

Systemic treatment in colorectal cancer

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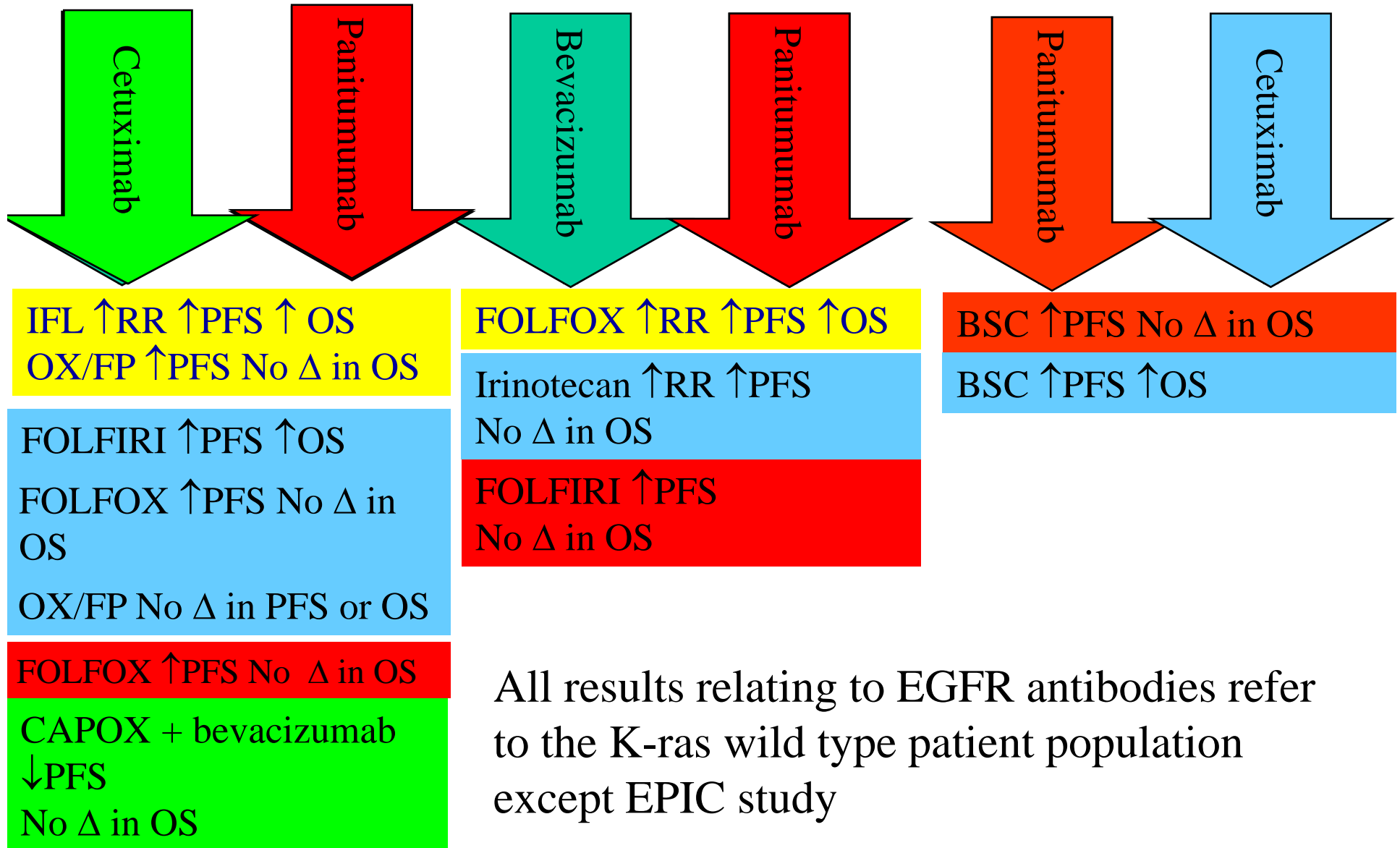


Molecular targeting in CRC 2010

First line

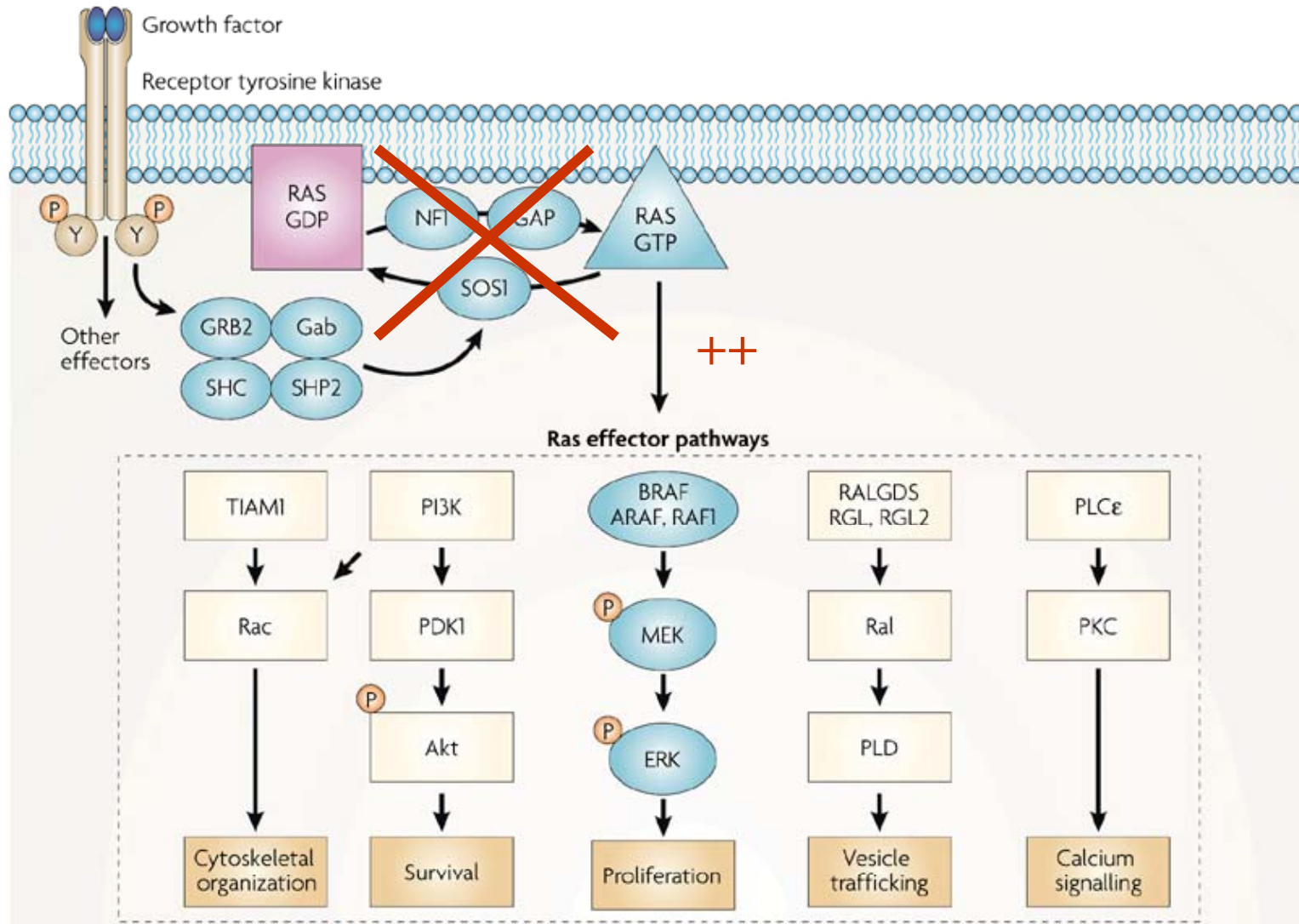
Second line

Last line



All results relating to EGFR antibodies refer to the K-ras wild type patient population except EPIC study

K-ras mutation in CRC



Distribution of mutations (COIN)

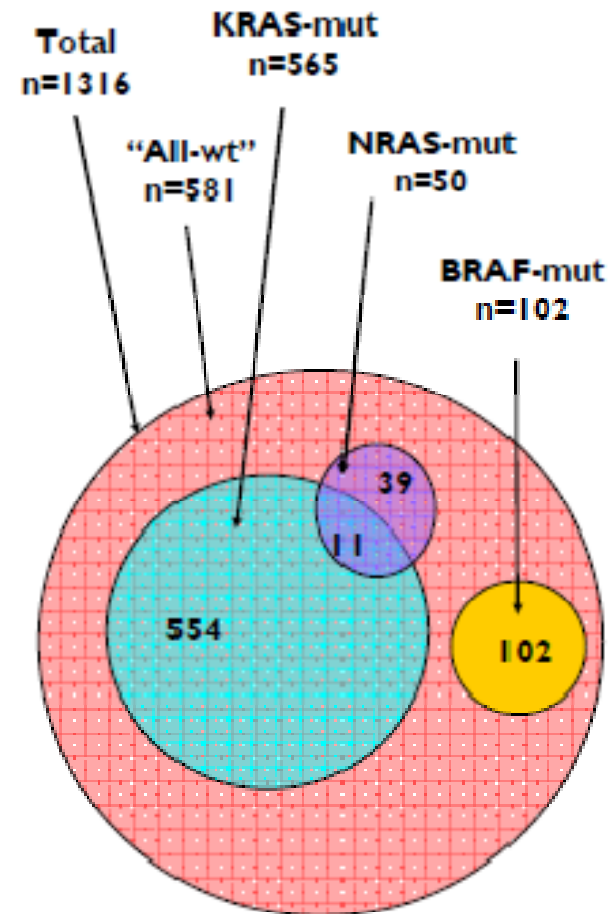
Sample Collection

Patients consented to collection of formalin fixed paraffin embedded (FFPE) tumour block collection for analysis of EGFR and in 91% for further unspecified research. Mutations were analysed by pyrosequencing and by Sequenom (Mass spec array) with 99% concordance.

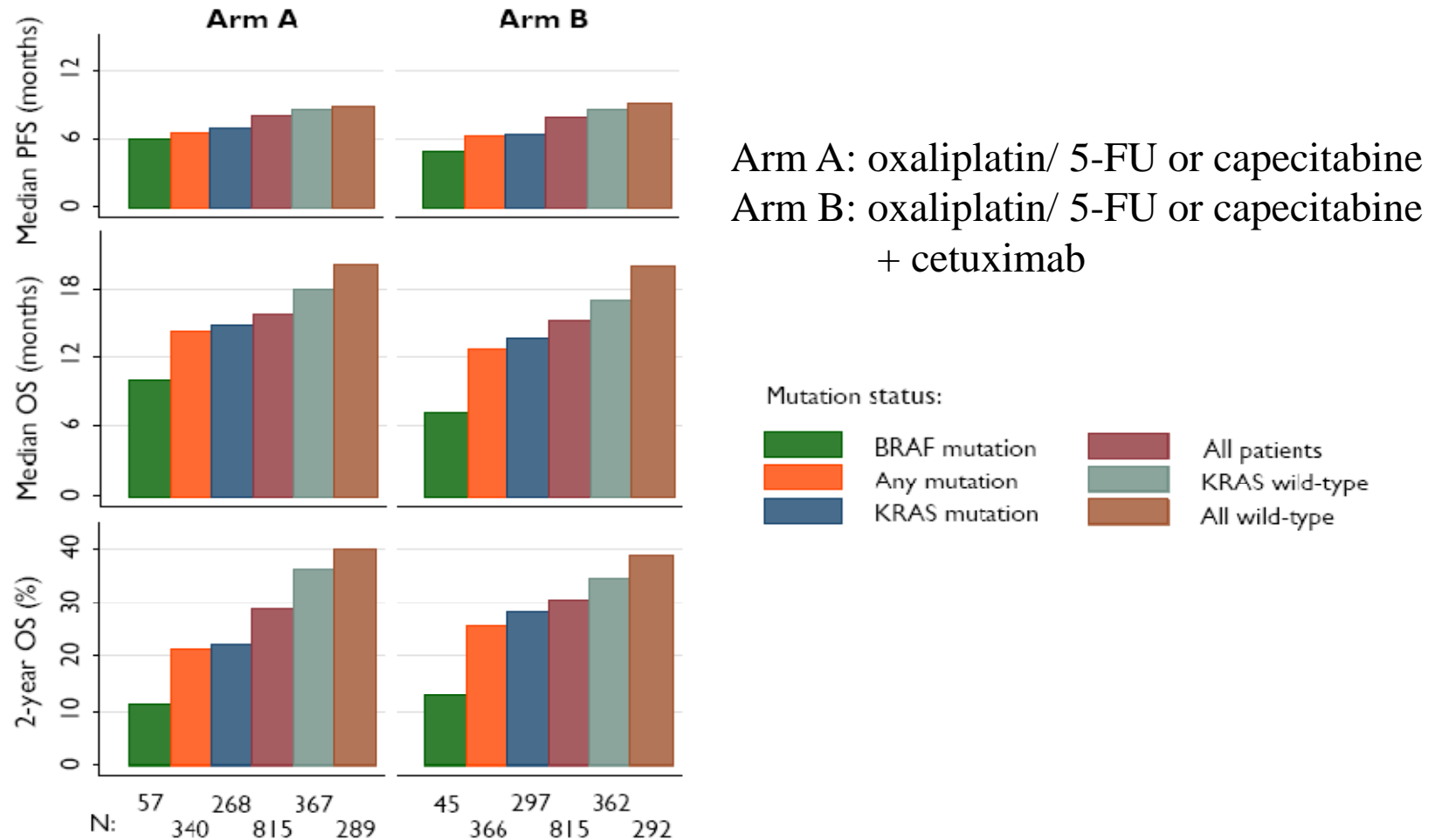
Population	N	Arm A	Arm B
ITT	1630	815	815
Assessed for mutations	1316	648	668
of which:			
- KRAS mutation	565 (43%)	268	297
- NRAS mutation	50 (4%)	18	32
- BRAF mutation	102 (8%)	57	45
KRAS wt	729 (55%)	367	306
KRAS/NRAS/BRAF-wt "All wild-type"	581 (44%)	289	292

Note on PIK3CA

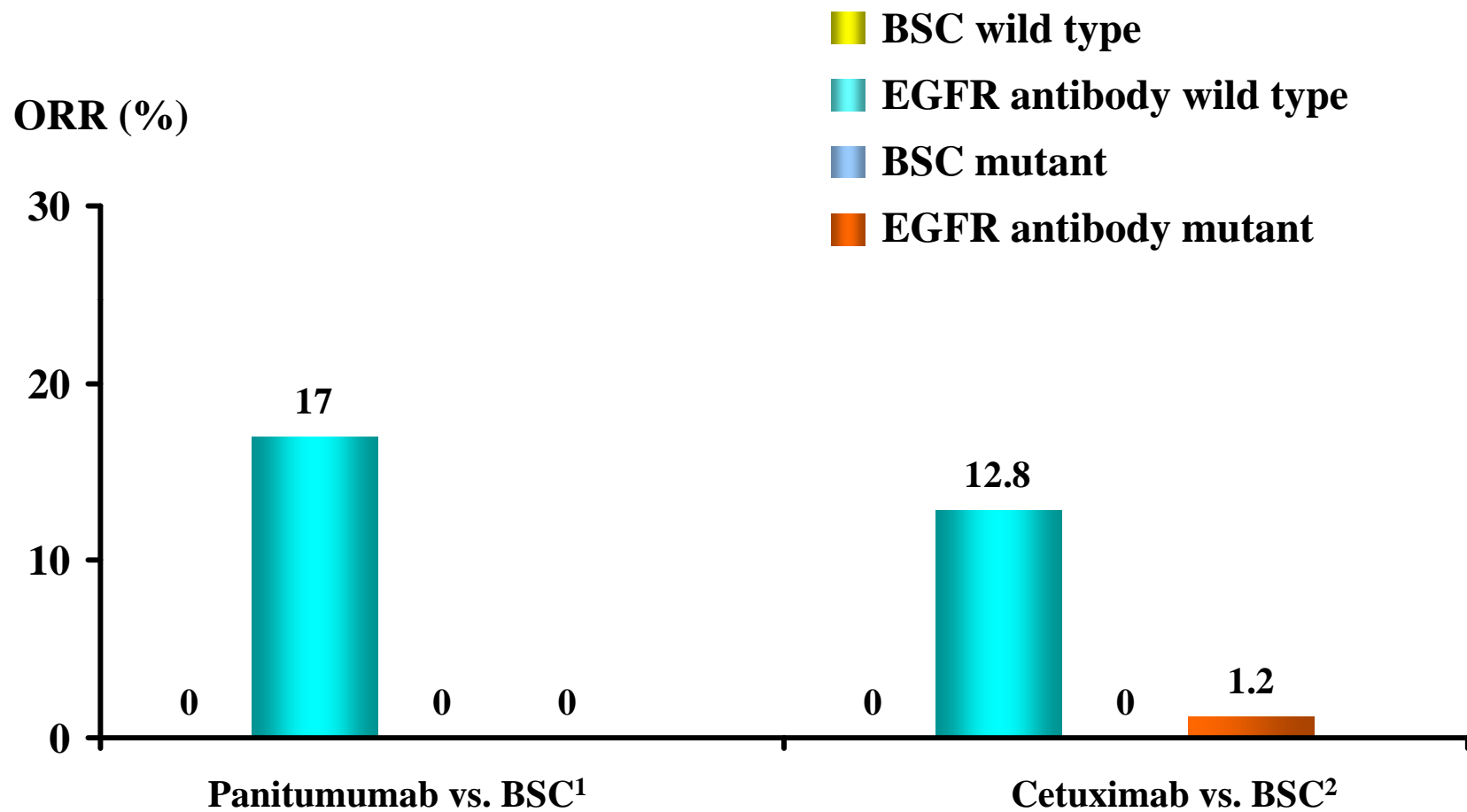
Although not included in the current analysis, samples were also tested for PIK3CA. Mutations were detected in 156 (12%) patients. Of these, 102 also had a mutation in one of the other genes tested: 86 KRAS; 6 NRAS; 3 both; 7 BRAF.



Prognostic effect of mutational status (COIN)



K-ras status and response rate



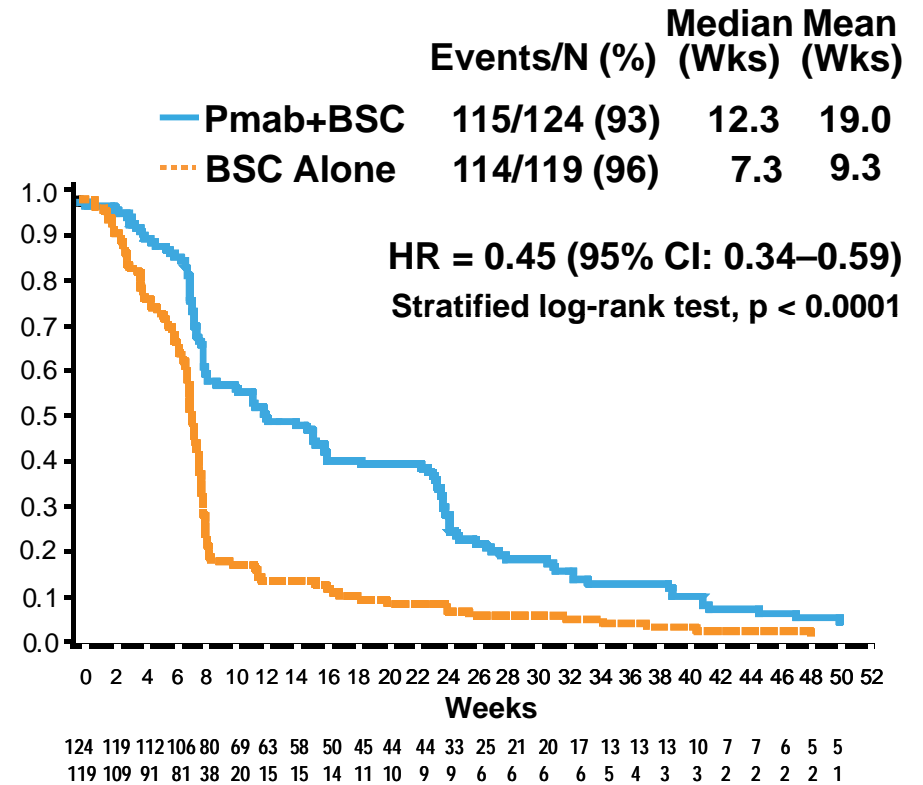
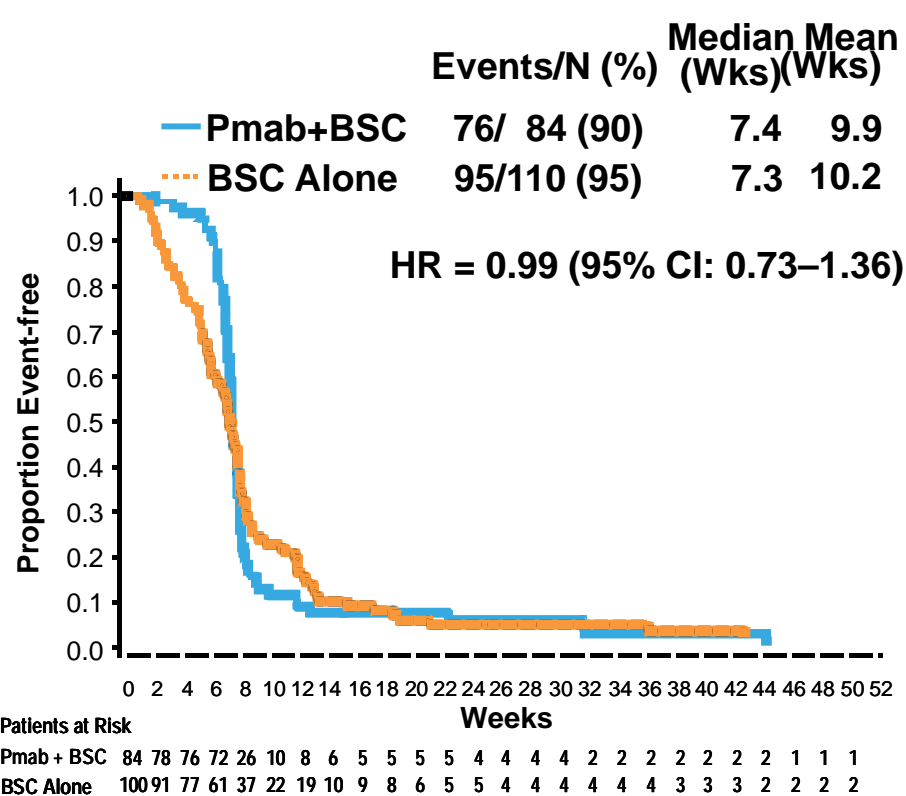
¹Amado et al J Clin Oncol 2008

²Karapetis et al New Eng J Med 2008

PFS by *KRAS* Status and Treatment

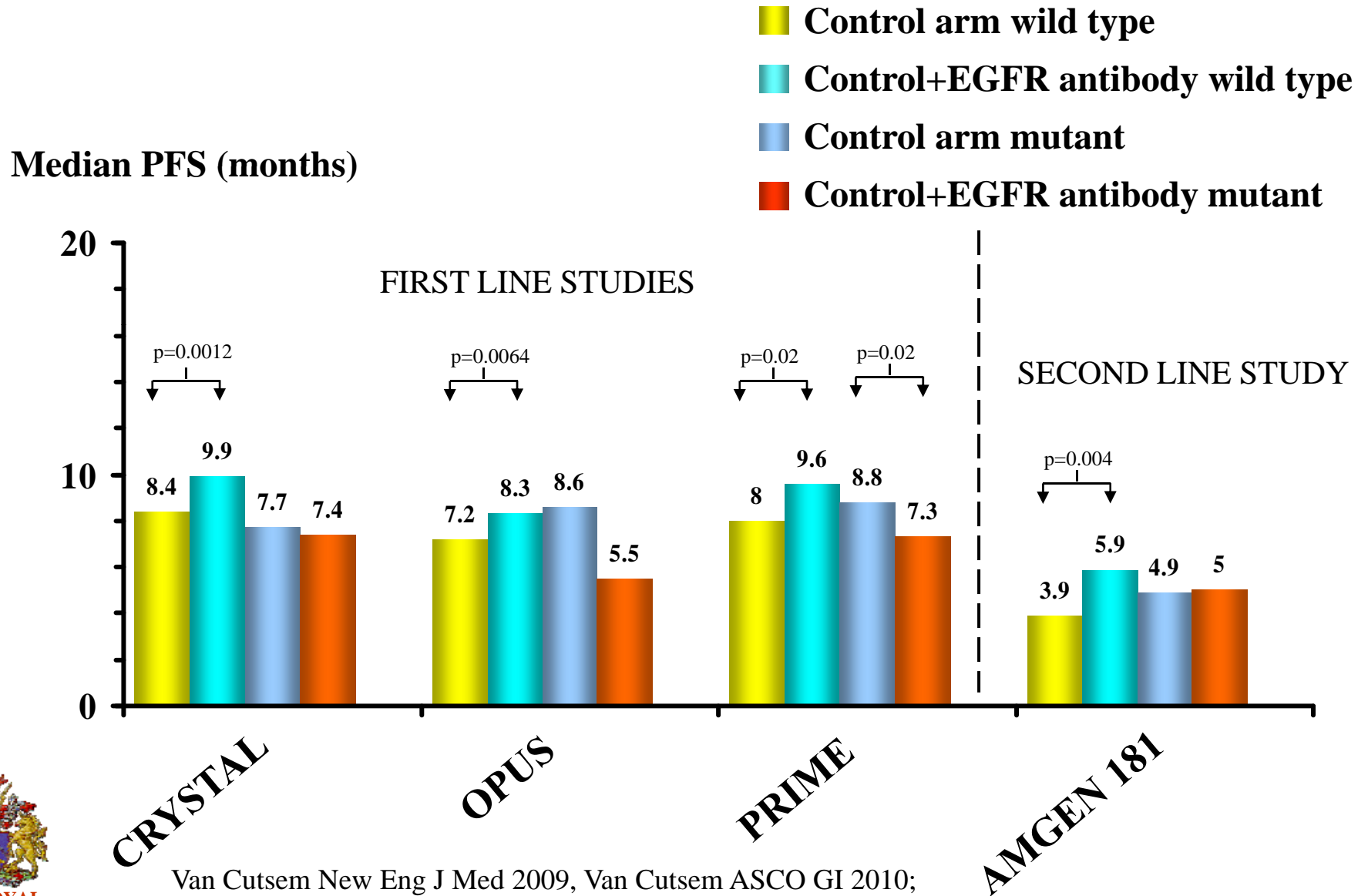
Mutant *KRAS*

WT *KRAS*



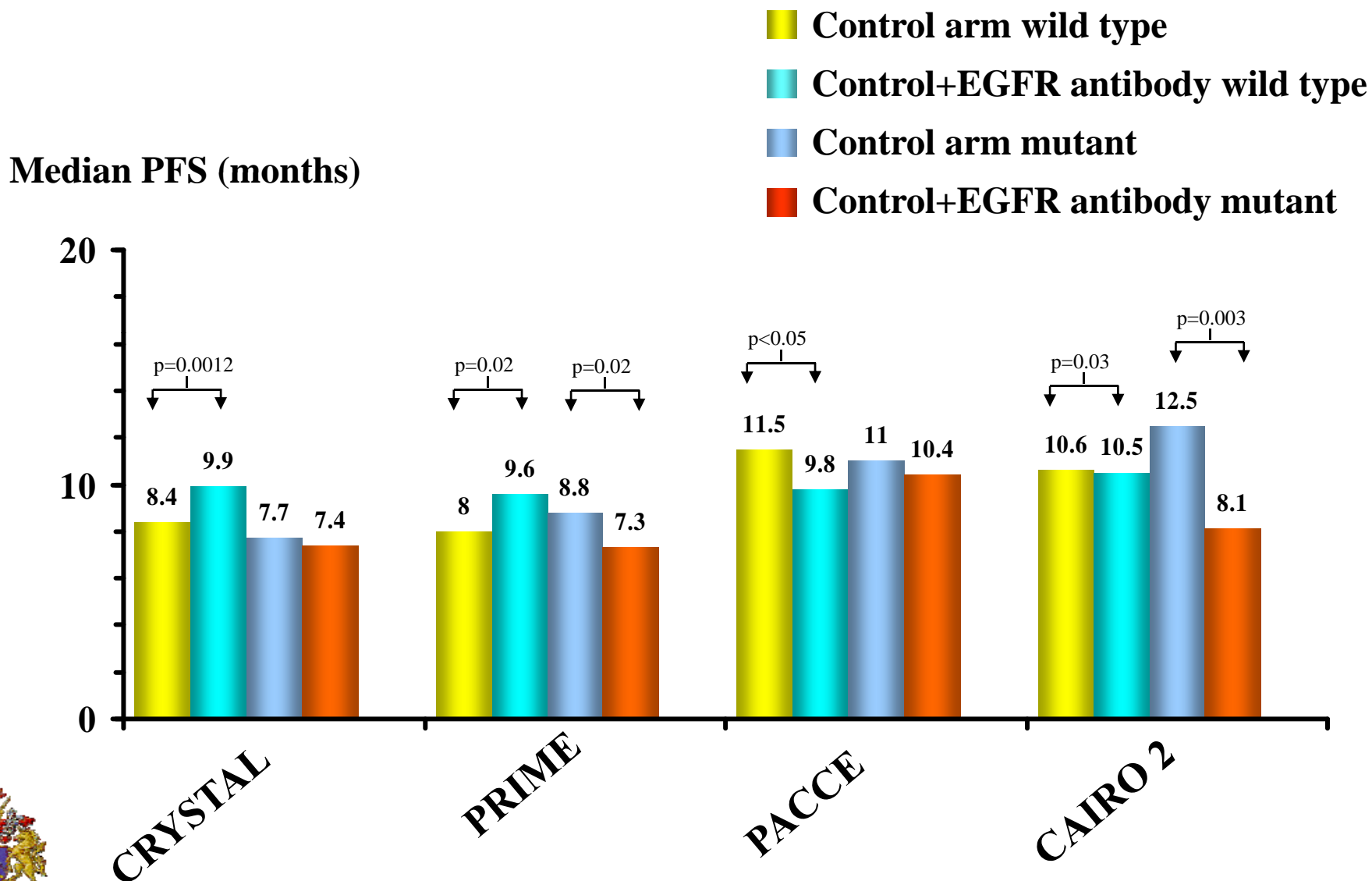
- PFS was significantly greater for panitumumab treatment compared with BSC in the WT *KRAS* group (stratified log-rank test p < 0.0001).

K-ras status and efficacy (PFS)

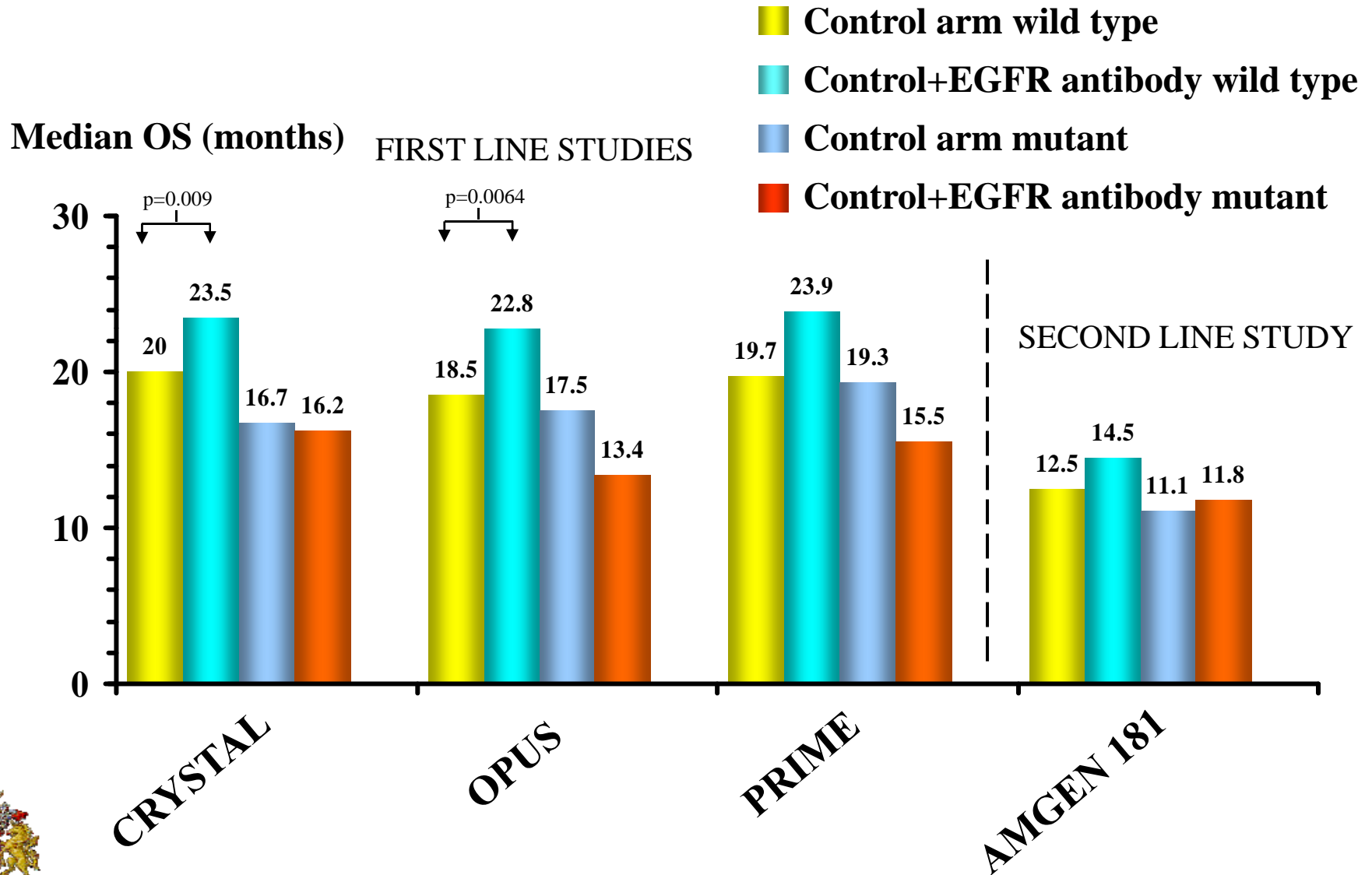


Van Cutsem New Eng J Med 2009, Van Cutsem ASCO GI 2010;
Bokemeyer et al J Clin Oncol 2009; Siena et al ASCO GI 2010; Peeters et al ASCO GI 2010

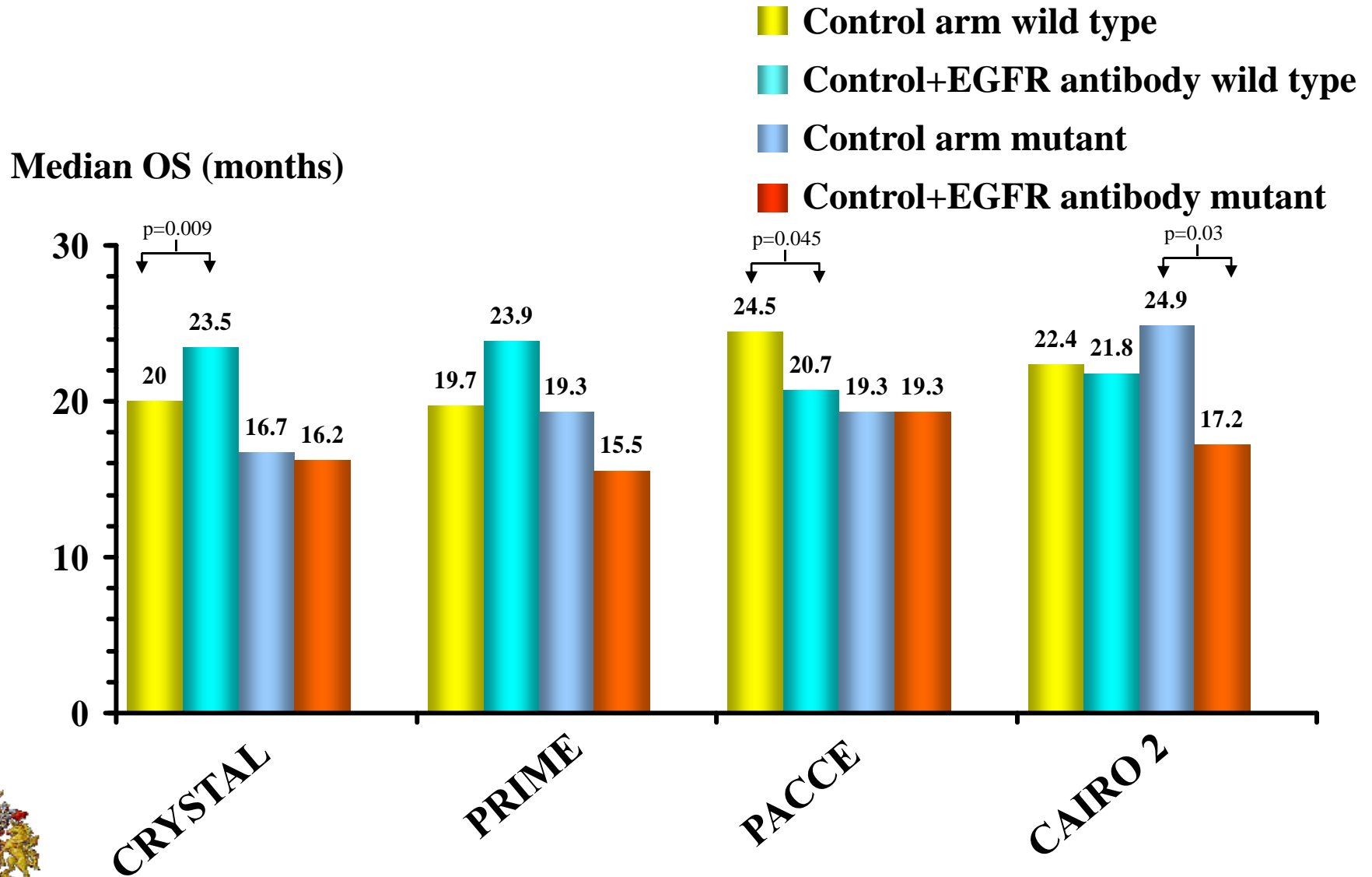
K-ras status and efficacy (PFS)



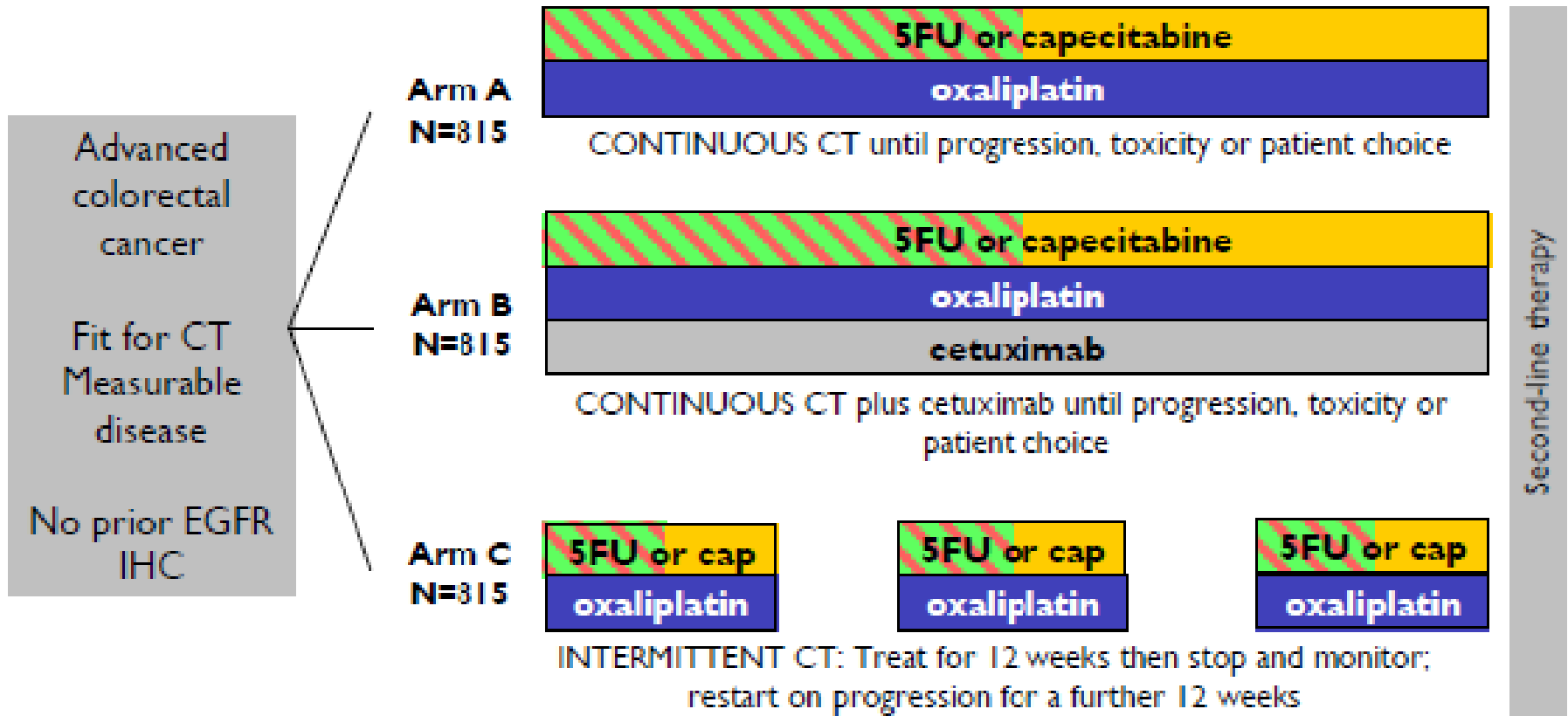
K-ras status and efficacy (OS)



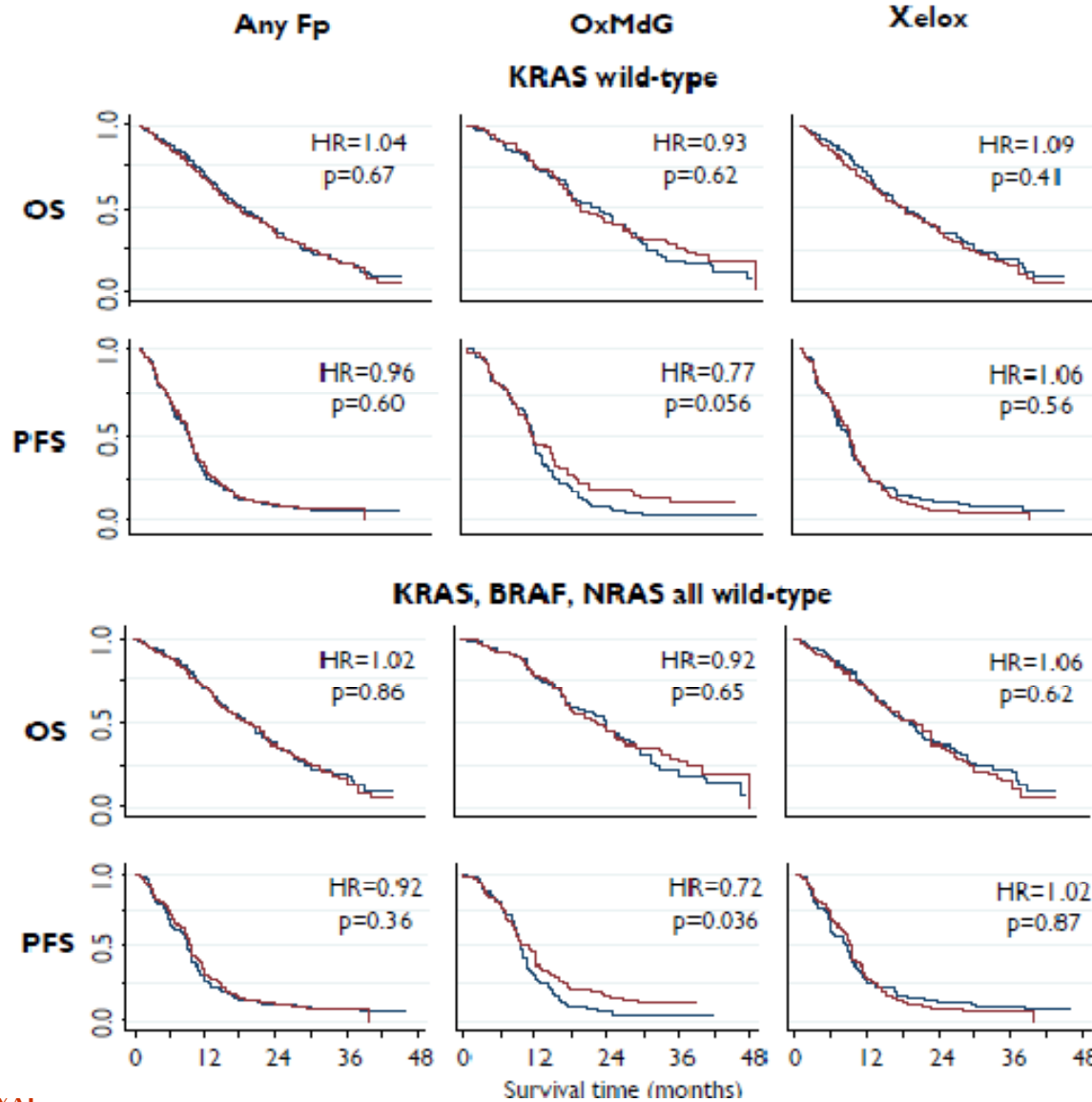
K-ras status and efficacy (OS)



MRC COIN trial



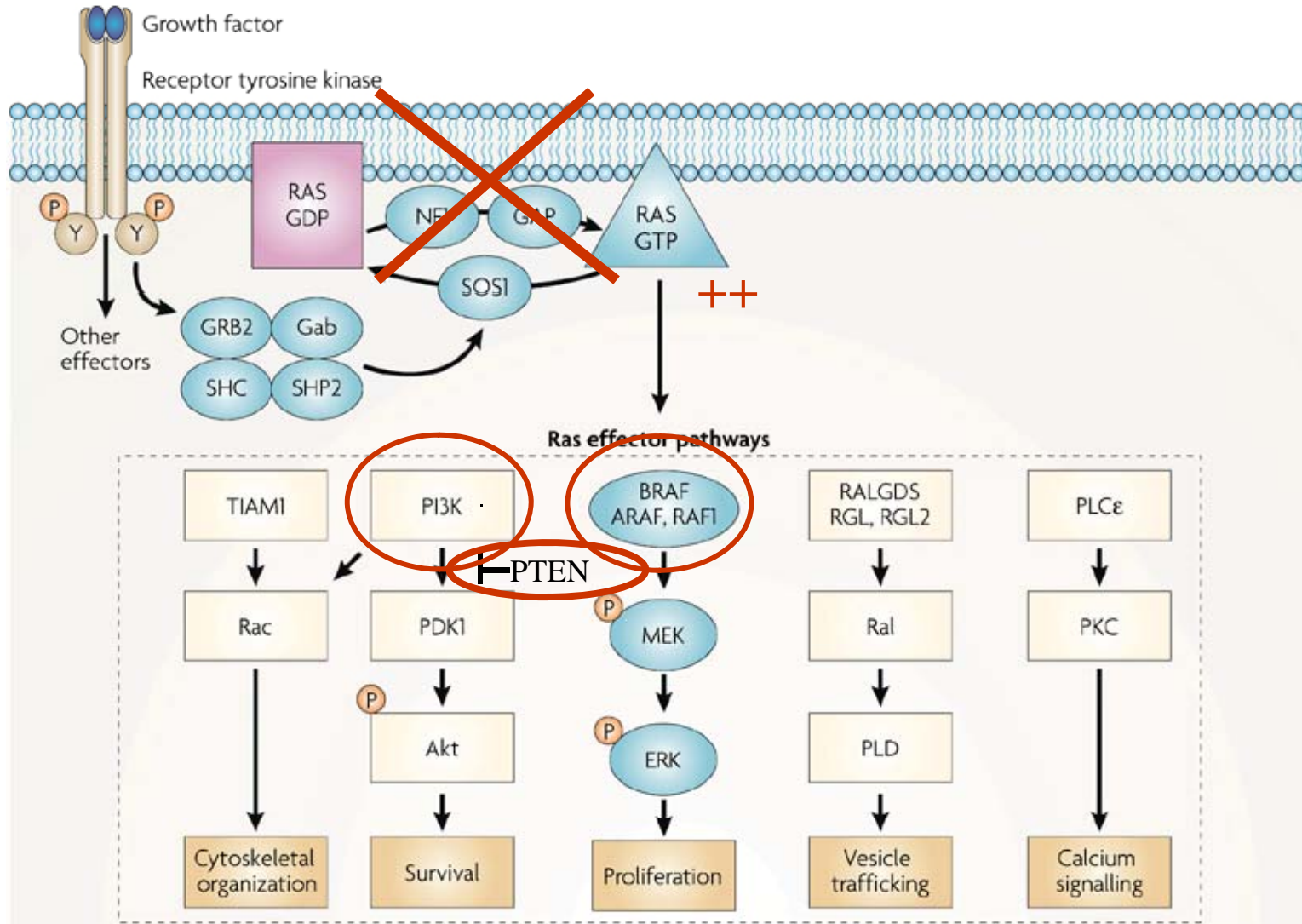
COIN survival outcomes



	OX/FP	OX/FP +C
N	367	362
Median OS (months)		
K-ras wild	17.9	17.0
K-ras mut	14.8	13.6
All wild	20.1	19.9
Any mut	14.4	12.7
Median PFS (months)		
K-ras wild	8.6	8.6
K-ras mut	6.9	6.5
All wild	8.8	9.2
Any mut	6.6	6.3



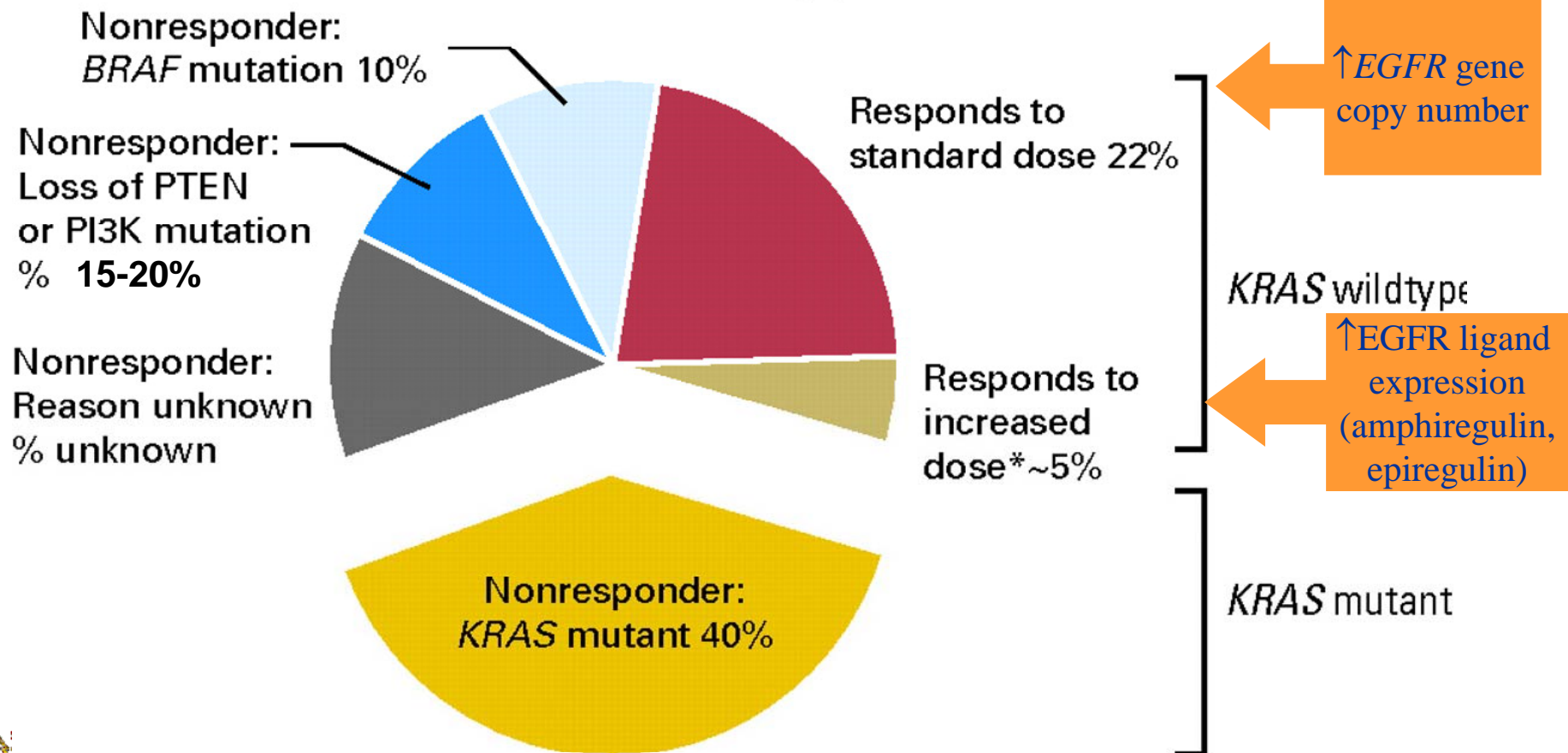
Molecular events associated with resistance to EGFR antibodies



Relationship between molecular events and response to EGFR antibodies

Possible -ve predictors

Possible +ve predictors

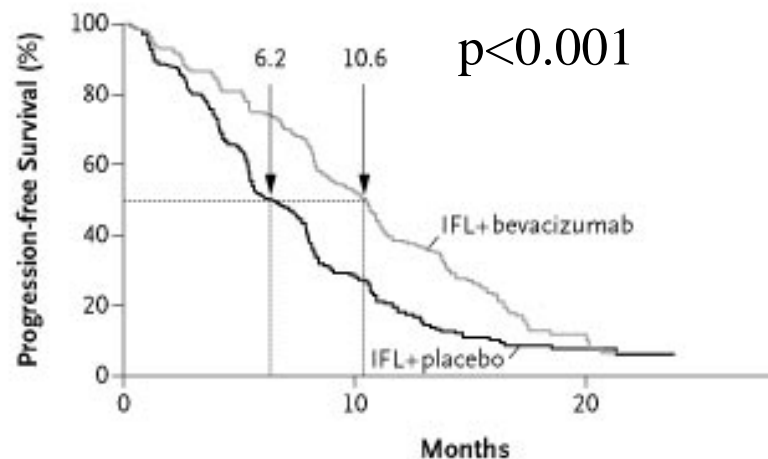


B-raf mutation: are they truly resistant to EGFR antibodies?

N	CRYSTAL		OPUS		POOLED	
	FOLFIRI	FOLFIRI+C	FOLFOX	FOLFOX+C	Control	Control +C
59			11		70	
Median OS (months)	10.3	14.1	4.4	20.7	9.9	14.1
HR (95% CI)	0.91 (0.51, 1.62)		0.10		0.62 (0.36, 1.06)	
p-value	0.74		0.02		0.07	
Median PFS (months)	5.6	8.0	1.7	7.1	3.7	7.1
HR (95% CI)	0.93 (0.43, 2.1)		0.45		0.67 (0.34, 1.29)	
p-value	0.87		0.33		0.23	

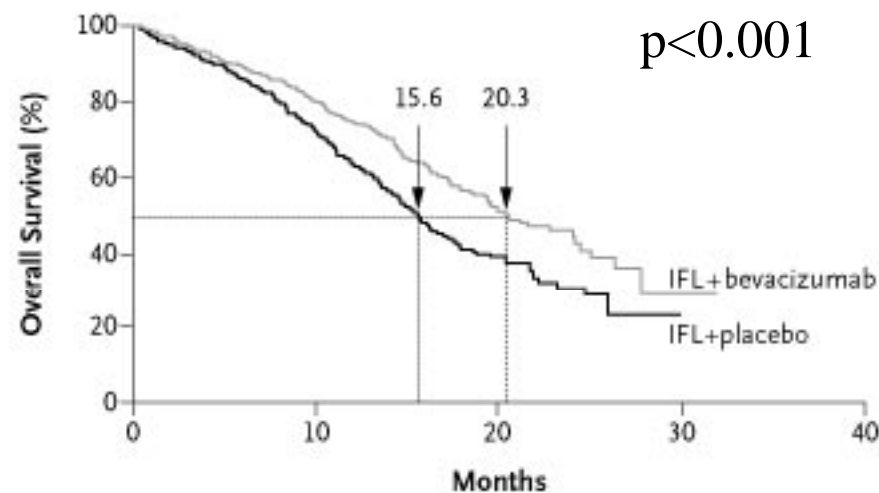
AVF2107: Pivotal IFL ± bevacizumab

Progression free survival



No. at Risk		0	6.2	10.6	15	20
IFL+bevacizumab	402	269	143	36	6	0
IFL+placebo	411	225	73	17	8	0

Overall survival



No. at Risk		0	6.2	10.6	15.6	20.3	25	30	40
IFL+bevacizumab	402	362	320	178	73	20	1	0	0
IFL+placebo	411	363	292	139	51	12	0	0	0



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Hurwitz et al New Eng J Med 2004

Clinical efficacy with bevacizumab in colorectal cancer

Study	Treatment	No. of patients	Response rates	Overall survival
FIRST LINE				
Hurwitz et al	Irinotecan/FU	411	34.8%	15.6 months
	Irinotecan/FU/BEV	402	44.8%	20.3 months
	FU/BEV	110	40.0%	18.3 months
Kabbinavar et al	FU	105	15.2%	12.9 months
	FU/BEV	104	26.0%	16.6 months
Kabbinavar et al	FU or Irinotecan/FU	241	24.5%	14.6 months
	FU/BEV	249	34.1%	17.9 months
SECOND LINE				
Giantonio et al	FOLFOX	290	9.2%	10.8 months
	FOLFOX/BEV	289	21.8%	12.9 months
	BEV	243	3%	10.2 months



NO16966 study design

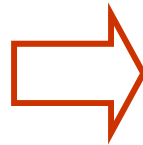
Recruitment
June 2003 – May
2004

CAPOX
N=317

FOLFOX4
N=317

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

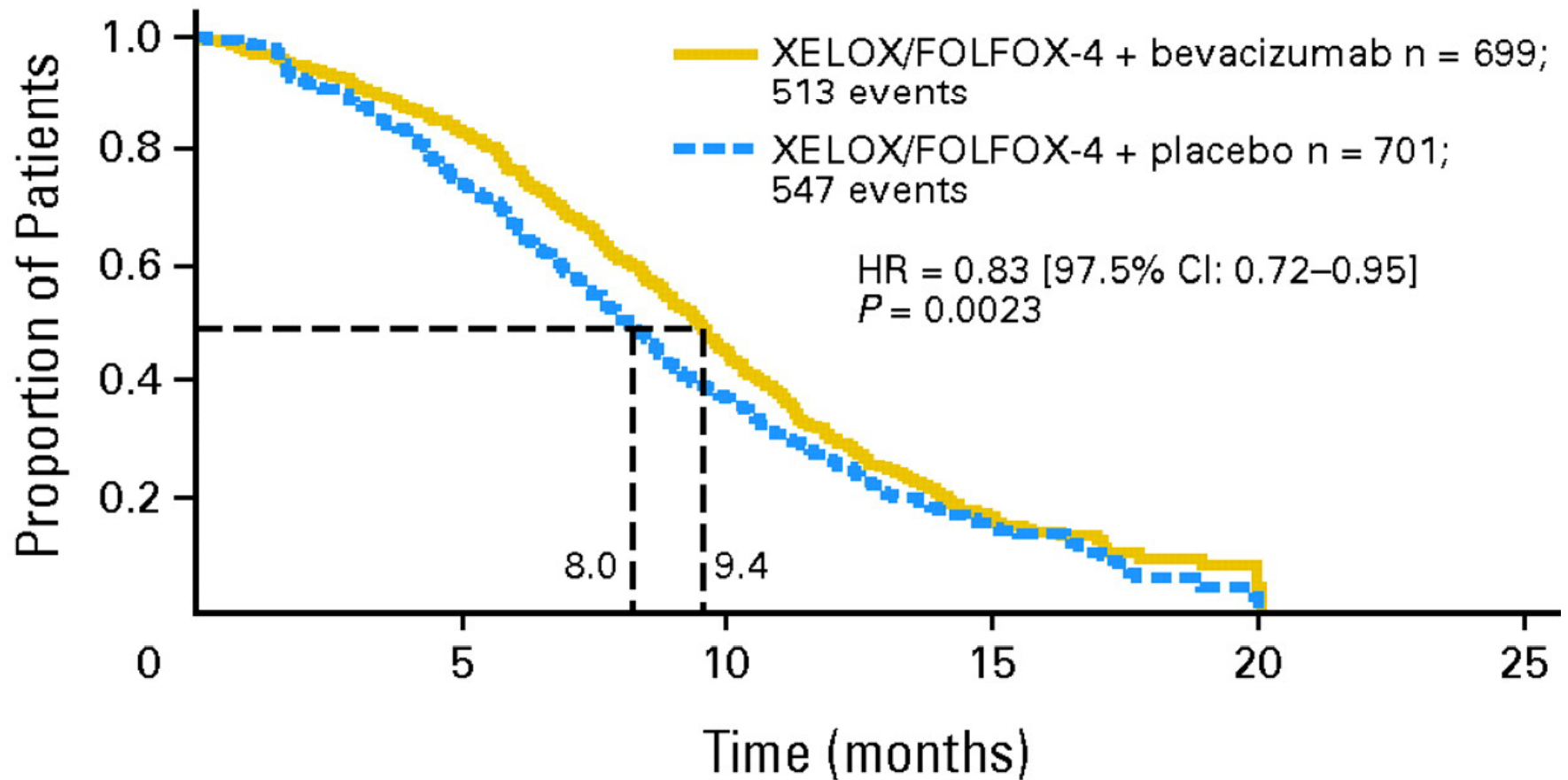
Recruitment
Feb 2004 – Feb
2005



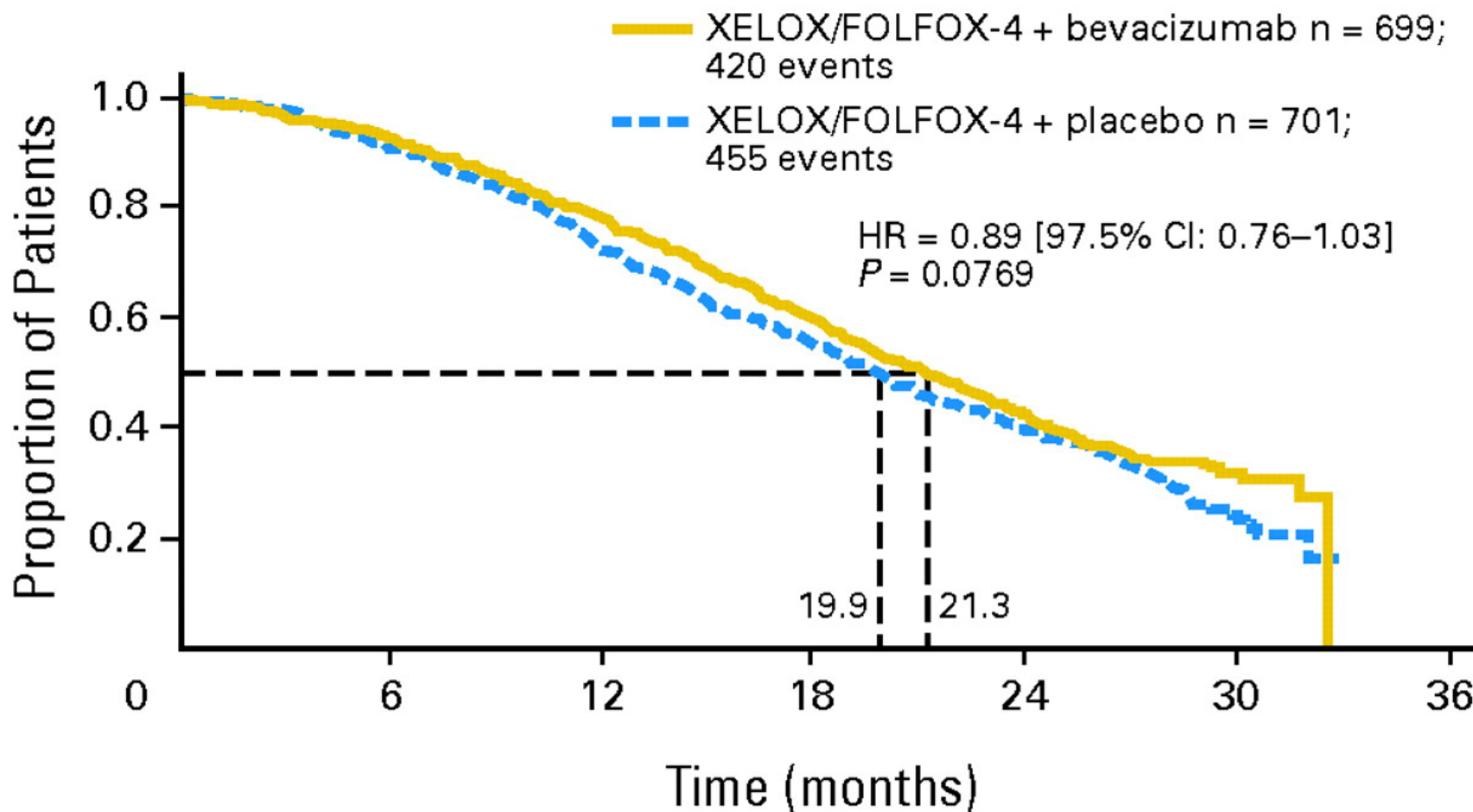
CAPOX + placebo N=350	CAPOX + bevacizumab N=350
FOLFOX4 + placebo N=351	FOLFOX4 + bevacizumab N=349

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

NO16966 Progression free survival



NO16966 Overall survival



XELOX-1: Response Rate

	Chemo+ placebo	Chemo + Bev	FOLFOX+ placebo	FOLFOX + Bev	XELOX+ placebo	XELOX + Bev
Investigator report	49%	47%	50%	47%	48%	46%
	p = 0.90		p = 0.88		p = 0.91	
IRC data	38%	38%	36%	38%	39%	37%
	p = 0.99		p = 0.49		p = 0.48	



How long should we continue bevacizumab for?



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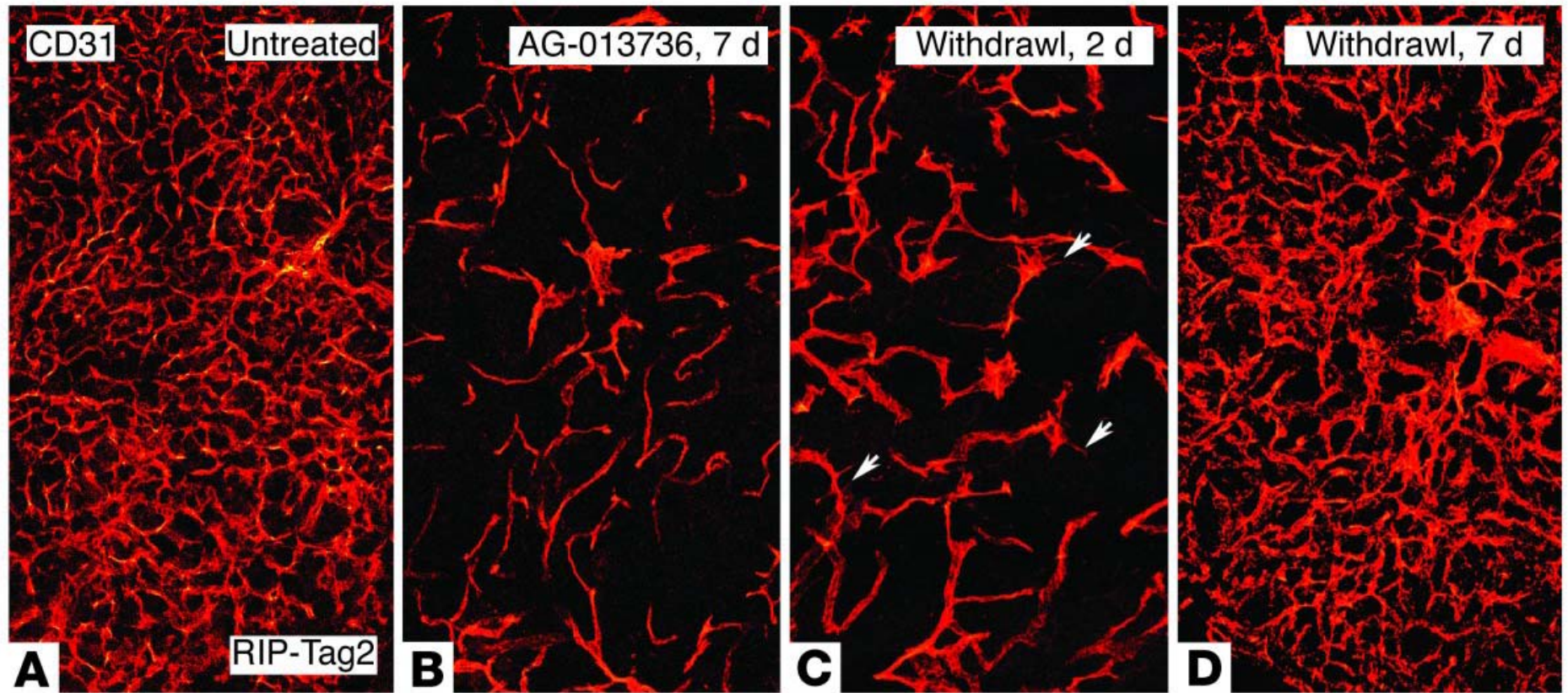
Patients stopping treatment due to non-progression events*

Study		n	% of patients stopping treatment due to non- progression events
Saltz et al	Ox/Fluro/bev	699	71%
N016966	Ox/Fluro	701	53%
Reinacher-Schick et al	CAPOX/bev	127	60%
German AIO	CAPIRI/bev	120	68%
Hecht et al	Ox/Fluro/bev	410	71%
PACCE	Ox/Fluro/bev/ panitumumab	413	65%
Tol et al	CAPOX/bev	378	46%
CAIRO 2	CAPOX/bev/ cetuximab	377	51%

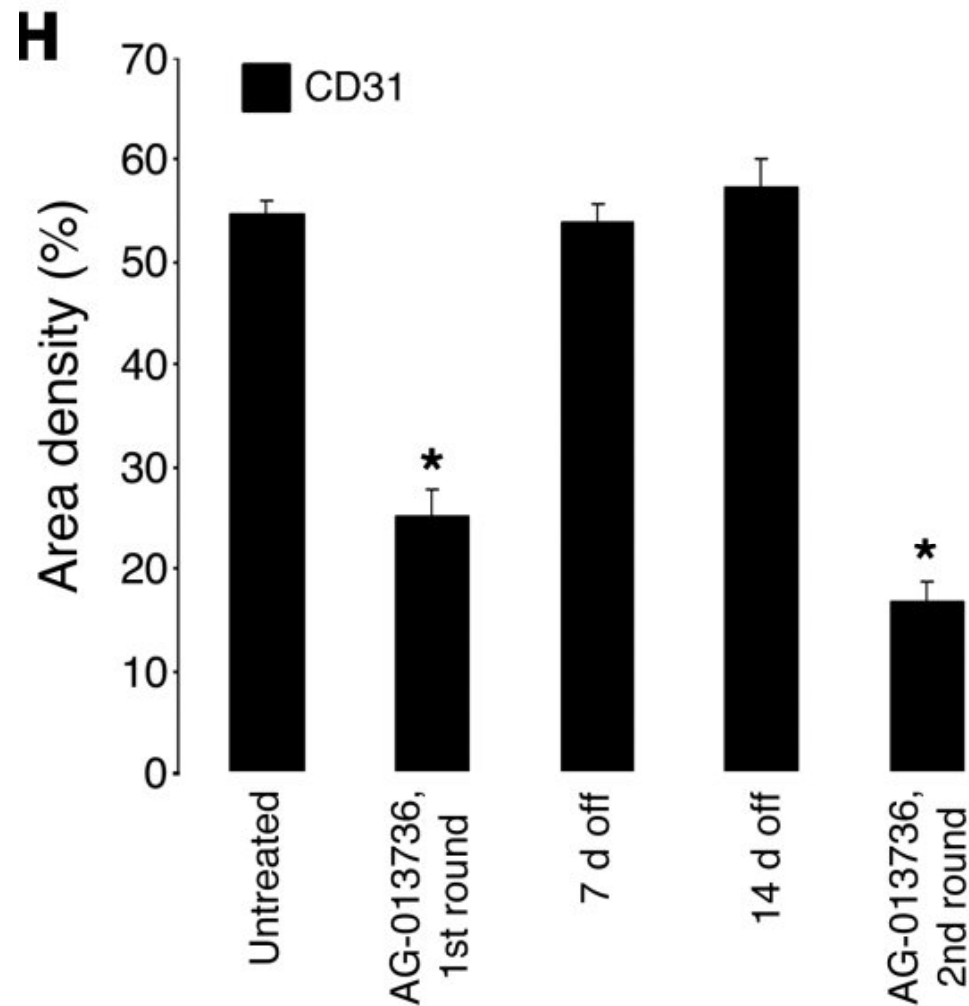


*Non-progression events included adverse events, death, violation of eligibility criteria, other protocol violation, refusal of treatment, failure to return and others

Early withdrawal of anti-VEGF therapy results in rapid vessel regrowth

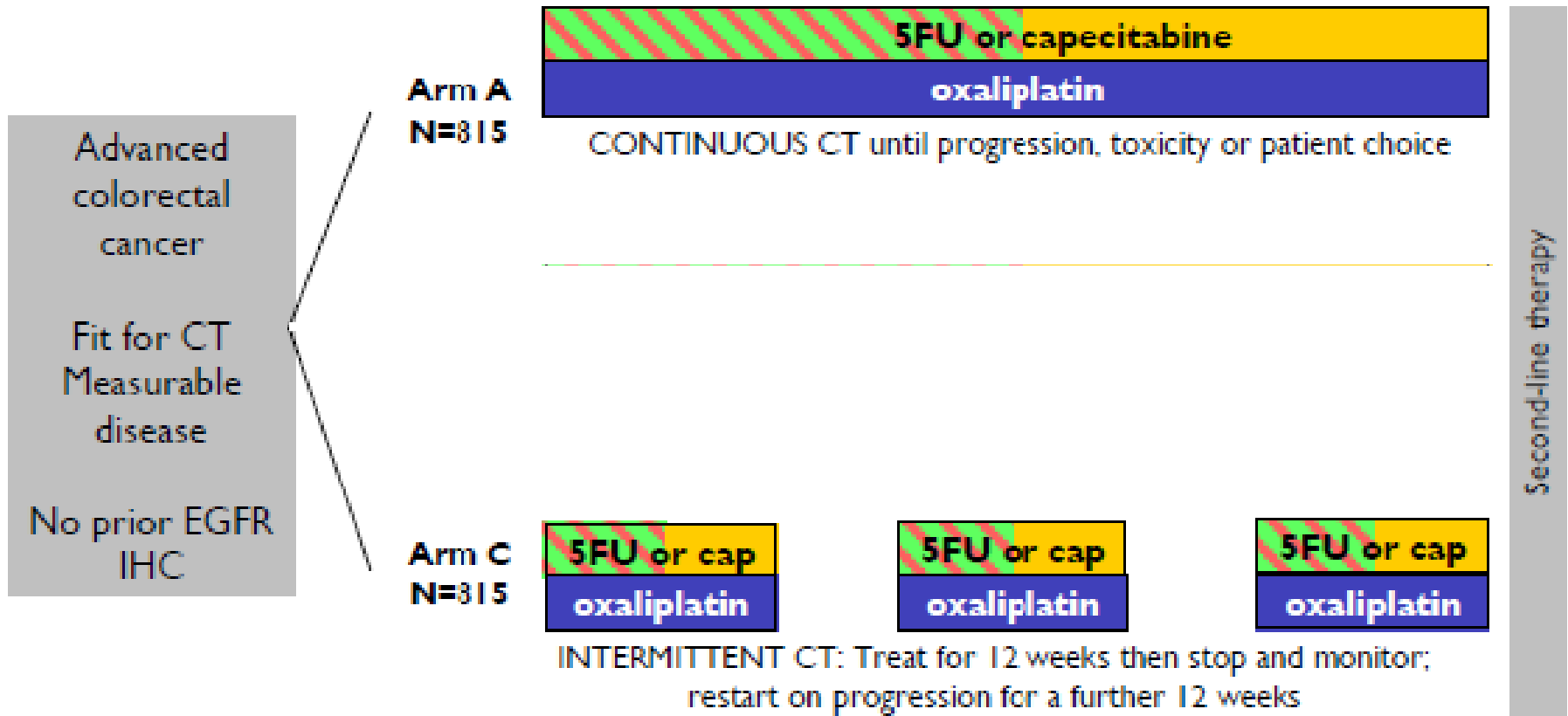


Much of the regrown tumor vasculature is still VEGF dependent



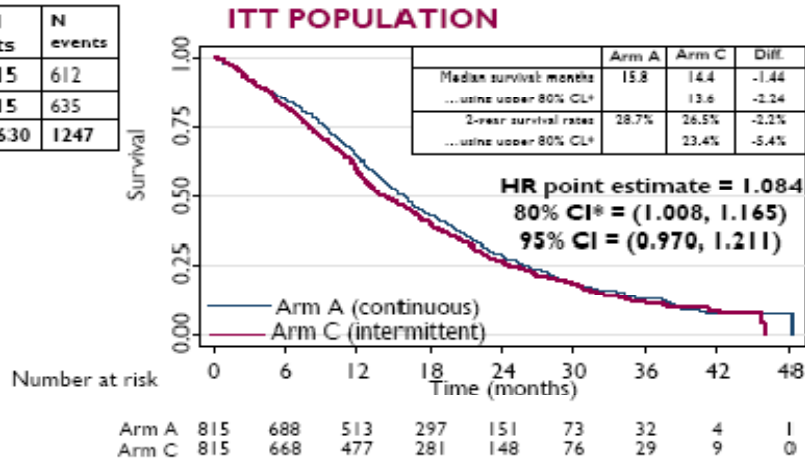
Mancuso et al. J Clin Invest 2006

MRC COIN trial



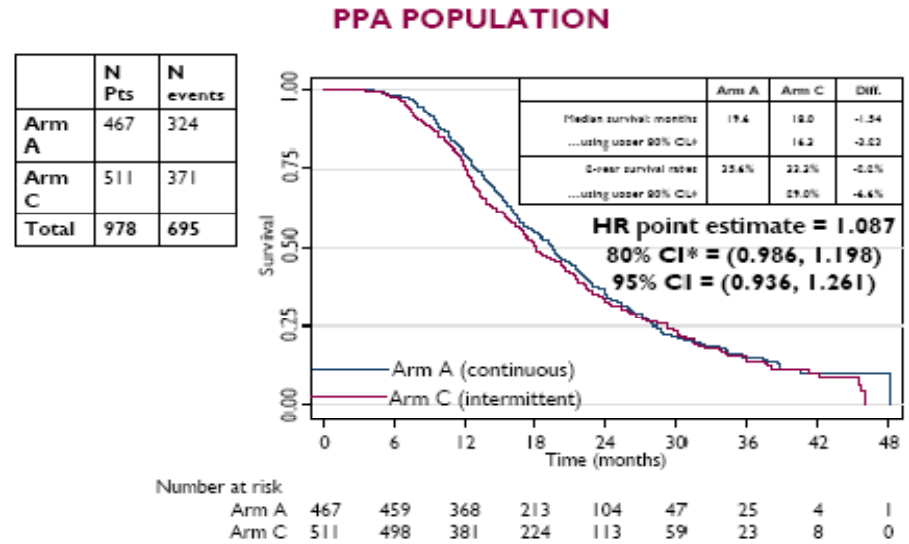
Overall survival

	N pts	N events
Arm A	815	612
Arm C	815	635
Total	1630	1247



* Non-inferiority bound is a one-sided 90% confidence limit (CL), equivalent to the upper limit of an 80% confidence interval (CI)

	Arm A	Arm C	Δ
Median survival (months)	15.8	14.4	-1.44
Using upper limit 80% CI		13.6	-2.24
2-yr survival (%)	28.7%	26.5%	-2.22
Using upper limit 80% CI		23.4%	-5.4%



* Non-inferiority bound is a one-sided 90% confidence limit (CL), equivalent to the upper limit of an 80% confidence interval (CI)

	Arm A	Arm C	Δ
Median survival (months)	19.6	18.0	-1.54
Using upper limit 80% CI		16.3	-3.23
2-yr survival (%)	35.6%	33.3%	-2.2
Using upper limit 80% CI		29.0%	-6.6%



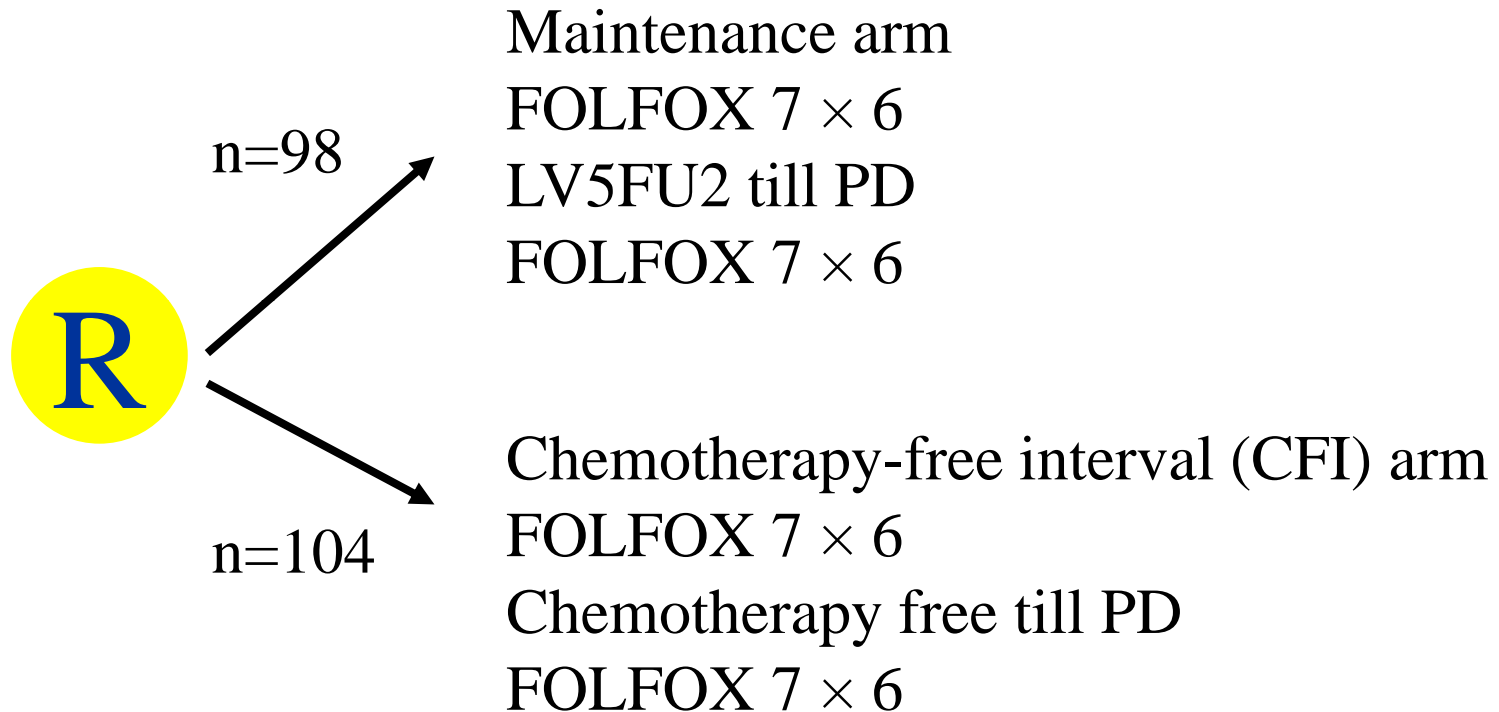
To meet non-inferiority the upper limit 80% CI needs to be <4.6%, ∴ non-inferiority not met in this trial

Per protocol analysis (PPA) population: Received full 12 weeks of treatment and had a disease assessment at 12 weeks

COIN: continuous vs intermittent other endpoints

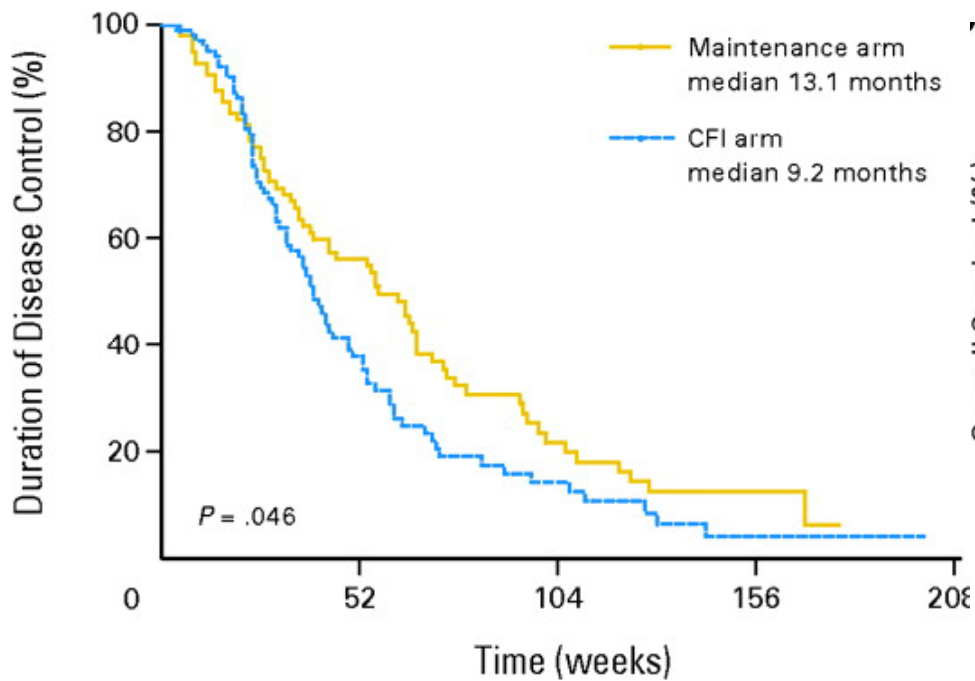
- Intermittent treatment patients stayed on treatment for less time than continuous treatment patients (median 2.3 months; $p < 0.001$)
- Length of chemotherapy free interval (CFI) = 16 weeks (IQR 14-27 weeks)
- Continuous treatment patients experienced more severe peripheral neuropathy \pm HFS
- Intermittent treatment patients had consistent advantage in QoL compared to continuous treatment

OPTIMOX 2

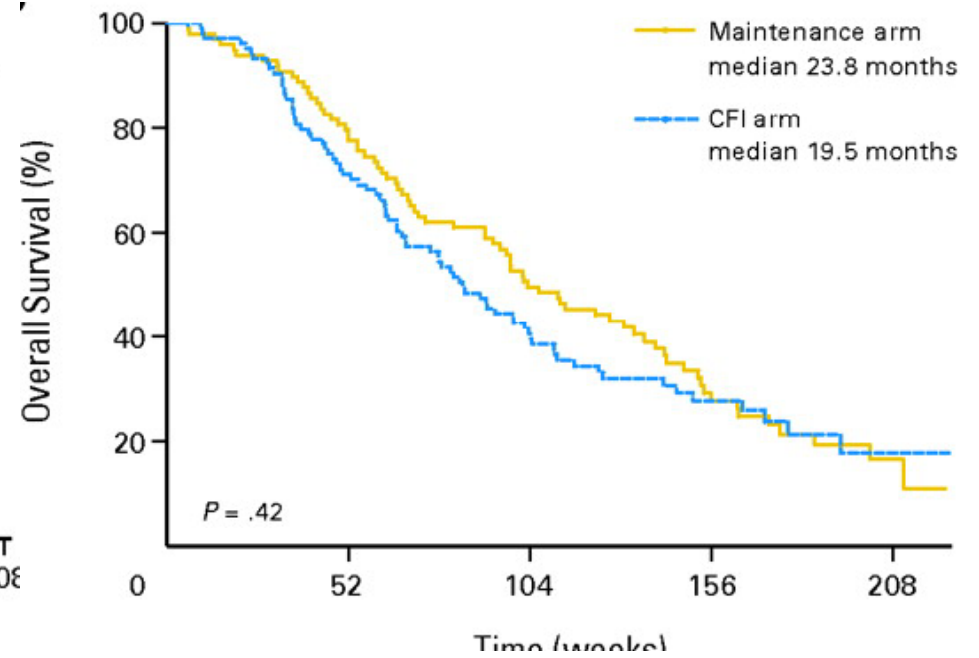


OPTIMOX 2

Duration of disease control



Overall survival

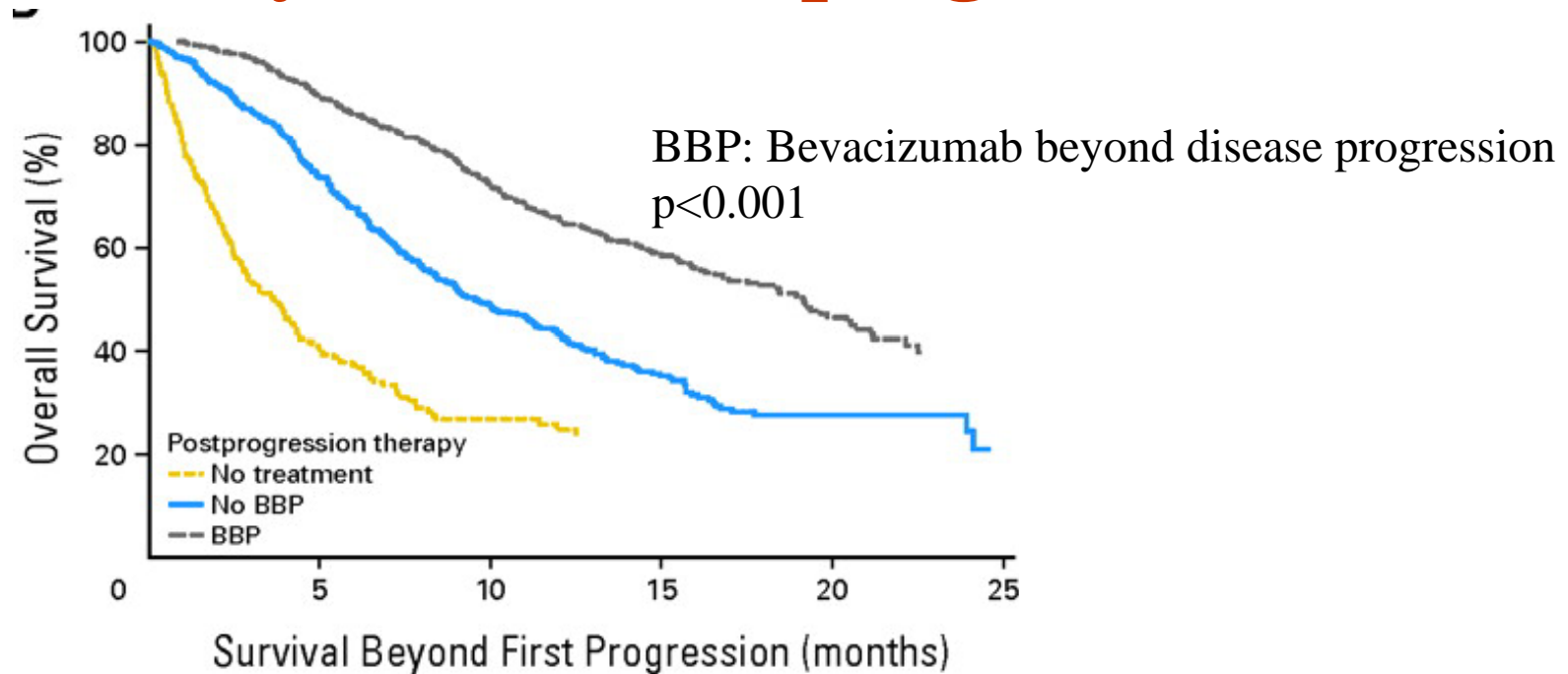


**Should we continue bevacizumab
when patients progress on first
line chemotherapy?**



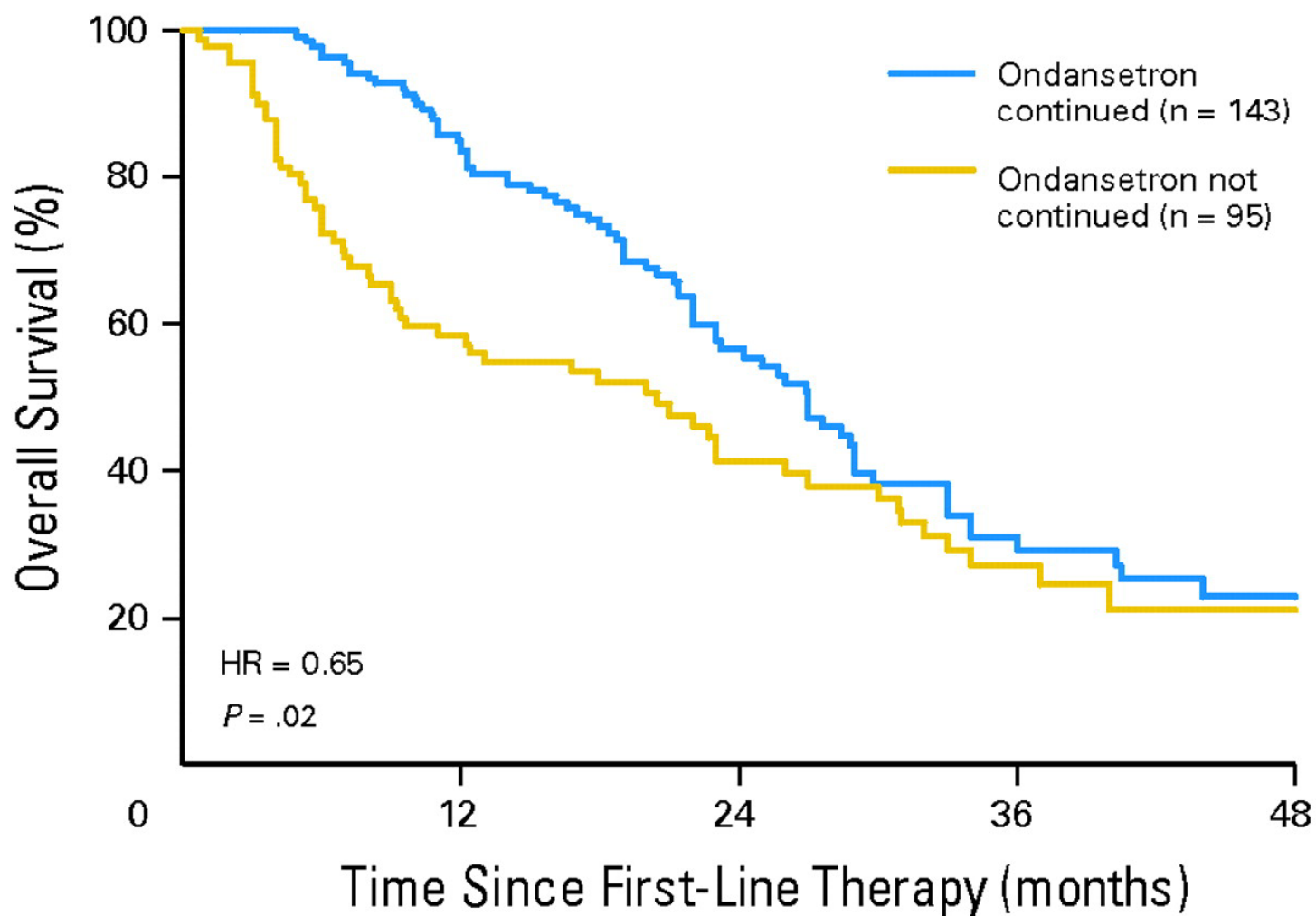
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BRiTE study: continuing bevacizumab beyond disease progression



	All pts	No post- progression RX	No BBP	BBP
1-yr OS	74.7%	52.5%	77.3%	87.7%
Median OS beyond first progression	12.0m	3.6m	9.5m	19.2m

Ondansetron beyond disease progression



**Can we predict who is going to
benefit from bevacizumab?**

NO



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Retrospective tumour tissue based biomarker analysis in NO16366

- Conducted in 247/1401 patients
 - FOLFOX/CAPOX + placebo n=157
 - FOLFOX/CAPOX + bevacizumab n=90
- Subgroup analysis suggested that time to progression might be prolonged by bevacizumab with
 - High CD31 expression (high vessel number)
 - Higher VEGF-A expression
 - Lower neuropilin and lower HER2 expression in tumour cells

How about VEGF TKI?



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Clinical efficacy with VEGF TKI in colorectal cancer

Study	Treatment	No. of patients	Response rates	Overall survival
FIRST LINE				
Hecht et al	FOLFOX	583	46%	20.5 months
CONFIRM 1	FOLFOX/PTK-ZK	585	42%	21.4 months
	FU/BEV	110	40.0%	18.3 months
HORIZON 3	FOLFOX/bev	Press release Mar 2010: Fails to meet primary endpoint		
	FOLFOX/cedirinib			
Pfizer	FOLFIRI	Press release July 2009: Fails to meet primary endpoint		
	FOLFIRI/sunitinib			
SECOND LINE				
Kohne et al	FOLFOX	429	18%	11.8 months
	FOLFOX/PTK-ZK	426	19%	12.1 months
Cunningham et al	FOLFOX/bev	66	27%	NR
HORIZON2	FOLFOX/cedirinib	71	18%	NR
	FOLFOX/cedirinib	73	19%	NR

All results are non-significant

Hecht et al ESMO 2007; Kohne et al ASCO 2007; Cunningham et al ASCO 2008

Conclusions

- Increasing tailoring of EGFR antibody therapy is possible with K-ras and other biomarker analysis
- Many randomised trials and large observational registry studies have been performed to refine the optimal use of bevacizumab – predictive biomarkers are much needed
- VEGF and EGFR tyrosine kinase inhibitors have not yet demonstrated efficacy in colorectal cancer