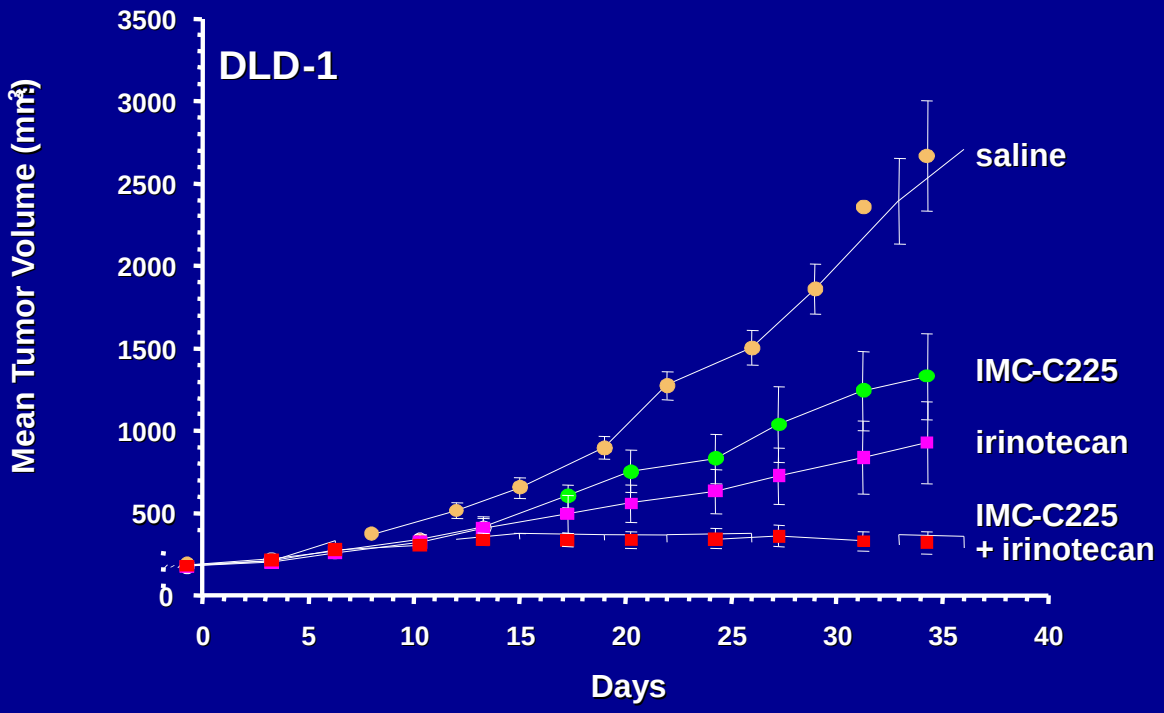
Reality

- FOLFOX preferred in US
  - CALGB/SWOG 80405: 73% choose FOLFOX
  - 2nd line trials almost all use irinotecan-based rx
- FOLFIRI use likelier in parts of Europe
- FOLFOXIRI not yet clear

Cytotoxic backbones

- Single agents
- FOLFOX = FOLFIRI
- CAPOX = FOLFOX
- Predictors of Efficacy:
  - Not really
- Predictors of Toxicity
  - Irinotecan

Combination Treatment of DLD-1 Colon Cancer Xenografts with C225 +/- high-dose irinotecan



Irinotecanadministered at 150mg/kg, q7d X3
Cetuximabadmininsteredat 1mg/dose, q3d

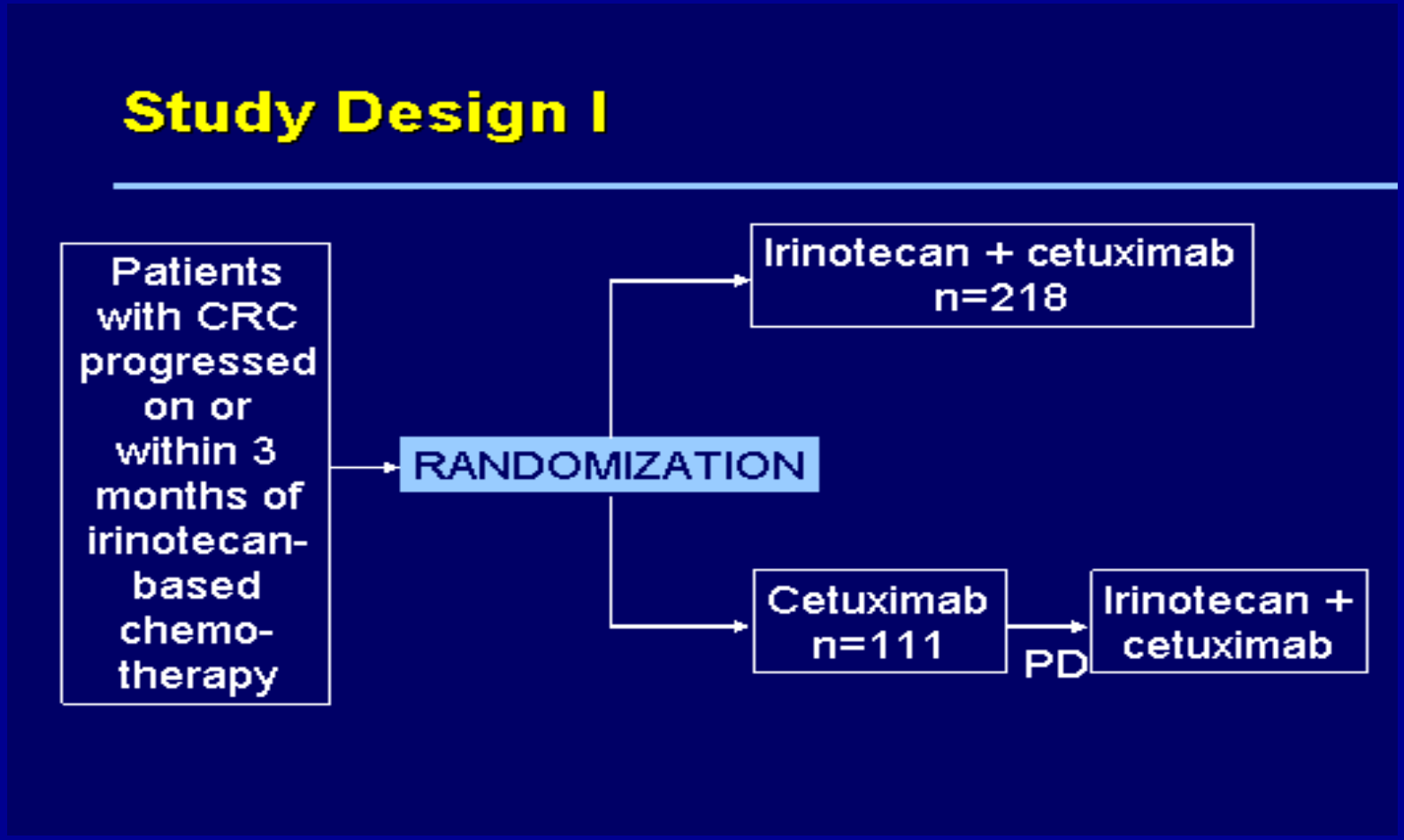
Efficacy Results
C-225 + CPT-11 in CPT-11 Failures

N = 120

- PR 27 (22.5%, 95% C.I. 15%-31%)
- SD 9 (7.5%; minimum 12 weeks)

Median Dur. of response (n=27): 186 days

Cetuximab Therapy: BOND Study Design



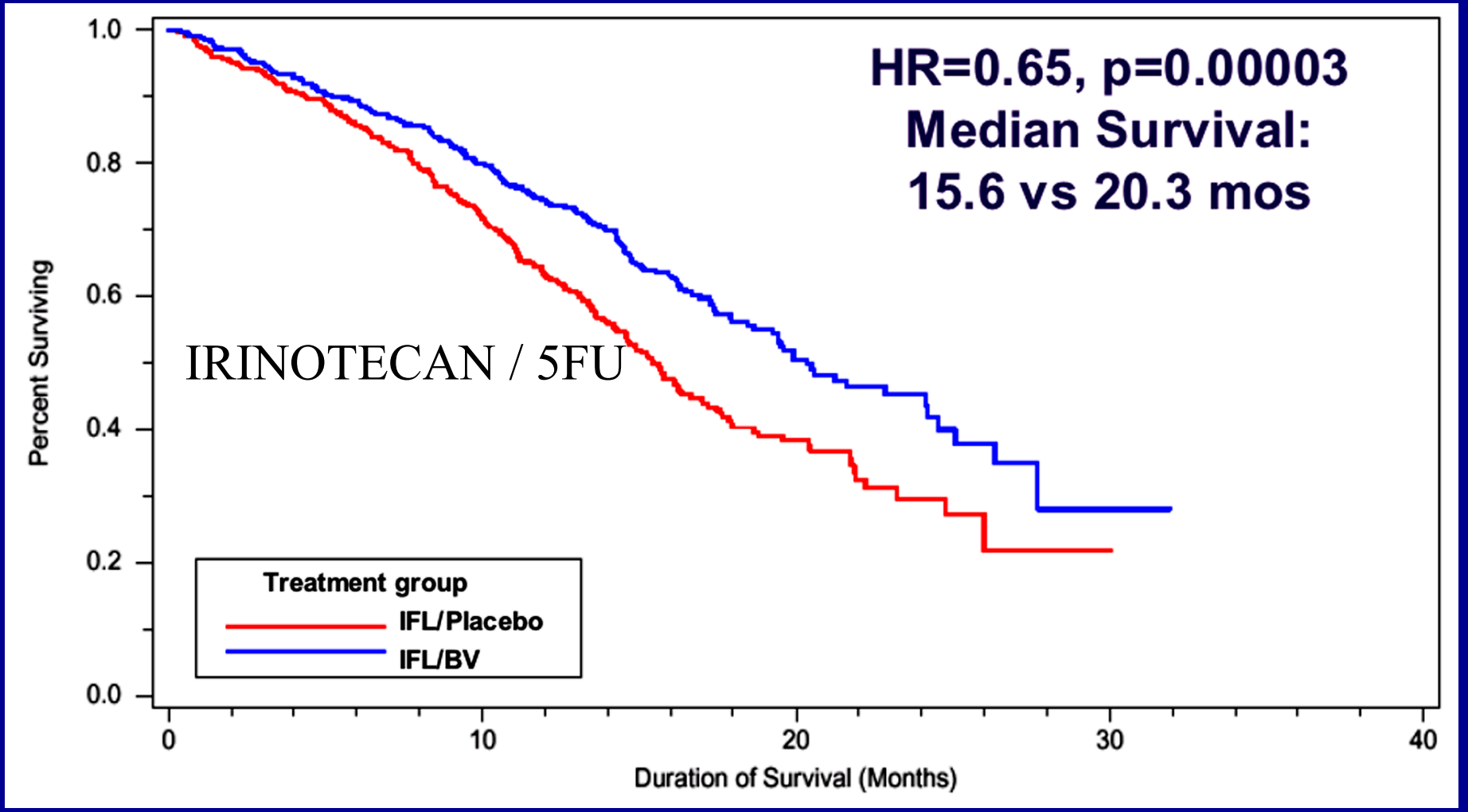
Cunningham et al, N Engl J Med, 2004

C-225 in Irinotecan- Refractory EGFR^{+} Patients

	C225 (n=111)	C225 + Irinotecan (n=218)	*P* Value
PR	10.8%	22.9%	.0074
TTP	1.5 mo	4.1 mo	<.0001
Overall Survival	6.9 mo	8.6 mo	NS

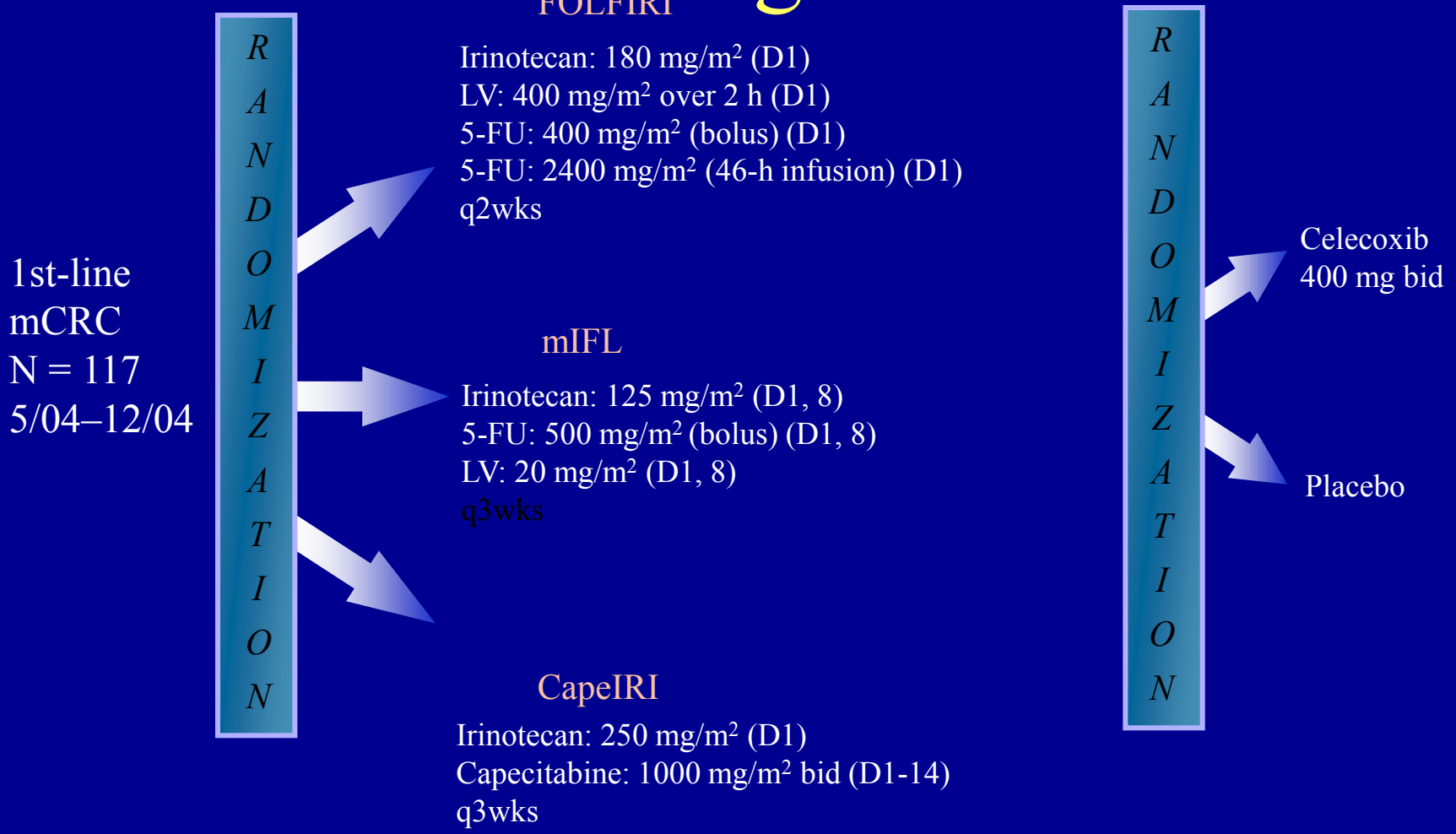
Cunningham et al, N Engl J Med, 2004

Bevacizumab: first and best results



Hurwitz, et al. NEJM, 2004

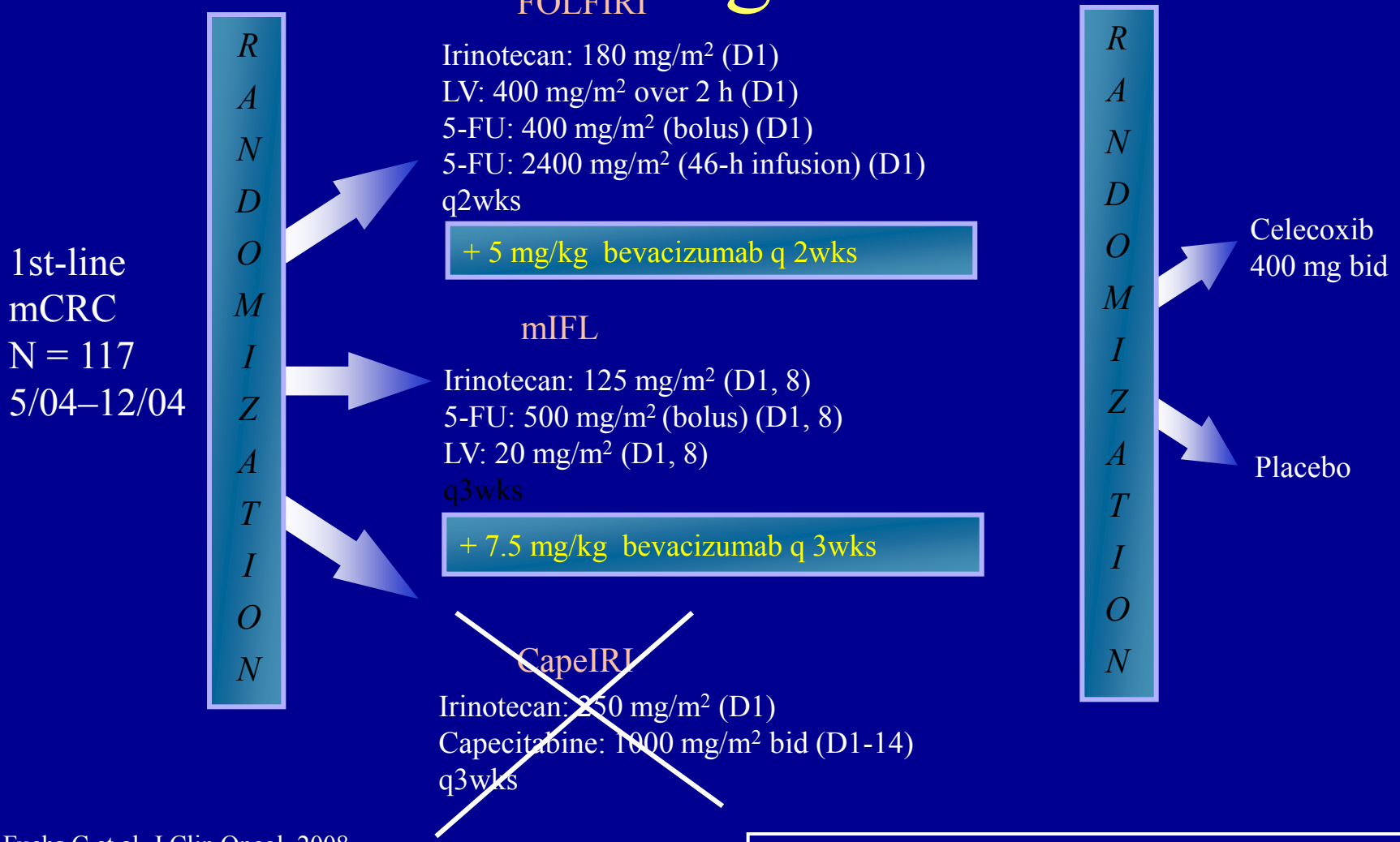
BICC-C: Period 2 Study Design



Fuchs C et al. J Clin Oncol, 2008

Stratification: Age, PS, Low dose aspirin use

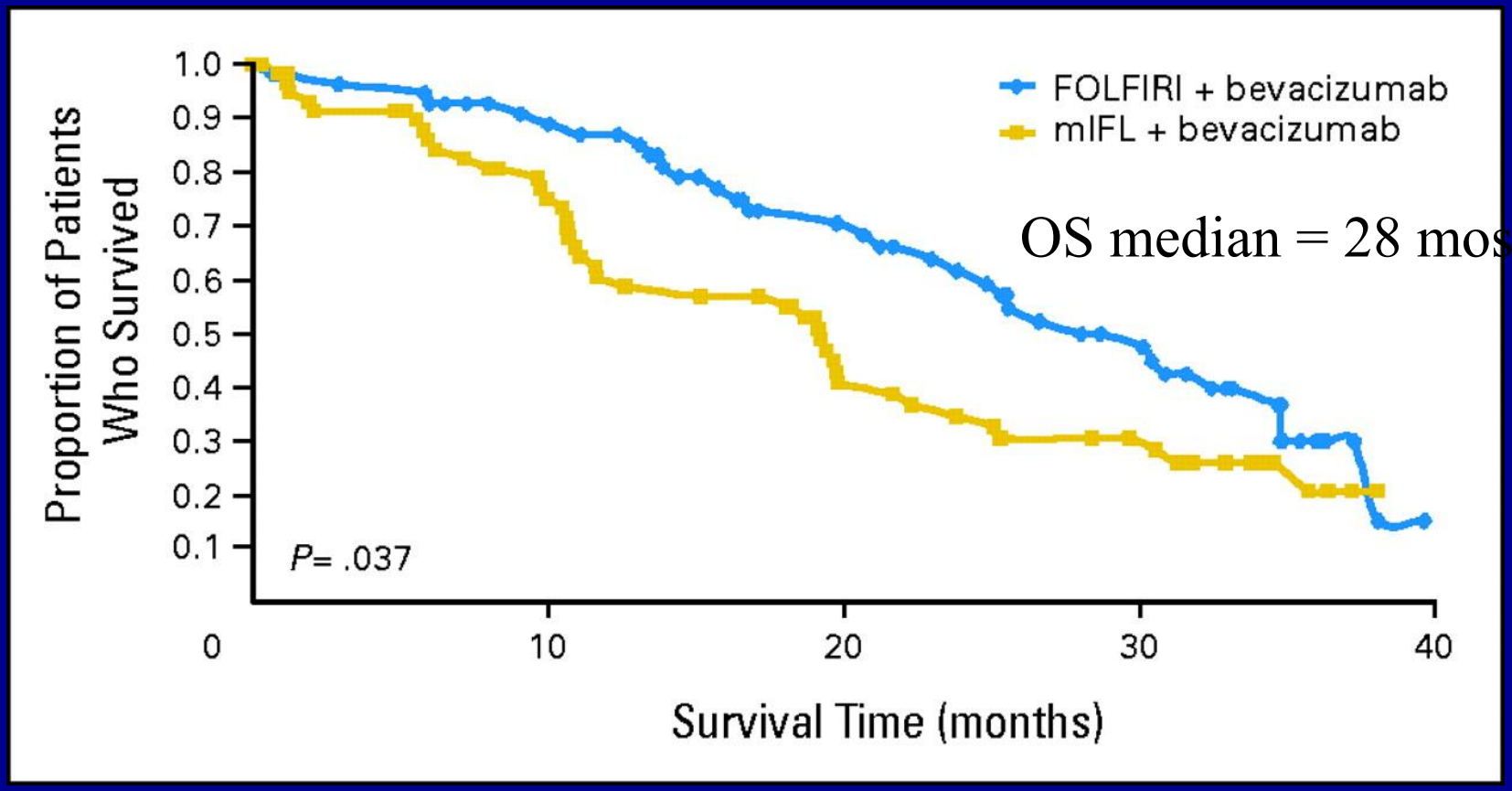
BICC-C: Period 2 Study Design



Fuchs C et al. J Clin Oncol, 2008

Stratification: Age, PS, Low dose aspirin use

Overall survival for period 2.



Fuchs C S et al. JCO 2008;26:689-690

NO16966 Study Design

Recruitment
June 2003 – May 2004

CAPOX N=317
FOLFOX4 N=317

Initial 2-arm
open-label study (N=634)

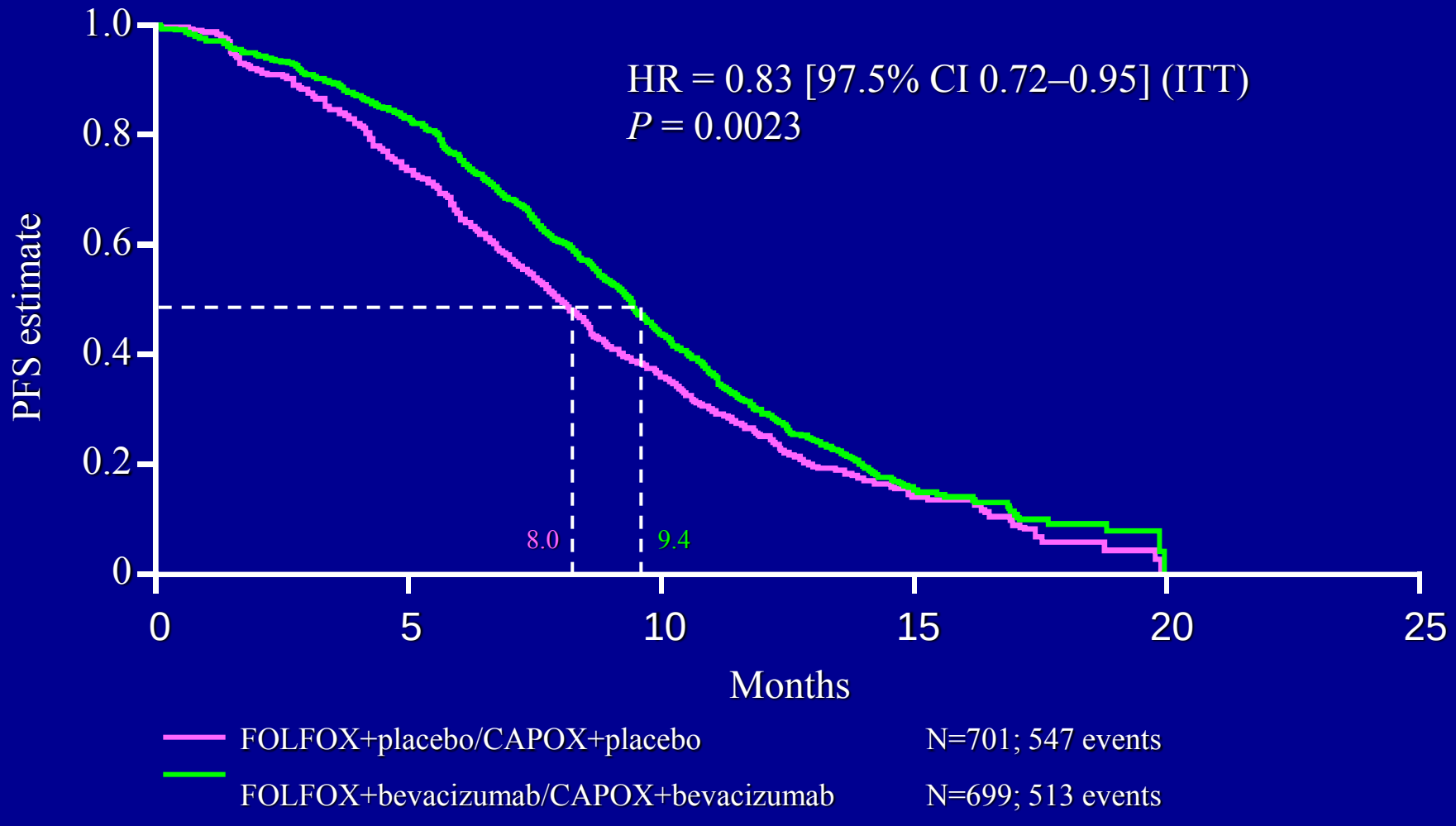
Recruitment
Feb 2004 – Feb 2005

CAPOX + placebo N=350	CAPOX + bevacizumab N=350
FOLFOX4 + placebo N=351	FOLFOX4 + bevacizumab N=350

Protocol amended to 2x2 placebo-controlled design after bevacizumab phase III data[1] became available (N=1401)

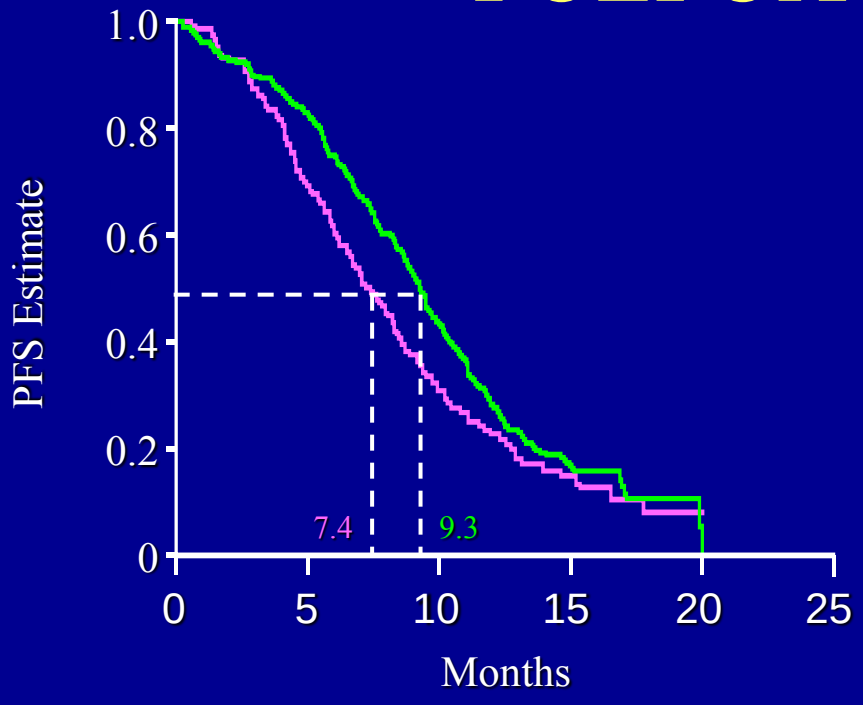
Cassidy J et al. J Clin Oncol, 2007

NO16966
PFS Chemotherapy + Bevacizumab Superiority

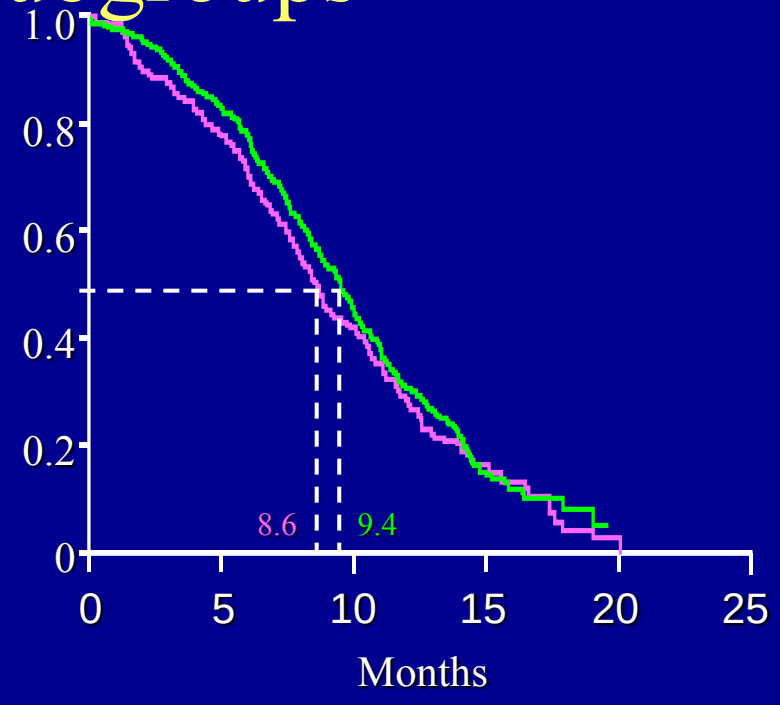


Saltz L, J Clin Oncol, 2008

NO16966: PFS: Chemotherapy + Bevacizumab Superiority: CAPOX and FOLFOX Subgroups



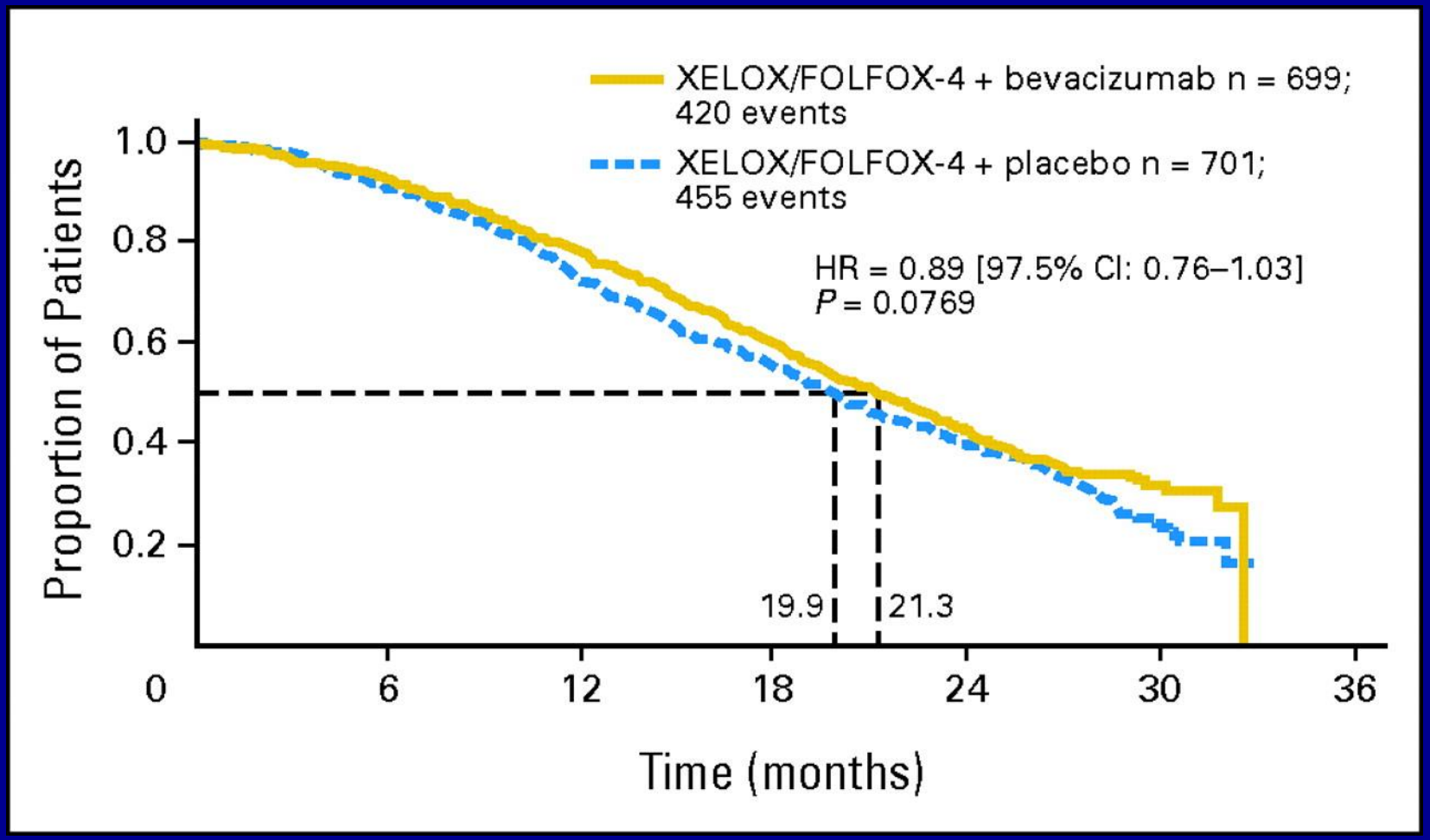
CAPOX subgroup
HR = 0.77 [97.5% CI 0.63–0.94] (ITT)
P = 0.0026



FOLFOX subgroup
HR = 0.89 [97.5% CI 0.73–1.08] (ITT)
P = 0.1871

Saltsz L, J Clin Oncol, 2008

Overall survival (intent to treat population).



Saltz L B et al. JCO 2008;26:2013-2019

JOURNAL OF CLINICAL ONCOLOGY ASCO

Clinical Impact: Whither FOLFOX / BEV?

History Lesson

Hurwitz data: BEV a difference-maker **with IFL**

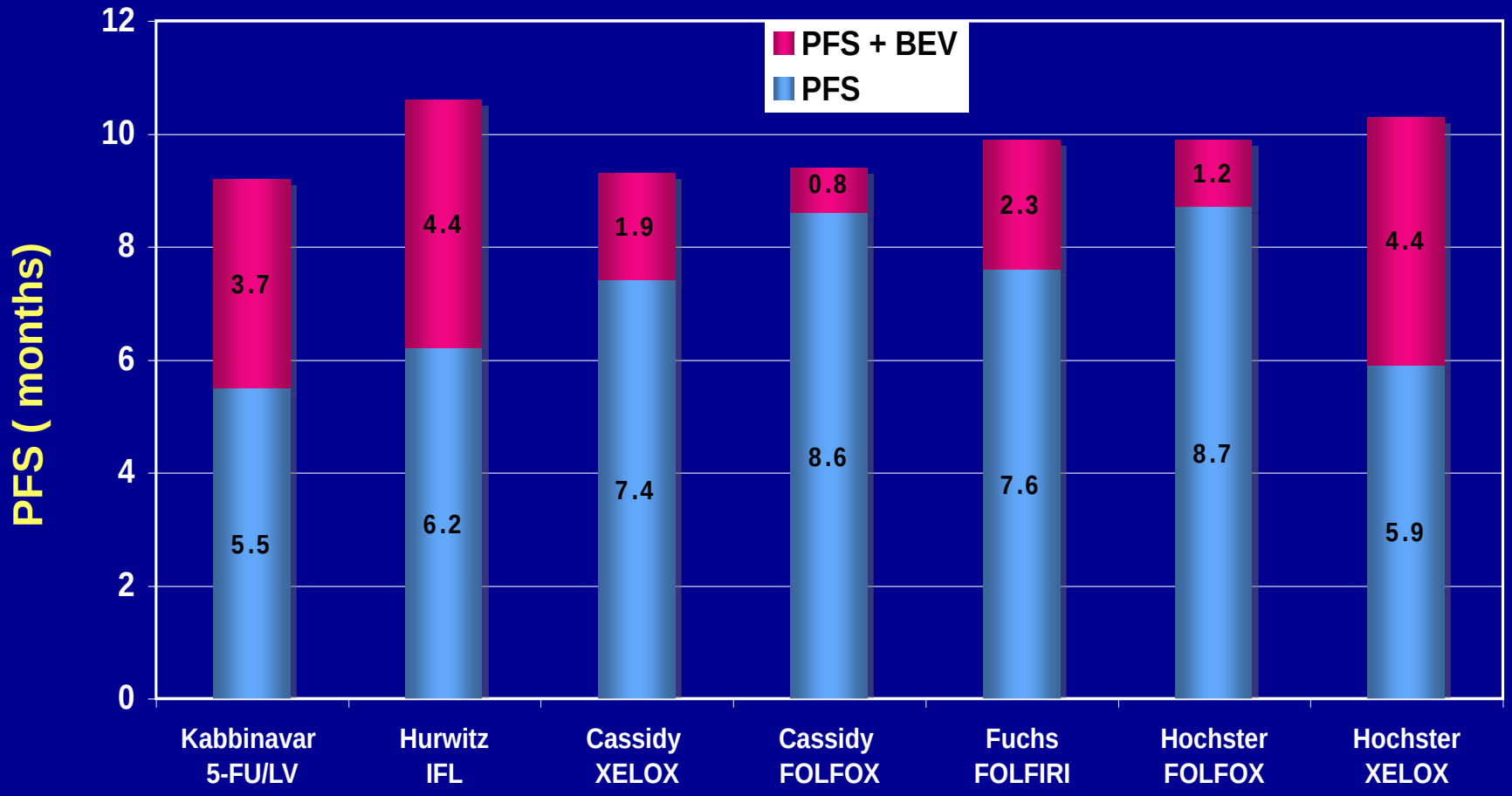
IN RETROSPECT:

- BEV approved “with FU regimen”; FOLFOX > IFL
- FOLFOX / BEV: 2nd-line in BEV naïve patients
- Subsequent studies: no increase RR, marginal OS

BY DEFAULT:

FOLFOX / BEV 1st-line metastatic CRC

Is there a ceiling on PFS with chemo/Bev?



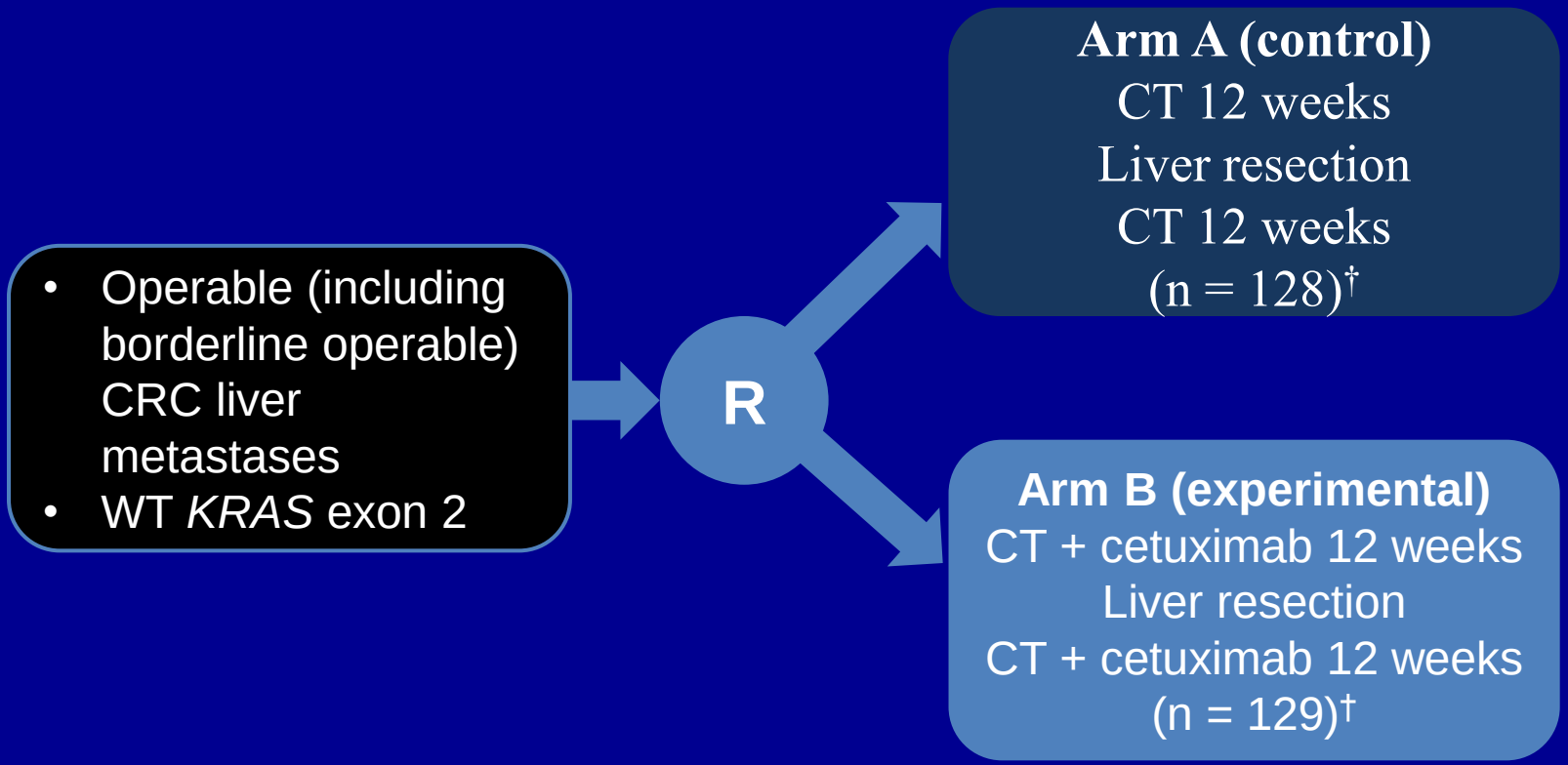
Courtesy A. Grothey

1st-line EGFR: Efficacy
KRAS *wild type*

	Comparative Regimens	Median PFS, Mos	Median OS, Mos
CRYSTAL[1]	FOLFIRI/Cetux vs FOLFIRI	**9.9 vs 8.4**	**23.5 vs 20.0**
OPUS[2]	FOLFOX4/Cetux vs FOLFOX4	**8.3 vs 7.2**	**22.8 vs 18.5**
PRIME[3-5]	FOLFOX4/Pmab vs FOLFOX4	**9.6 vs 8.0**	**23.8 vs 19.4**
	FOLFOX4/Pmab vs FOLFOX4 (KRAS/NRAS WT)	**10.1 vs 7.9**	**26.0 vs 20.2**
COIN[6]	FOLFOX/XELOX/Cetux vs FOLFOX/XELOX	**8.6 vs 8.6**	**17.0 vs 17.9**

1. Van Cutsem E, et al. J Clin Oncol. 2011;29:2011-2019. 2. Bokemeyer C, et al. Ann Oncol. 2010;22:1535-1546. 3. Douillard JY, et al. J Clin Oncol. 2010;28:4697-4705. 4. Douillard JY, et al. ASCO 2013. Abstract 3620. 5. Douillard JY, et al. N Engl J Med. 2013;369:1023-1034. 6. Maughan TS, et al. Lancet. 2011;377:2103-2114.

New EPOC



†117 and 119 patients in Arms A and B, respectively, were included in the primary analysis. CT = oxaliplatin 85 mg/m² IV over 2h and 5-FU bolus 400 mg/m² IV over 5 min followed by fluorouracil 2400 mg/m² 46h infusion every 2 weeks (regimen one) or oxaliplatin 130 mg/m² IV over 2 h and oral capecitabine 1000 mg/m² twice daily on Days 1–14 every 3 weeks (regimen two). Patients who had received adjuvant oxaliplatin could receive irinotecan with fluorouracil instead of oxaliplatin (regimen three).

Primrose J, et al. Lancet Oncol 2014;15:601–11.

New EPOC: PFS and OS

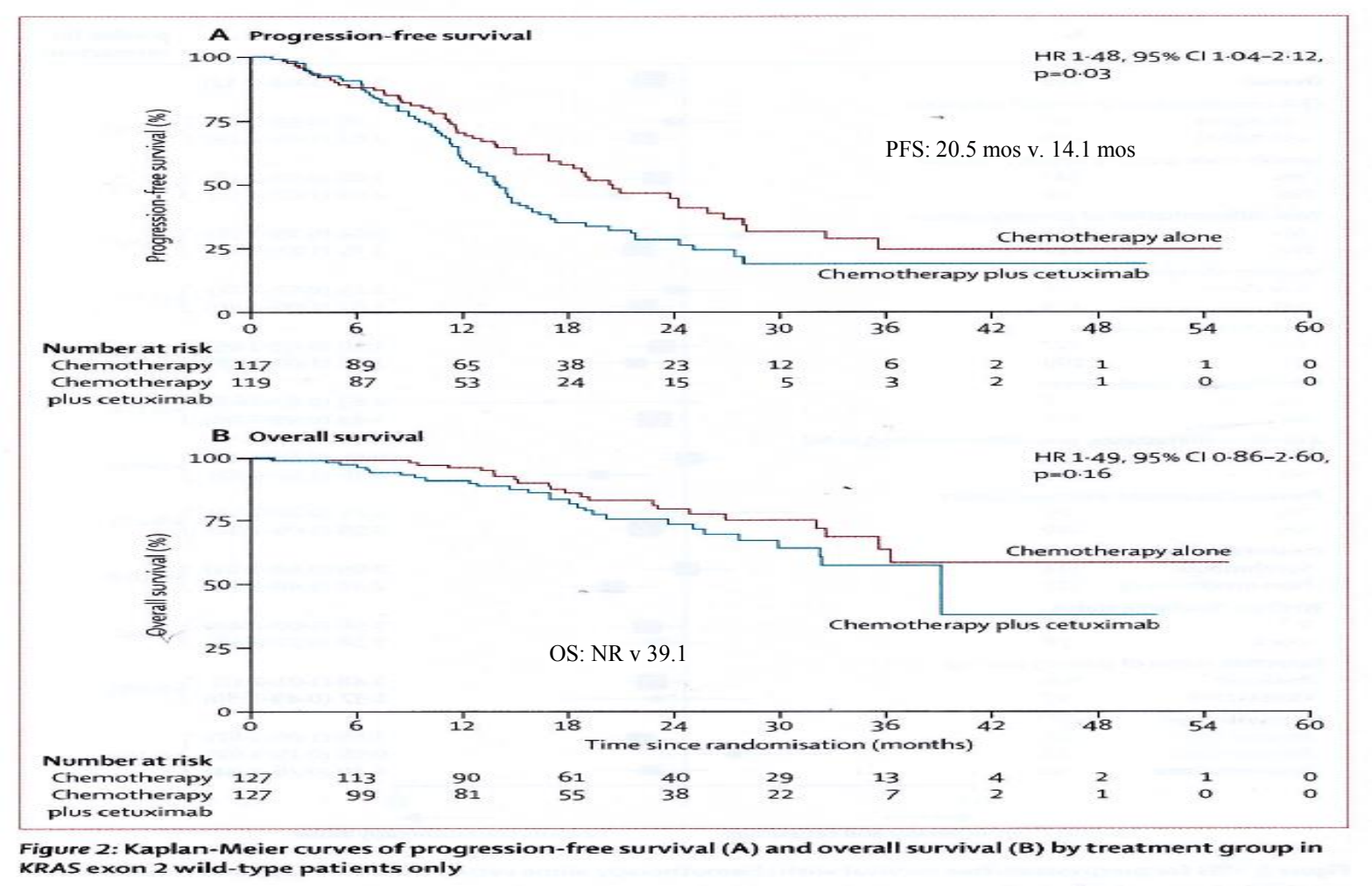


Figure 2: **Kaplan-Meier curves of progression-free survival (A) and overall survival (B) by treatment group in *KRAS* exon 2 wild-type patients only**

Primrose, et al, Lancet Oncol, 2014.

New EPOC: potential limitations

- Quality assurance:[1]
  - Surgery: margin < 1 cm (40% of patients)
  - R1 resection (cetuximab: 12%; no cetuximab 8%)
  - Entry criteria (13% not assessable)
- CapOx: 20%[1]

SLIDE COURTESY B. NORDLINGER

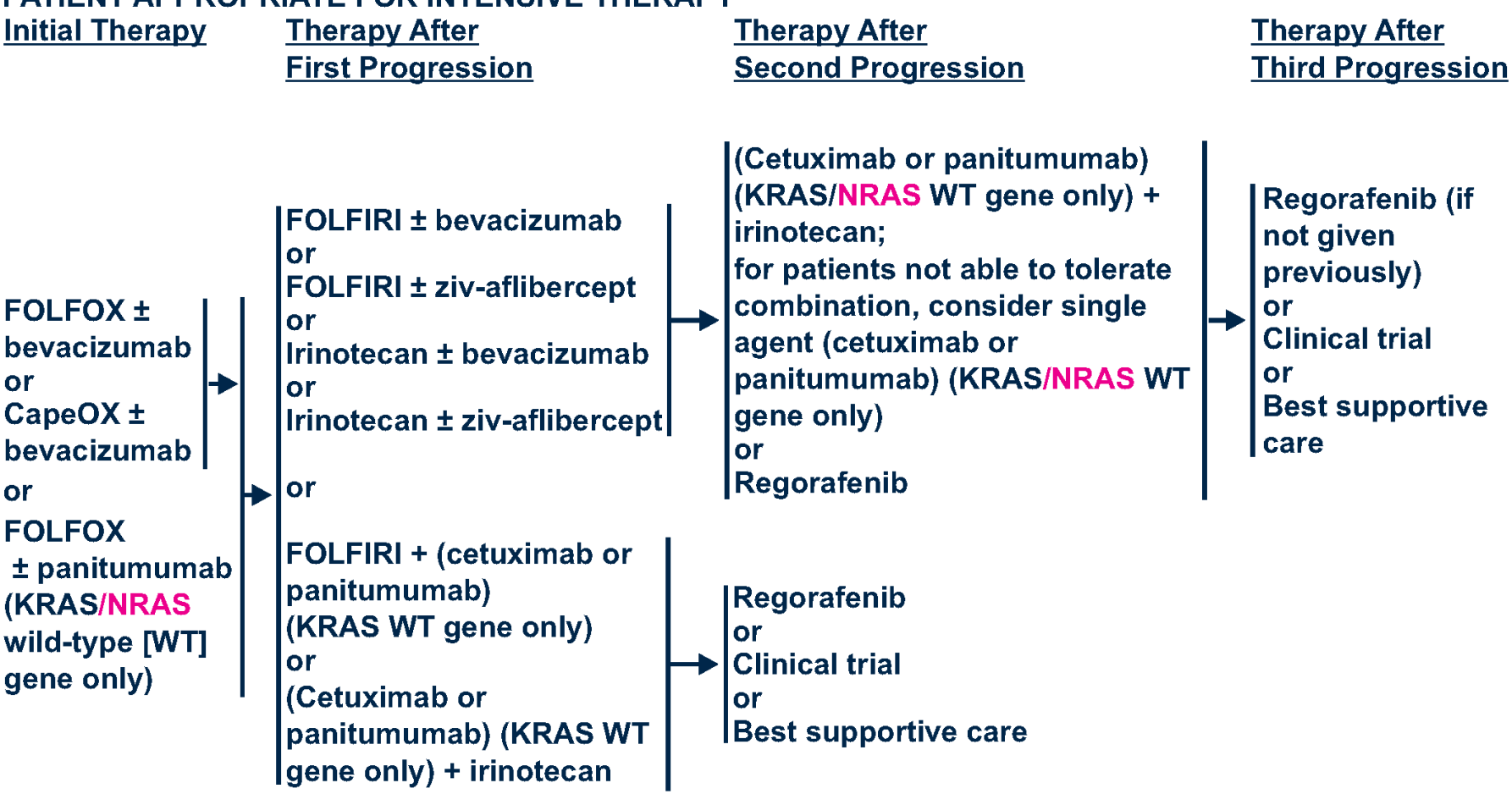
1. Primrose J, et al. Lancet Oncol 2014;15:601–11.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014
Colon Cancer

CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE

PATIENT APPROPRIATE FOR INTENSIVE THERAPY

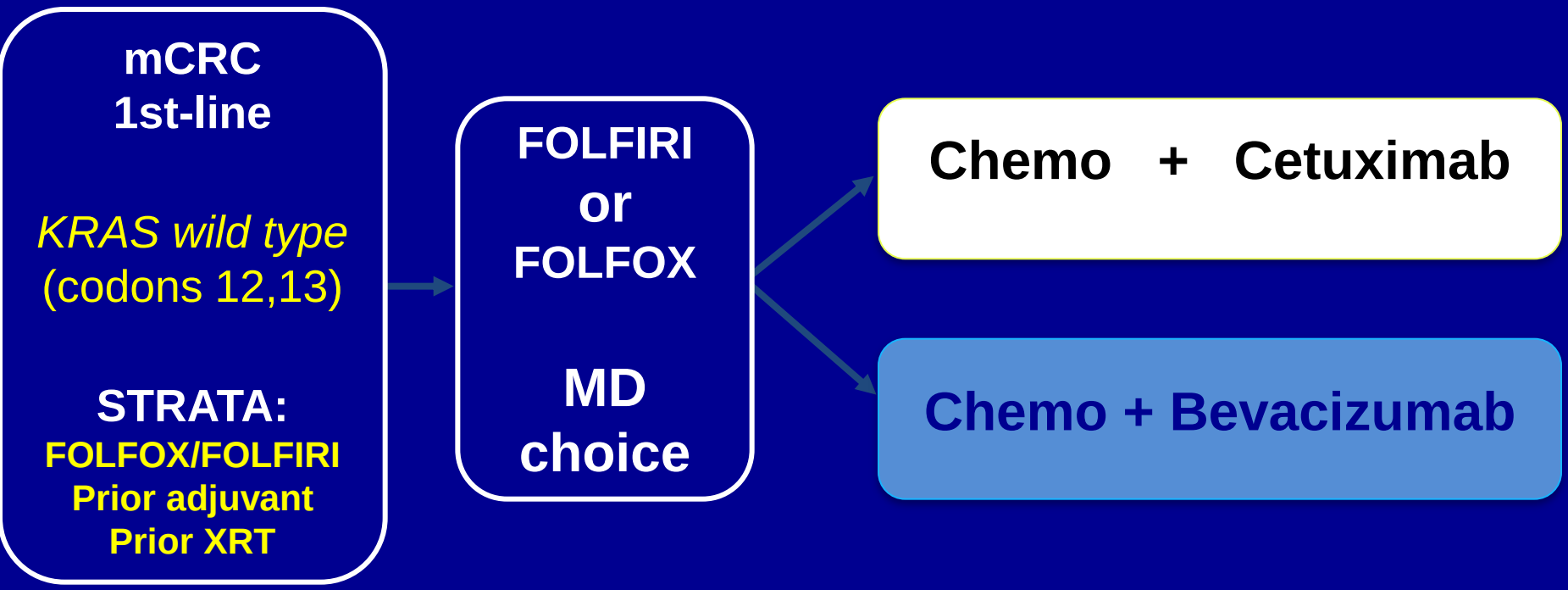


First-line Therapy in KRAS WT mCRC: EGFR- vs VEGF-Targeted mAbs

Trial	Comparative Regimens	PFS, Mos	OS, Mos
PEAK[1] (N = 285)	mFOLFOX6/Pmab vs mFOLFOX6/Bev	10.9 vs 10.1	NR vs 25.4
FIRE-3[2] (N = 592)	FOLFIRI/Cetux vs FOLFIRI/Bev	10.0 vs 10.3	28.7 vs 25.0*
CALGB/SWOG 80405 (N = 1137) N = 302 N = 835	CHEMO/Cetux v. CHEMO/Bev FOLFIRI/Cetux v. FOLFIRI/Bev FOLFOX/Cetux v. FOLFOX/Bev	10.4 vs 10.8 10.3 vs 11.6 10.6 vs 10.3	29.9 vs 29.0 28.9 vs 33.4 30.1 vs 26.9

1. Schwartzberg LS, et al. ASCO GI 2013. Abstract 446. 2. Heinemann V, et al. ASCO 2013. Abstract LBA3506.

CALGB/SWOG 80405: FINAL DESIGN



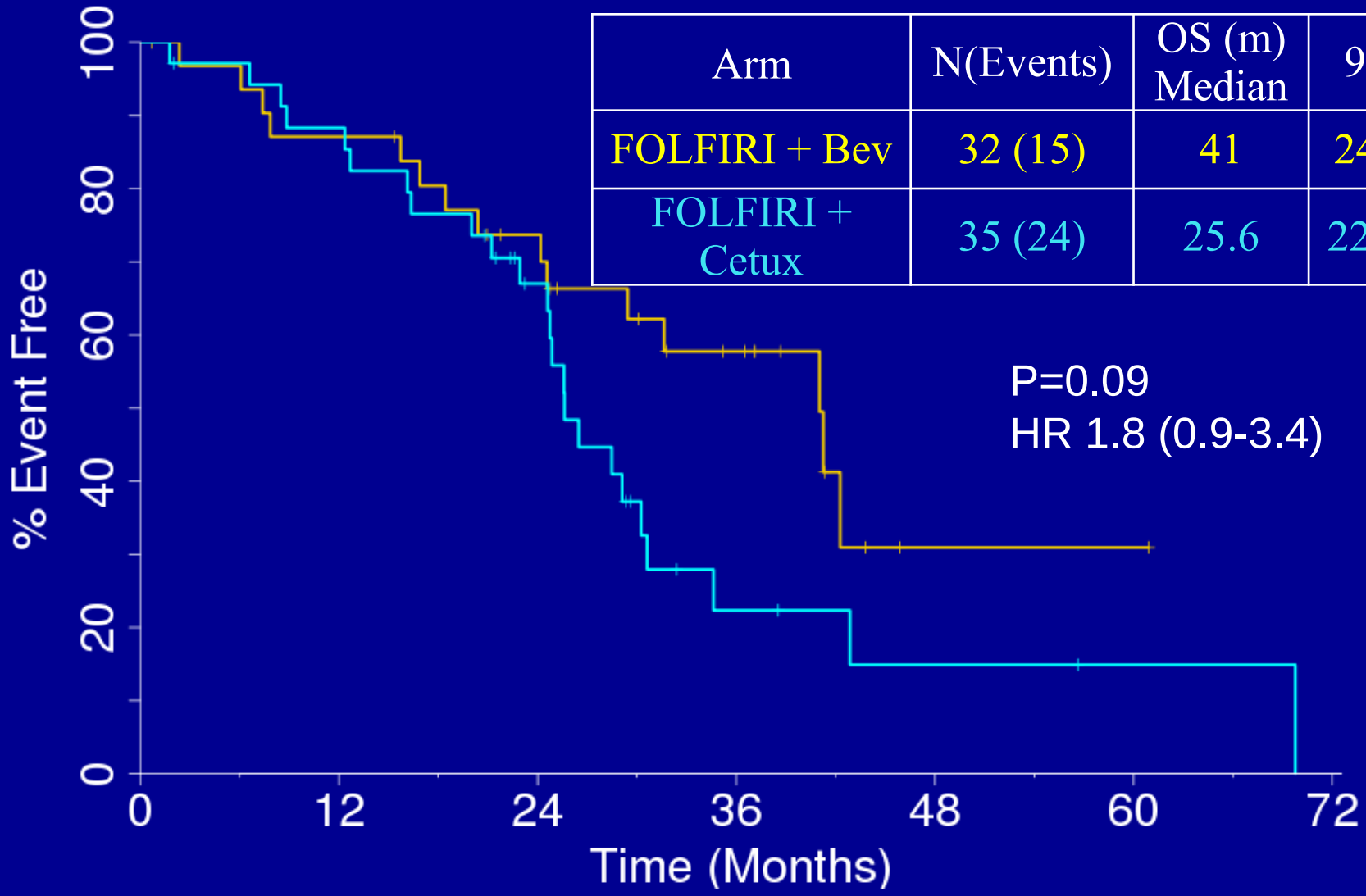
N = 1140

1˚ Endpoint: Overall Survival

CALGB/SWOG 80405: Overall Survival, FOLFIRI *KRAS* WT

Patients Previously Treated with Oxaliplatin

Arm	N(Events)	OS (m) Median	95% CI
FOLFIRI + Bev	32 (15)	41	24.6-NA
FOLFIRI + Cetux	35 (24)	25.6	22.9-30.6



P=0.09
HR 1.8 (0.9-3.4)

Presented by:

CALGB/SWOG 80405: Overall Survival, FOLFIRI *KRAS* WT

Patients Previously Treated with Oxaliplatin

Arm	N(Events)	OS (m) Median	95% CI
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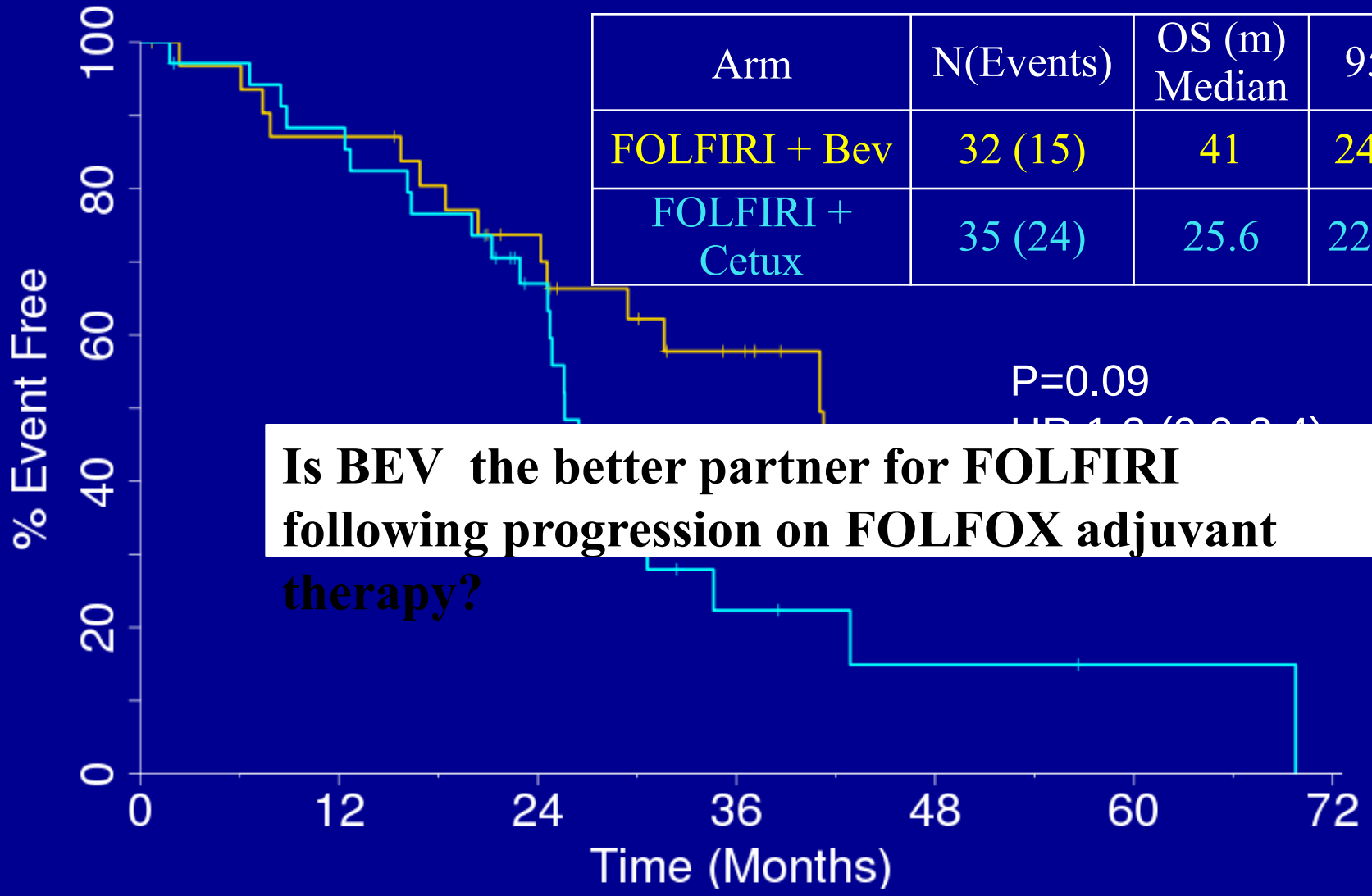


Is BEV the better partner for FOLFIRI following progression on FOLFOX adjuvant therapy?

Presented by:

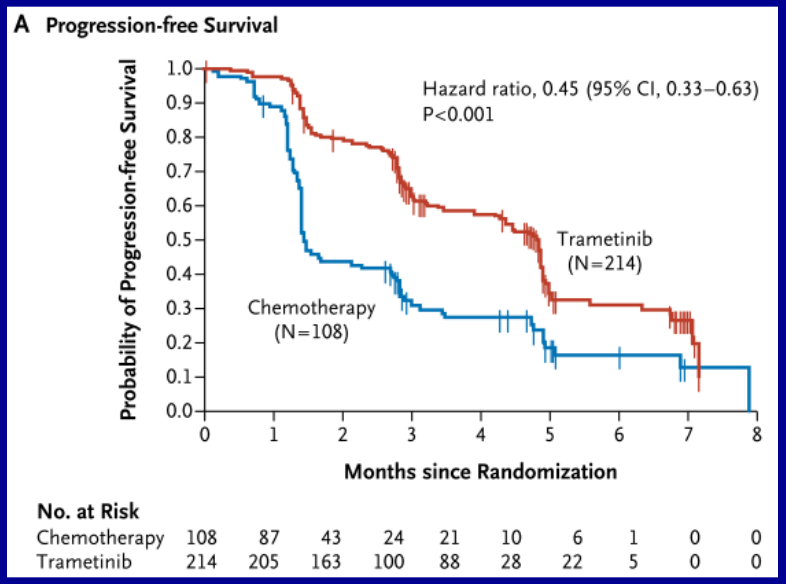
What is the best cytotoxic backbone?

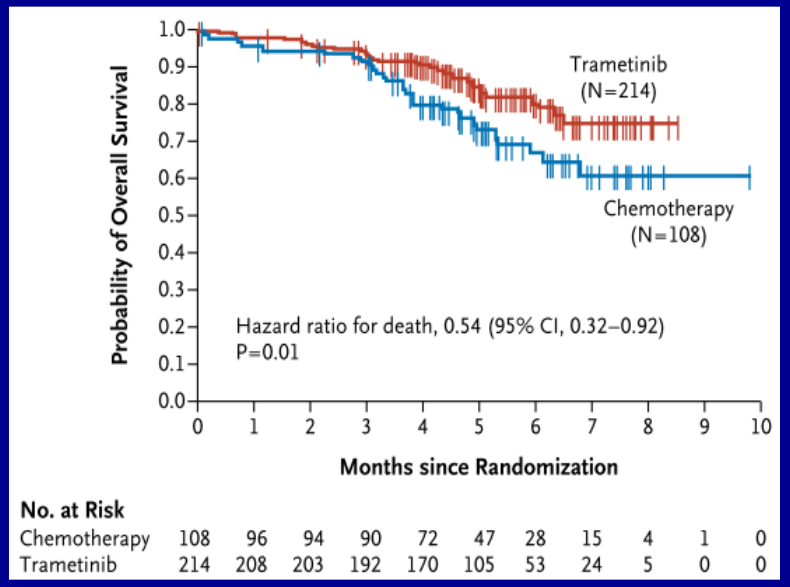
Opinion

- FOLFOX backbone:
  - marginalizes BEV benefit at least in 1st line
  - New EPOC data probably aberration
  - FOLFOX / CETUX not detrimental
- May get better understanding in enriched populations
- Choice (as of today) function of factors other than biologic interaction

IS A BACKBONE NECESSARY ?

MEK in BRAF + Mel





	Trametinib	Chemotherapy
PFS	4.8 m	1.5 m
6 month OS	81%	67%
ORR	22%	8%

Flaherty New England Journal of Medicine **367**(2): 107-114

Study Design -- “BOND II”

- Randomized phase II
- EGFR expression *not* required for study entry
- Initially planned for 75 pts/arm
- Statistics recalculated for 37 pts/arm

Saltz, et al, JCO, 2007

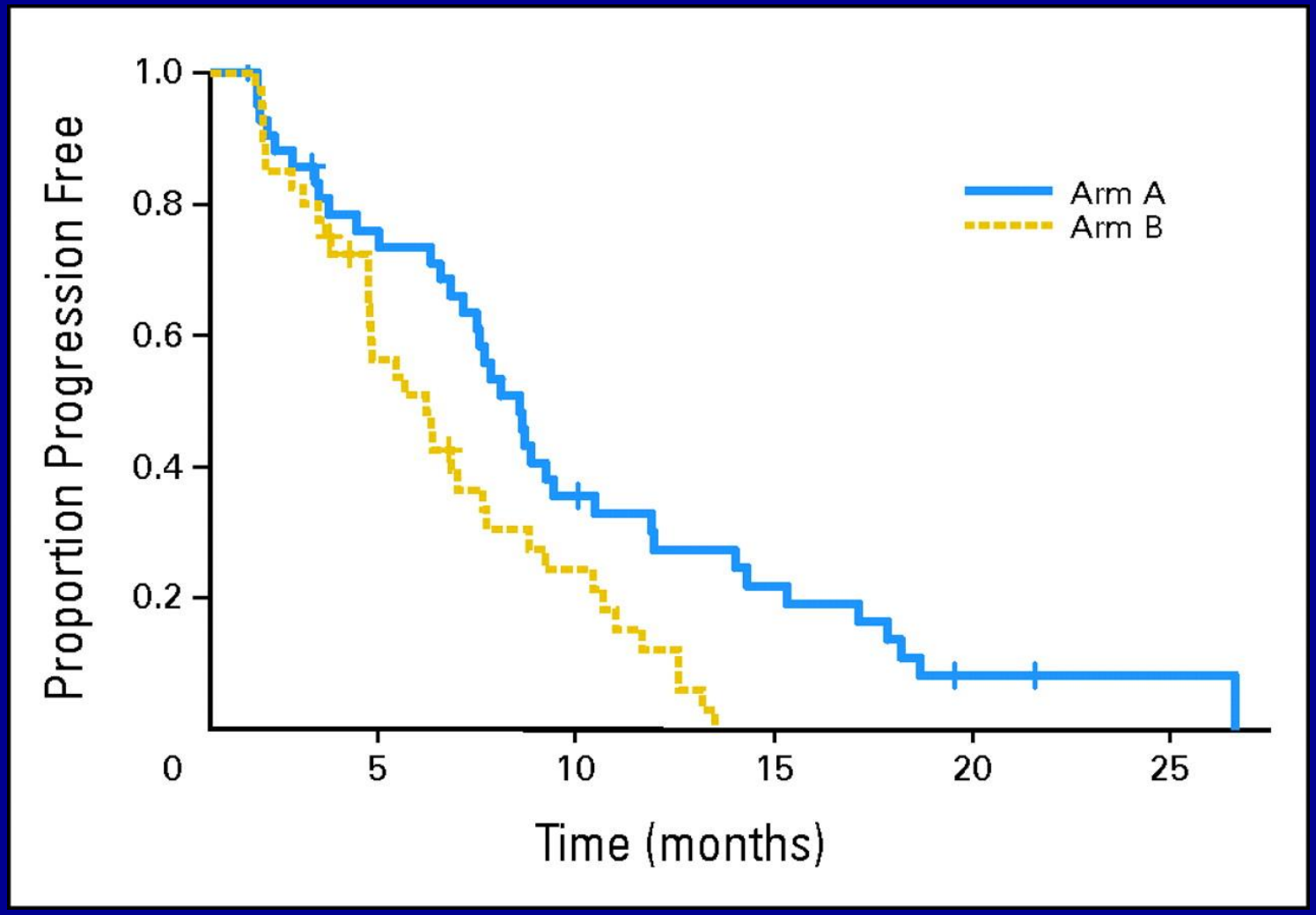
Treatment Plan

- Arm A (CBI)
  - Cetuximab, 400 mg/m2 loading dose, then 250 mg/m2 weekly
  - Bevacizumab 5 mg/kg every other week
  - Irinotecan at same dose and schedule as *last* given prior to study entry
- Arm A (CB)
  - Cetuximab, 400 mg/m2 loading dose, then 250 mg/m2 weekly
  - Bevacizumab 5 mg/kg every other week

Patient Characteristics

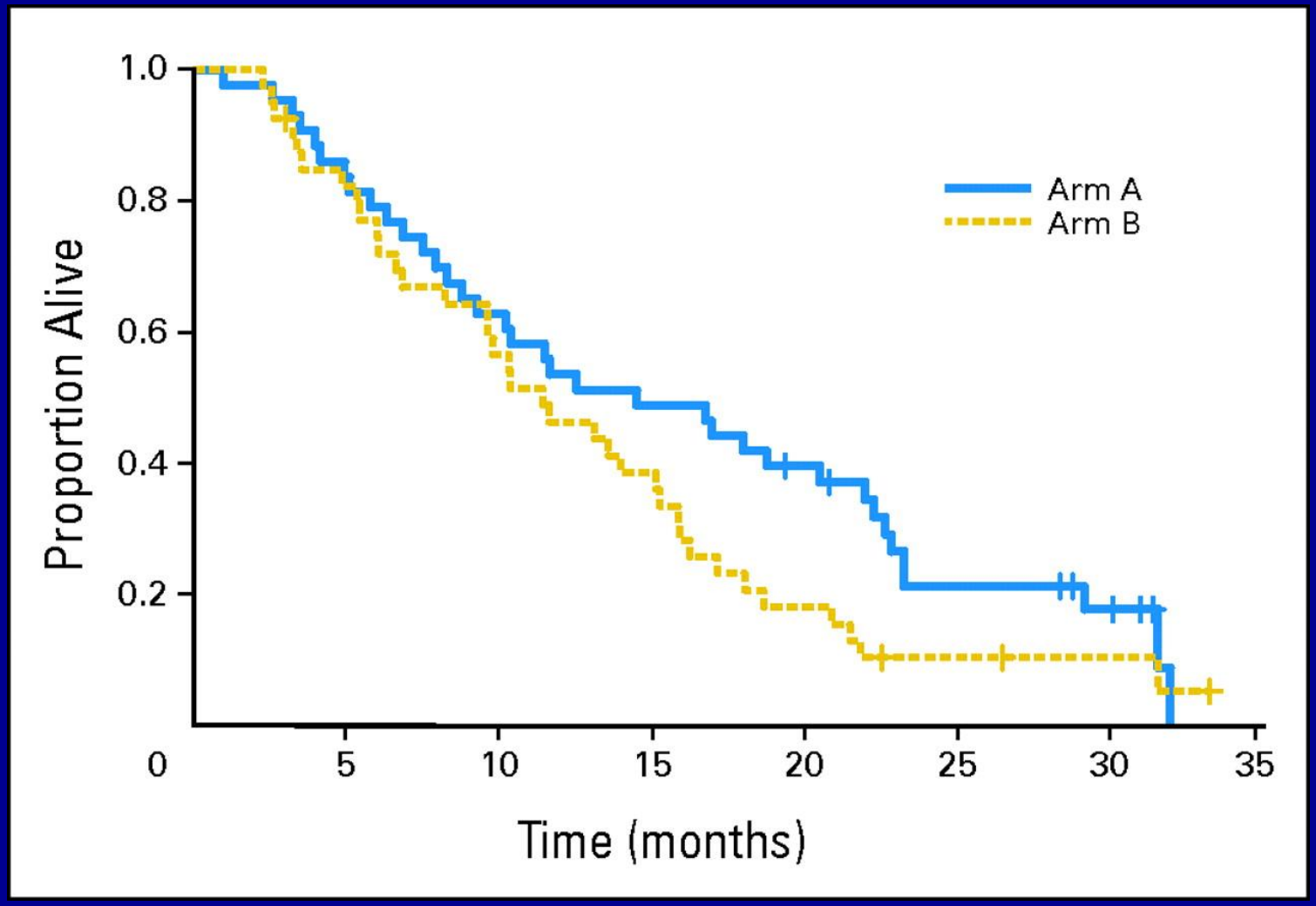
	CBI (n=39)	CB (n=35)	P
% male	64%	71%	ns
Median Age (range)	62 (43-78)	(24-80)	.01
PS = 0	41 %	57 %	ns
PS = 1	59 %	43 %	ns
Prior oxaliplatin	87 %	89 %	ns
Med. prior regimens (range)	3 (range1-6)	3 (range 1-6)	ns
Prior Pelvic RT	4 (10%)	5 (14%)	ns

Kaplan-Meier estimates of time to tumor progression: arm A (cetuximab, bevacizumab, irinotecan) versus arm B (cetuximab, bevacizumab).



Saltz L B et al. JCO 2007;25:4557-4561

Kaplan-Meier estimates of survival: arm A (cetuximab, bevacizumab, irinotecan) versus arm B (cetuximab, bevacizumab).



Saltz L B et al. JCO 2007;25:4557-4561

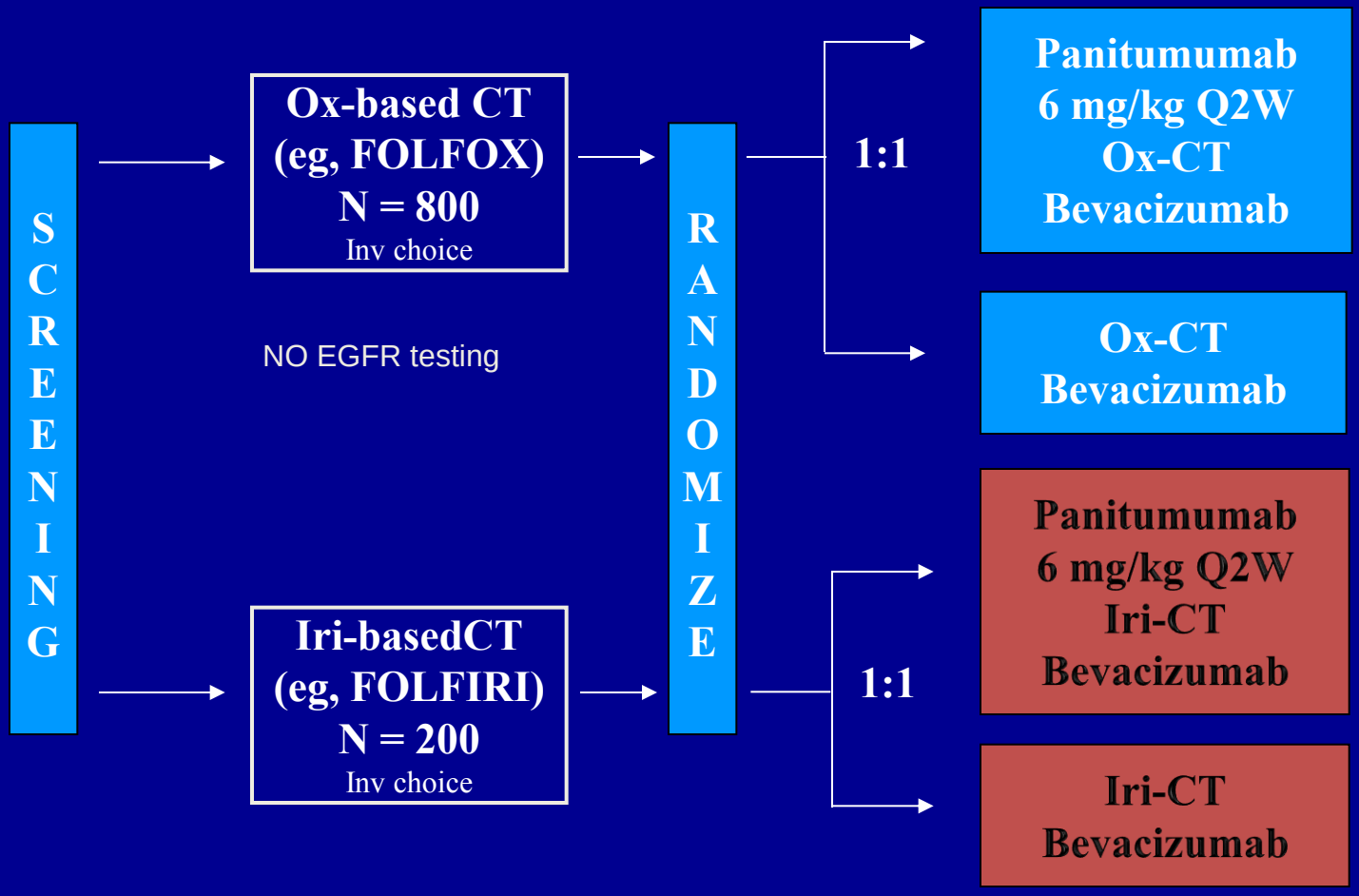
Efficacy Comparison (Historical Controls)

	Cetux-Irino (historical)	Cetux-Irino + Bev	P value
Resp Rate	23%	38%	0.03
TTP	4 m	8.5 m	> 0.01

	Cetux alone (historical)	Cetux + Bev	P value
Resp Rate	11%	23%	0.05
TTP	1.5 m	6.9 m	> 0.01

PACCE

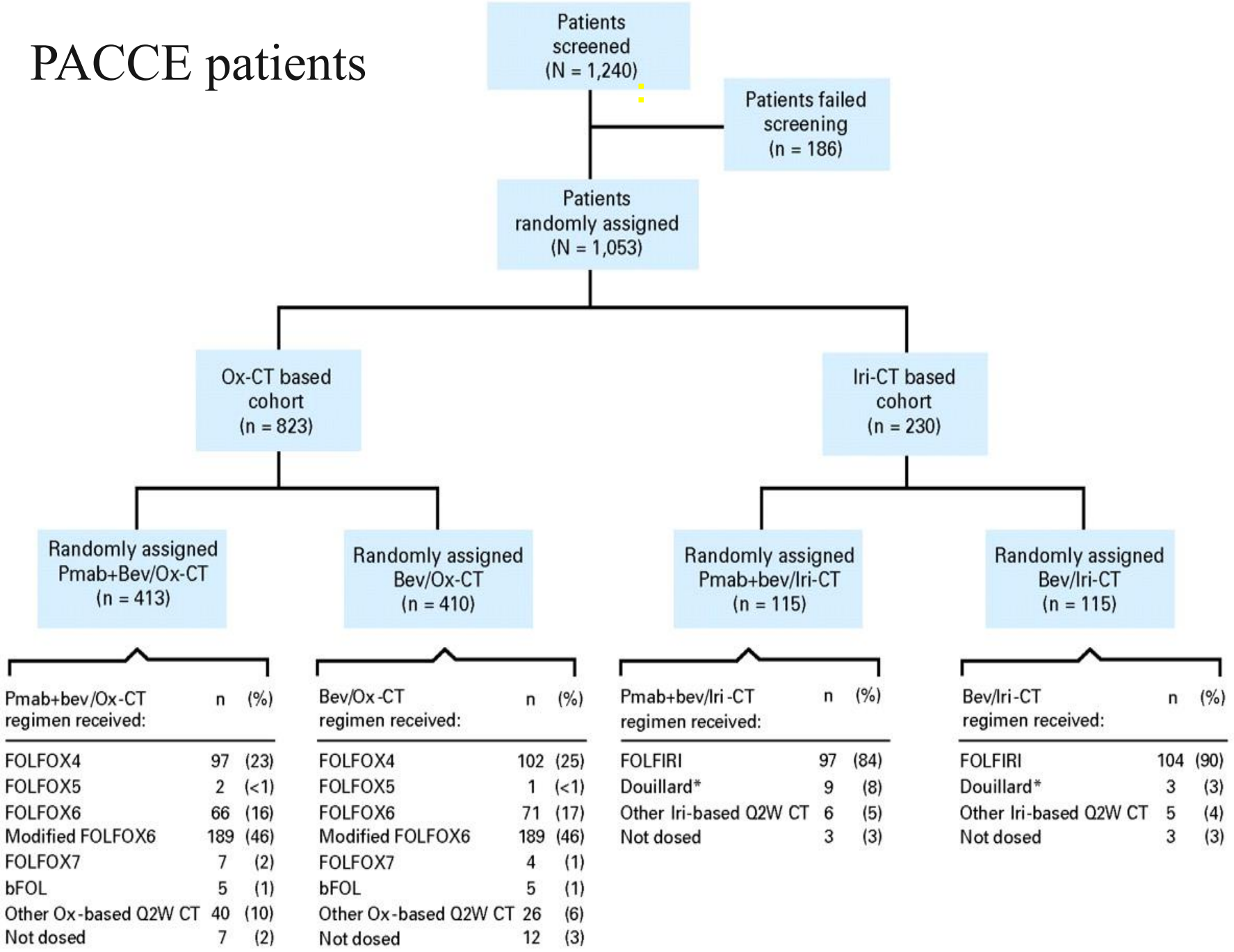
Panitumumab Advanced Colorectal Cancer Evaluation



Stratification Factors: ECOG score, prior adjuvant tx, disease site, Ox doses/Iri regimen, number of metastatic organs

Hecht et al, J Clin Oncol, 2009

PACCE patients



Pmab+bev/Ox-CT regimen received:	n	(%)
FOLFOX4	97	(23)
FOLFOX5	2	(<1)
FOLFOX6	66	(16)
Modified FOLFOX6	189	(46)
FOLFOX7	7	(2)
bFOL	5	(1)
Other Ox-based Q2W CT	40	(10)
Not dosed	7	(2)

Bev/Ox-CT regimen received:	n	(%)
FOLFOX4	102	(25)
FOLFOX5	1	(<1)
FOLFOX6	71	(17)
Modified FOLFOX6	189	(46)
FOLFOX7	4	(1)
bFOL	5	(1)
Other Ox-based Q2W CT	26	(6)
Not dosed	12	(3)

Pmab+bev/Iri-CT regimen received:	n	(%)
FOLFIRI	97	(84)
Douillard*	9	(8)
Other Iri-based Q2W CT	6	(5)
Not dosed	3	(3)

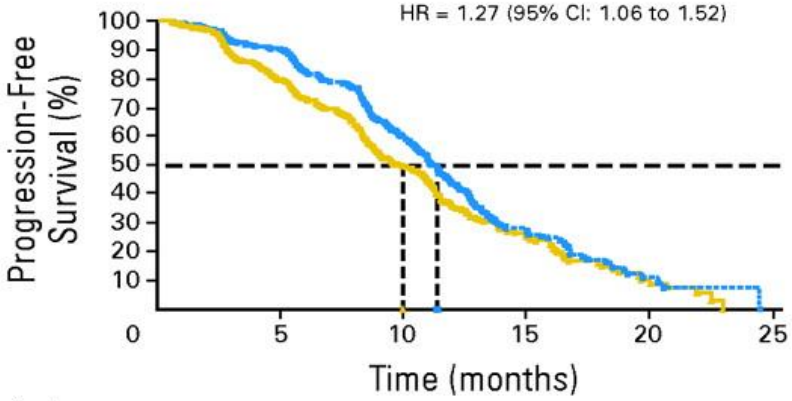
Bev/Iri-CT regimen received:	n	(%)
FOLFIRI	104	(90)
Douillard*	3	(3)
Other Iri-based Q2W CT	5	(4)
Not dosed	3	(3)

Hecht J R et al. JCO 2009;27:672-680

A

Ox-CT Cohort

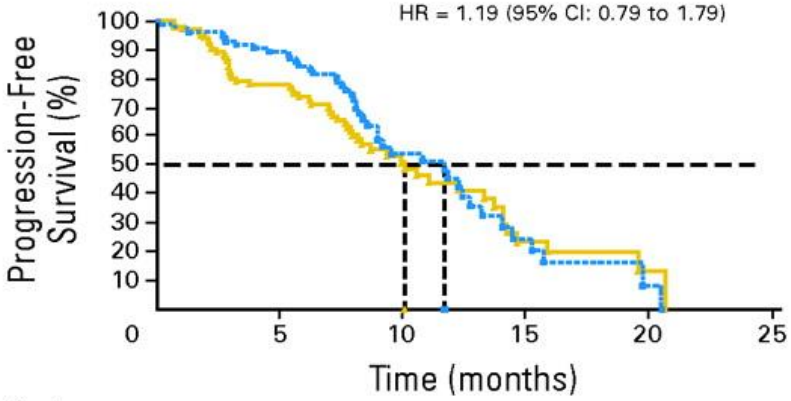
	No. of events	(%)	Median (95% CI), mos	
Pmab+bev/Ox-CT	246	(60)	10.0	(8.9 to 11.0)
Bev/Ox-CT	221	(54)	11.4	(10.5 to 11.9)



No. of patients						
Panitumumab	413	287	135	39	8	0
Censored	0	51	57	43	13	3
No Panitumumab	410	320	155	42	7	0
Censored	0	54	71	45	15	4

Iri-CT Cohort

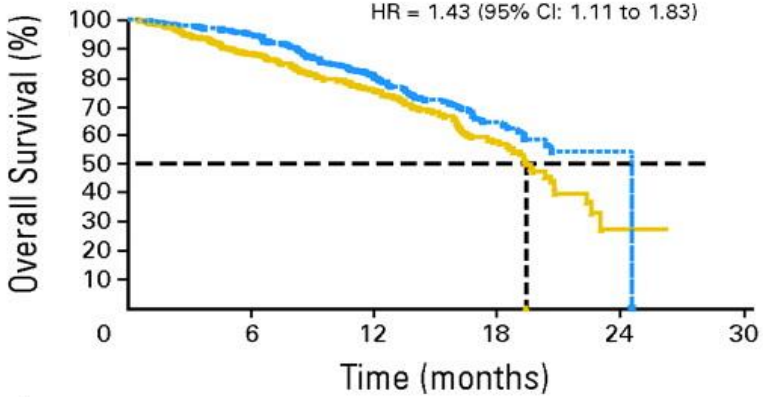
	No. of events	(%)	Median (95% CI), mos	
Pmab+bev/Iri-CT	54	(47)	10.1	(8.2 to 13.7)
Bev/Iri-CT	44	(38)	11.7	(9.0 to 13.2)



No. of patients						
Panitumumab	115	74	23	7	1	0
Censored	0	19	32	6	4	0
No Panitumumab	115	77	22	6	1	0
Censored	0	28	34	7	2	0

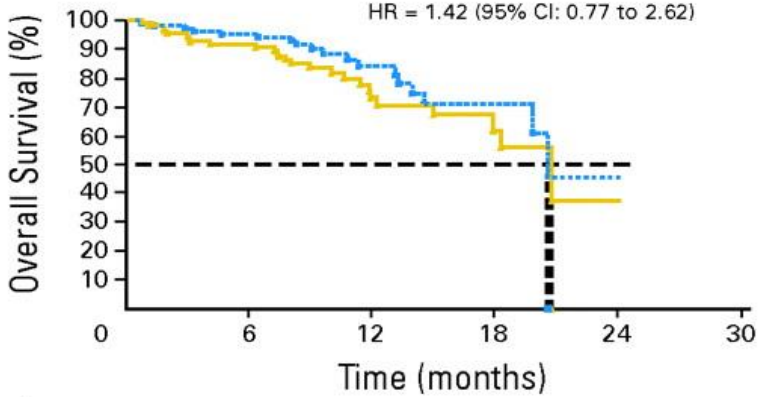
B

	No. of events	(%)	Median (95% CI), mos	
Pmab+bev/Ox-CT	143	(35)	19.4	(18.4 to 20.8)
Bev/Ox-CT	108	(26)	24.5	(20.4 to 24.5)



No. of patients						
Panitumumab	413	334	205	73	1	0
Censored	0	34	84	96	55	1
No Panitumumab	410	347	221	71	3	0
Censored	0	44	75	120	61	2

	No. of events	(%)	Median (95% CI), mos	
Pmab+bev/Iri-CT	26	(23)	20.7	(17.8 to NE)
Bev/Iri-CT	18	(16)	20.5	(19.8 to NE)



No. of patients						
Panitumumab	115	92	30	11	1	0
Censored	0	14	50	16	8	1
No Panitumumab	115	95	34	11	1	0
Censored	0	15	54	19	8	1

KRAS status and outcomes

Outcome	Ox-CT (n = 664)					
	Wild-Type *KRAS*, n = 404 (61%)			Mutant *KRAS*, n = 260 (39%)		
	Panitumumab (n = 201)	Control (n = 203)	HR	Panitumumab (n = 135)	Control (n = 125)	HR
Response rate, %*	50	56	n/a	47	44	n/a
PFS*						
Median, months	9.8	11.5	1.36	10.4	11.0	1.25
95% CI	8.4 to 11.3	10.6 to 12.3	1.04 to 1.77	9.1 to 11.3	9.9 to 12.8	0.91 to 1.71
OS						
Median, months	**20.7**	**24.5**	1.89	19.3	19.3	1.02
95% CI			1.30 to 2.75	16.2 to 23.0	16.7 to NE	0.67 to 1.54

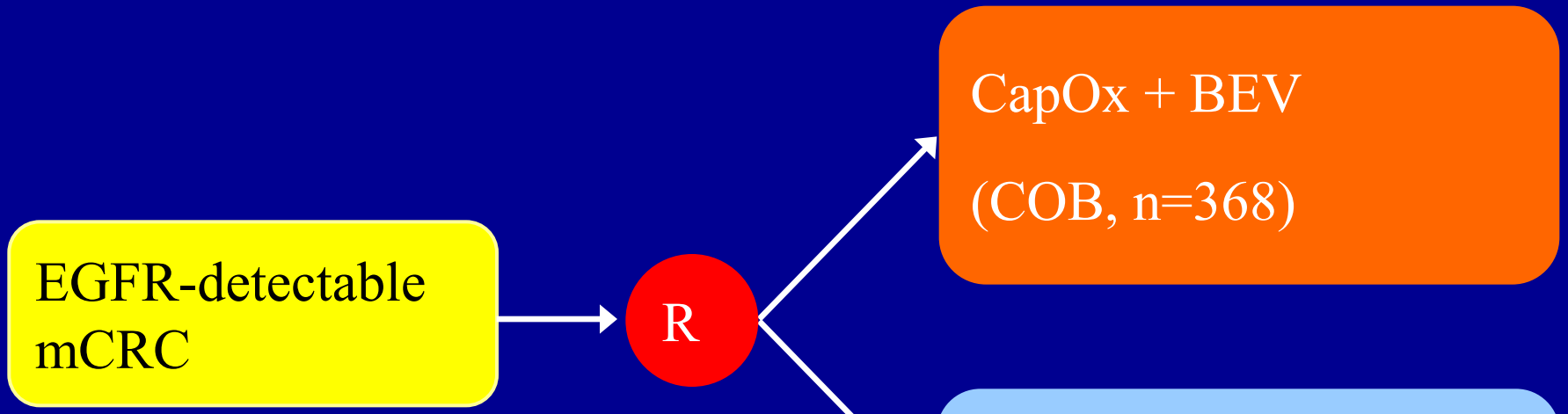
Outcome	Iri-CT (n = 201)					
	Wild-Type *KRAS*, n = 115 (57%)			Mutant *KRAS*, n = 86 (43%)		
	Panitumumab (n = 57)	Control (n = 58)	HR	Panitumumab (n = 47)	Control (n = 39)	HR
Response rate, %*	54	48	n/a	30	38	n/a
PFS*						
Median, months	10.0	12.5	1.50	8.3	11.9	1.19
95% CI	8.2 to 14.1	9.0 to 15.7	0.82 to 2.76	6.3 to 14.3	8.1 to 13.2	0.65 to 2.21
OS						
Median, months	NE	19.8	1.28	17.8	20.5	2.14
95% CI	NE	19.8 to NE	0.50 to 3.25	11.9 to NE	20.5 to NE	0.82 to 5.59

Abbreviations: Ox-CT, oxaliplatin-based chemotherapy; HR, hazard ratio; PFS, progression-free survival; n/a, not applicable; NE, not estimable; OS, overall survival; Iri-CT, irinotecan-based chemotherapy.

*Central review.

Hecht et al, JCO, 2009

CAIRO2: Study design



Primary endpoint

- Progression-free survival

Secondary endpoints

- RR
- OS time
- Toxicity
- Translational research

Oxaliplatin stopped after 6 cycles (18 weeks = 4.5 months)

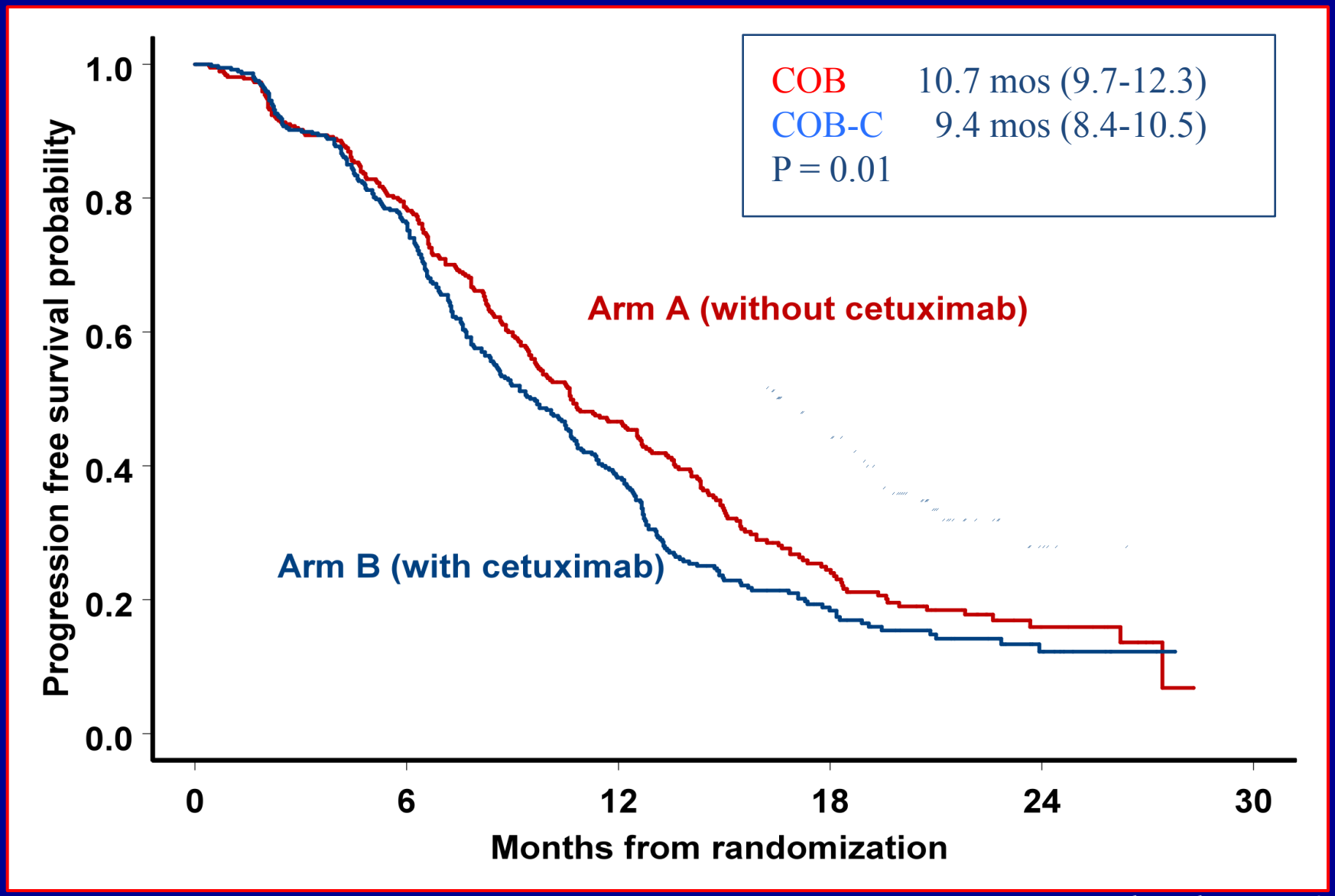
Tol et al. NEJM 2009

CAIRO2 – Summary Efficacy results

	COB n = 368	COB-C n = 368	P-value
Median PFS (mos) (HR; 95% CI)	10.7 (9.7-12.3)	9.4 (8.4-10.5)	**0.01**
Median OS (mos) (HR; 95% CI)	20.3 (17.8-24.7)	19.4 (17.5-21.4)	0.16
Response rate (CR + PR)	50%	52.7%	0.49
Disease control rate (CR + PR + SD)	94%	94.6%	0.72

Tol et al. NEJM 2009

CAIRO2 – Progression-free survival



Tol et al. NEJM 2009

CAIRO2 - KRAS genotyping (n=510)

	KRAS wild-type n = 314 (61%)	*KRAS* mutated n = 196 (39%)	p value
Median PFS (months)			
COB	10.6	12.5	0.80
COB-C	10.5	8.1	0.04
p value	0.30	0.003	
Median OS (months)			
COB	22.4	24.9	0.82
COB-C	21.8	17.2	0.06
p value	0.64	0.03	

Tol et al. NEJM 2009

WHAT CAN ONE CONCLUDE?

- FOLFOX MOST POPULAR BACKBONE
- HARD TO KNOW IF ONE IS WORSE THAN THE OTHER
- BIOLOGICS MAY NOT REQUIRE CYTOTOXICS