This house believes that all patients with RAS wt tumours should be treated with EGFR inhibitors plus chemotherapy in 1st line

- No evidence for bevacizumab in (K)RAS mut disease -

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

Randomised trilas has shown:

a. **FOLFOX improves survival over FU/FA**

b. **FOLFIRI improves survival over FU/FA**

c. **FOLFOX and FOLFIRI both improve survival over FU/FA**

Metastatic CRC Oxaliplatin

Regimen	N	RR	PFS	OS	Author
LV5FU2	210	22%			DeGramont
+ Oxaliplatin	210	57%		16.2	JCO 2000
FU_{CM}/LV	100		6.1	19.9	Giacchetti
+ Oxaliplatin	100	53%	8.7	19.4	JCO 2000
Mayo	124	23%	5.3	16.1	Grothey
AIO+O	125	49%	7.8	21.4	ASCO 01/ 02
FU/FA	710	29%	6.3	13.7	Seymour
FOLFOX	357	57%	8.8	15.0	Lancet 2007

No effect on survival

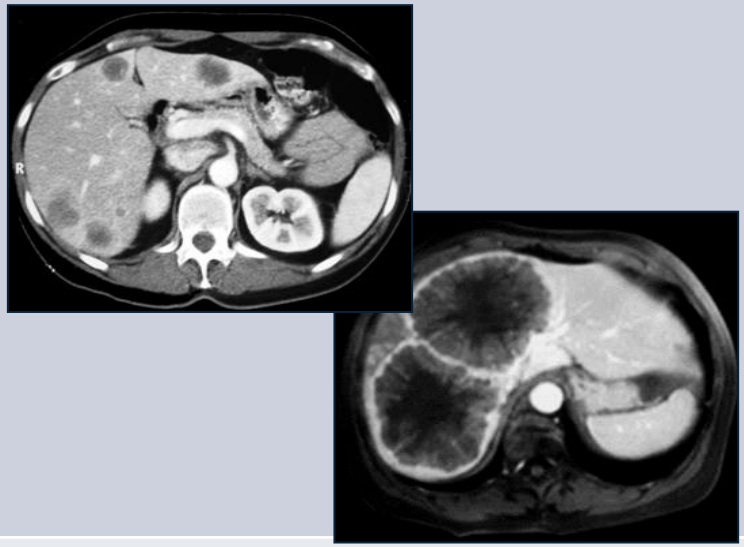
Metastatic CRC Irinotecan

Regimen	N	RR	PFS	OS	hor
Douillard/AIO	338	23%	4.4		Douillard
+ Irinotecan		35%		.4	Lancet 2000
FL (Saltz)	440		4.3	12.6	Saltz
+ Irinotecan			7.0	14.8	NEJM 2000
AIO		34%	6.4	16.9	Köhne
AIO+Iri		62%	8.5	20.1	JCO 2005
FU/FA	710	29%	6.3	13.7	Seymour
FOLFIRI	356	51%	8.6	16.2	Lancet 2007

3 of 4 trials positive for survival

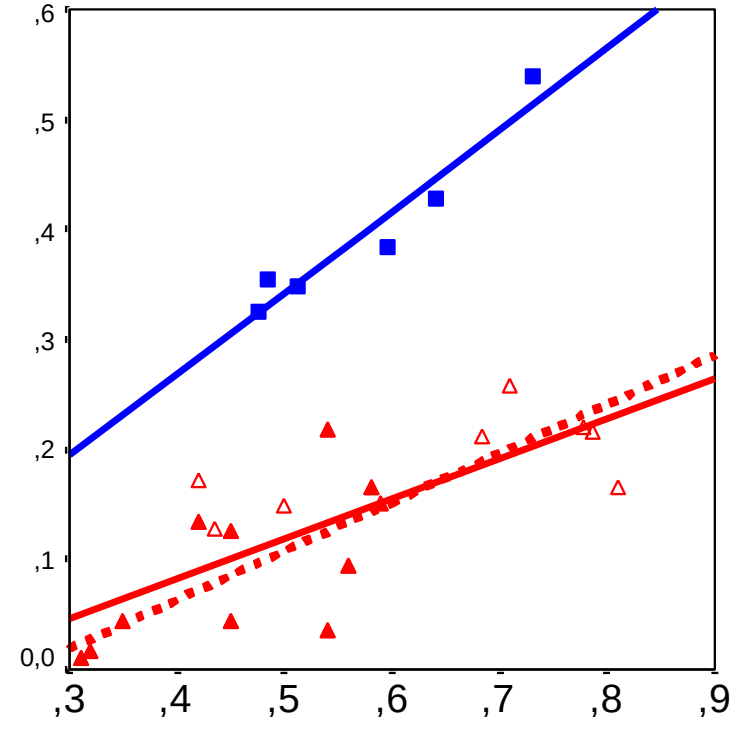
ESMO approach: Grouping of patients

Liver / Lung limited disease



Optimal therapy + surgery

resectable	***unresectable***
ESMO Group 0	***ESMO Group 1***

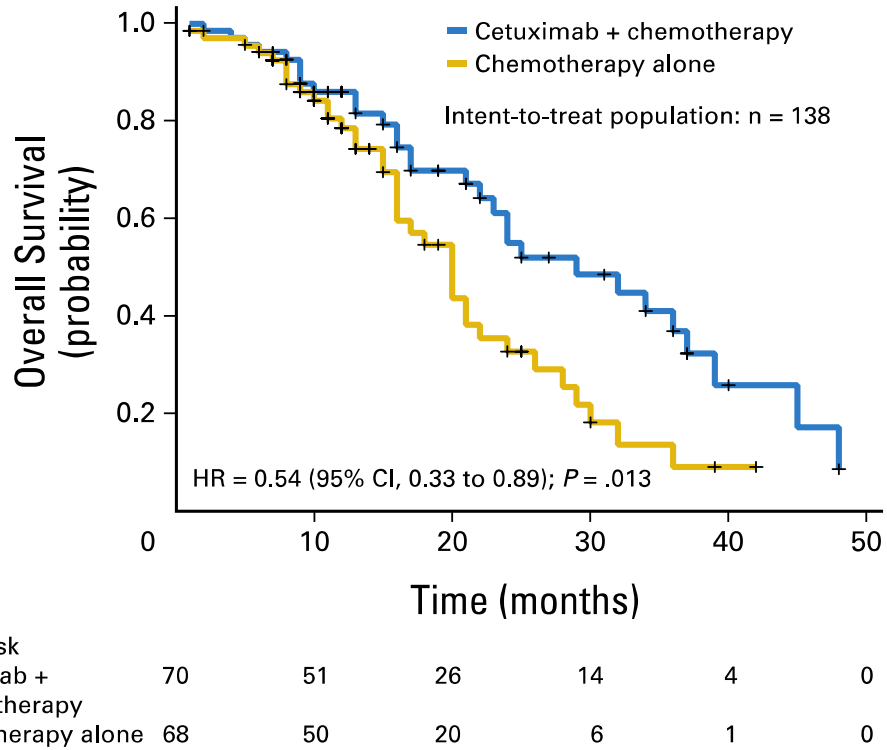


Response rate

Randomised trials of EGFR antibodies – 1st line k-ras exon 2 wt only

Trial	Therapy	ORR
CRYSTAL *(n=666)*	*FOLFIRI +/- Cetux*	40% v
Chinese* *(n=138)*	*FOLFIRI or FOLFOX+/- C*	% vs. **57%**
PRIME *(n=656)*	*FOLFOX +/- P*	48% vs. **57%**
OPUS *(n=1[illegible])*	*[illegible]OX Cetux*	34% vs. **57%**
([illegible]29)	*XELOX/FOLFOX +/- Cetux*	57% vs. **64%**
NORDIC *(n=194)*	*FLOX +/- Cetux*	47 vs. 46%

RR LLD 70 – 80 %



sig. diff; **(**clinically relevant not statist. Sig); no sig. diff * LLD only

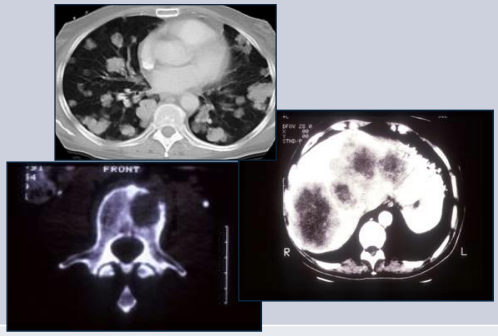
Randomized trial on bevacizumab plus chemotherpay NO16966 Response Rate

	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	

Saltz, ASCO-GI 2007

ESMO approach: Grouping of patients

Definitely unresectable



Palliative therapy

symptomatic	*asymptomatic*
ESMO Group 2	*ESMO Group 3*

OS – Infusional Combo by PS

6286 pts

Other ~ PS 0-1 (median = 15.5 mos)

Infusional Combo ~ PS 0-1 (median = 18.8 mos)

Other ~ PS 2 (median = 6.4 mos)

Infusional Combo ~ PS 2 (median = 11.8 mos)

p-value < 0.0001

HR: 0.84 (0.78-0.91)

p-value < 0.0001

HR: 0.69 (0.54-0.88)

Interaction p-value = 0.004

% Alive

0 10 20 30 40 50 60 70 80 90

0 5 10 15 20 25 30

Months

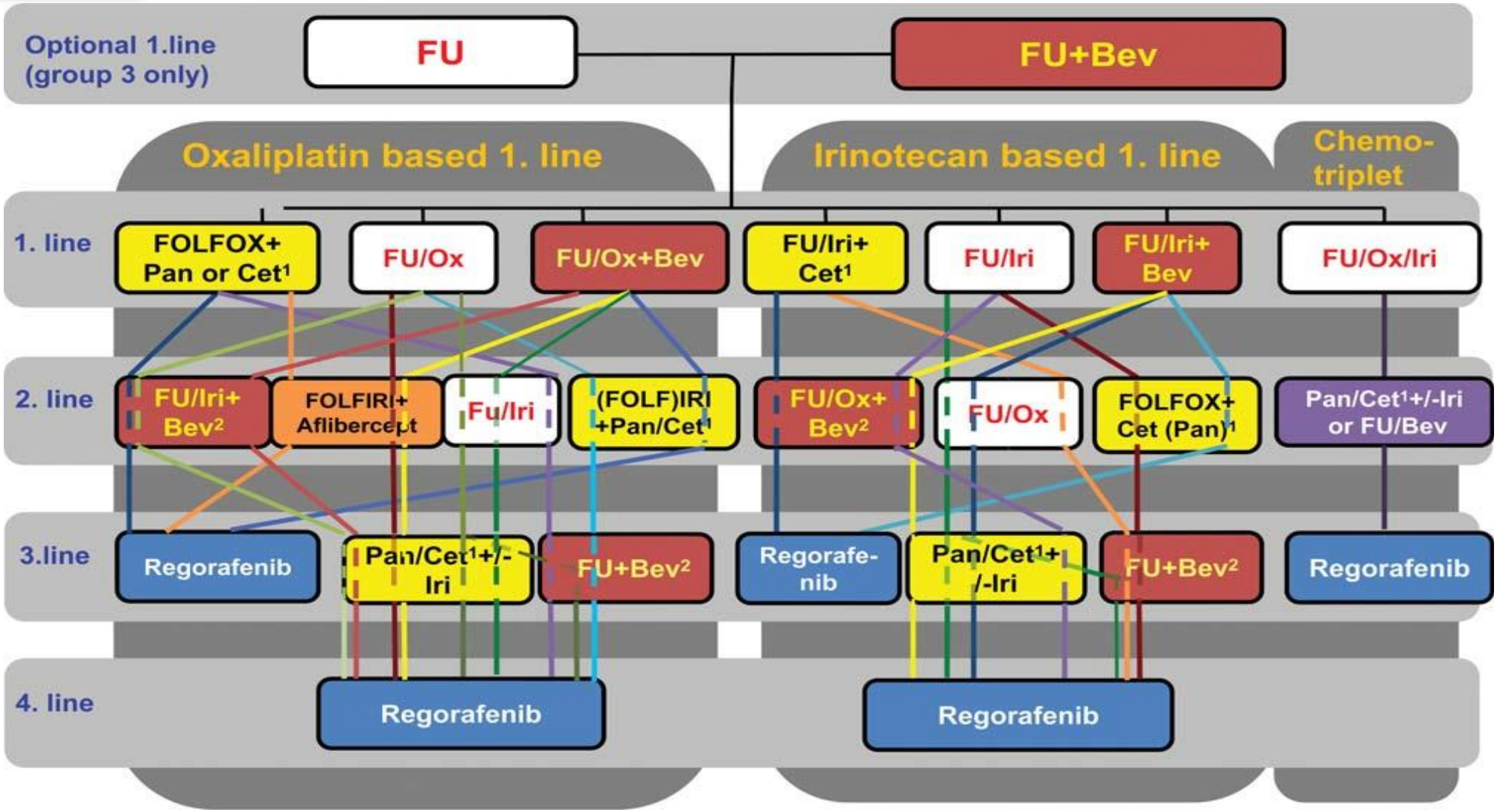
Goldberg, Köhne et al, JCO 2008

CM923700-10

Group 2 + 3

non-resectable metastases, asymptomatic and less aggressive disease

ESMO Proposal sequencing chemotherapy for group 2 and 3 patients



Randomised trials of EGFR antibodies – 1st line k-ras exon 2 w[illegible]ly

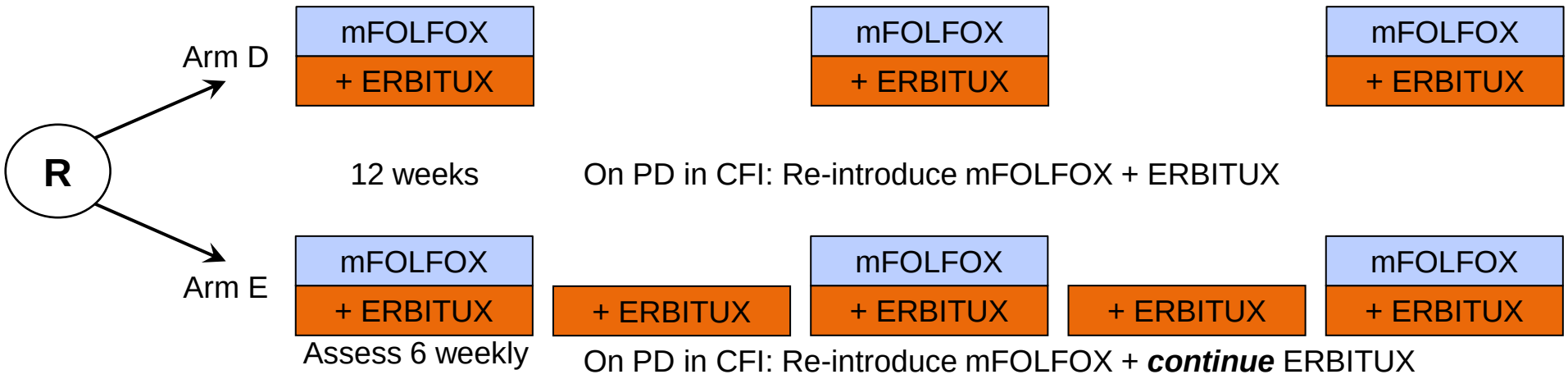
Trial	Therapy	ORR	PFS (mo)	[illegible])
CRYSTAL *(n=666)*	*FOLFIRI +/- Cetux*	40% vs. **57%**	8,4 vs. **9,9**	20.0 vs. **23,5**
Chinese* *(n=138)*	*FOLFIRI or FOLFOX+/- Cetux*	40% vs. **57%**	5 [illegible],2	21,0 vs. **30,9**
PRIME *(n=656)*	*FOLFOX +/- Pani*	48% vs. [illegible]	8,6 vs.**10.0**	19,4 vs. **23,8**
OPUS *(n=197)*	*FOLFOX +/- Cetux*	[illegible]. **57%**	7,2 vs. **8,3**	18,5 vs.(22,8)
COIN *(n=729)*	*XELOX/FO +/- Ce*	57% vs. **64%**	8,6 vs.8,6	17,9 vs.17,0
NORDIC *(n=19*	*Cetux*	47 vs. 46%	8,7 vs. 7,9	22,0 vs. 21,0

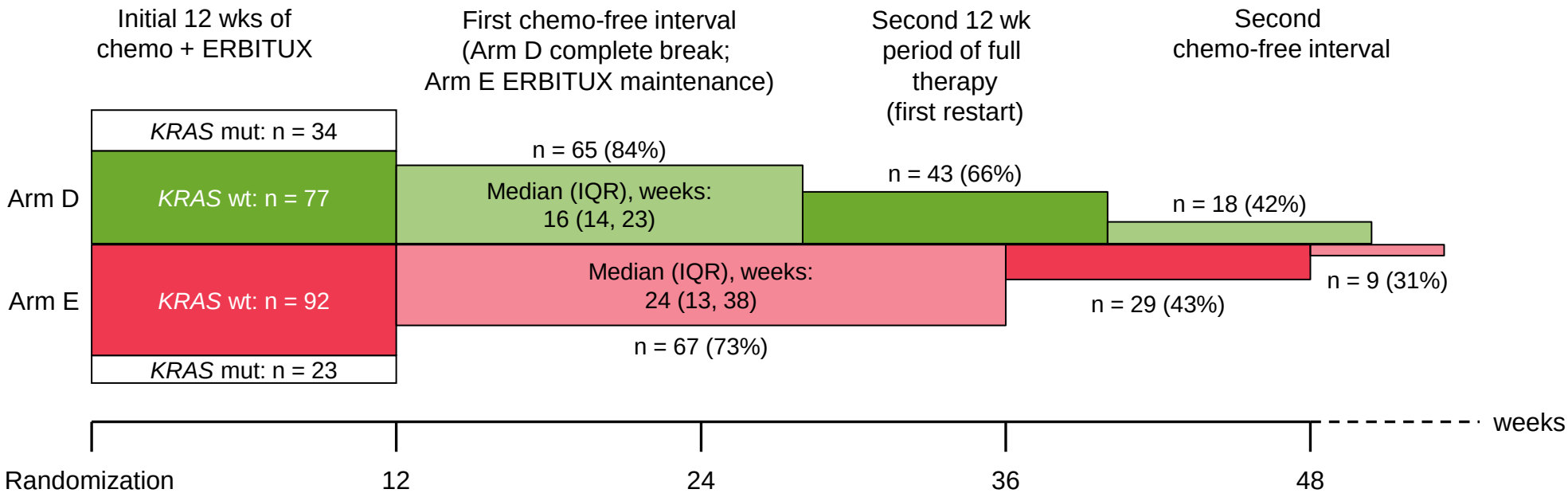
3 of 4 trials with infusional 5-FU regimens positive for OS

sig. diff; **(**clinically relevant not statist. Sig); no sig. diff * LLD only

Two-arm phase II COIN-B design
Is biological maintenance beneficial with ERBITUX in KRAS wt mCRC in first line?

Wasan et al., ESMO 2011, # 6006; Lancet Oncology 2014

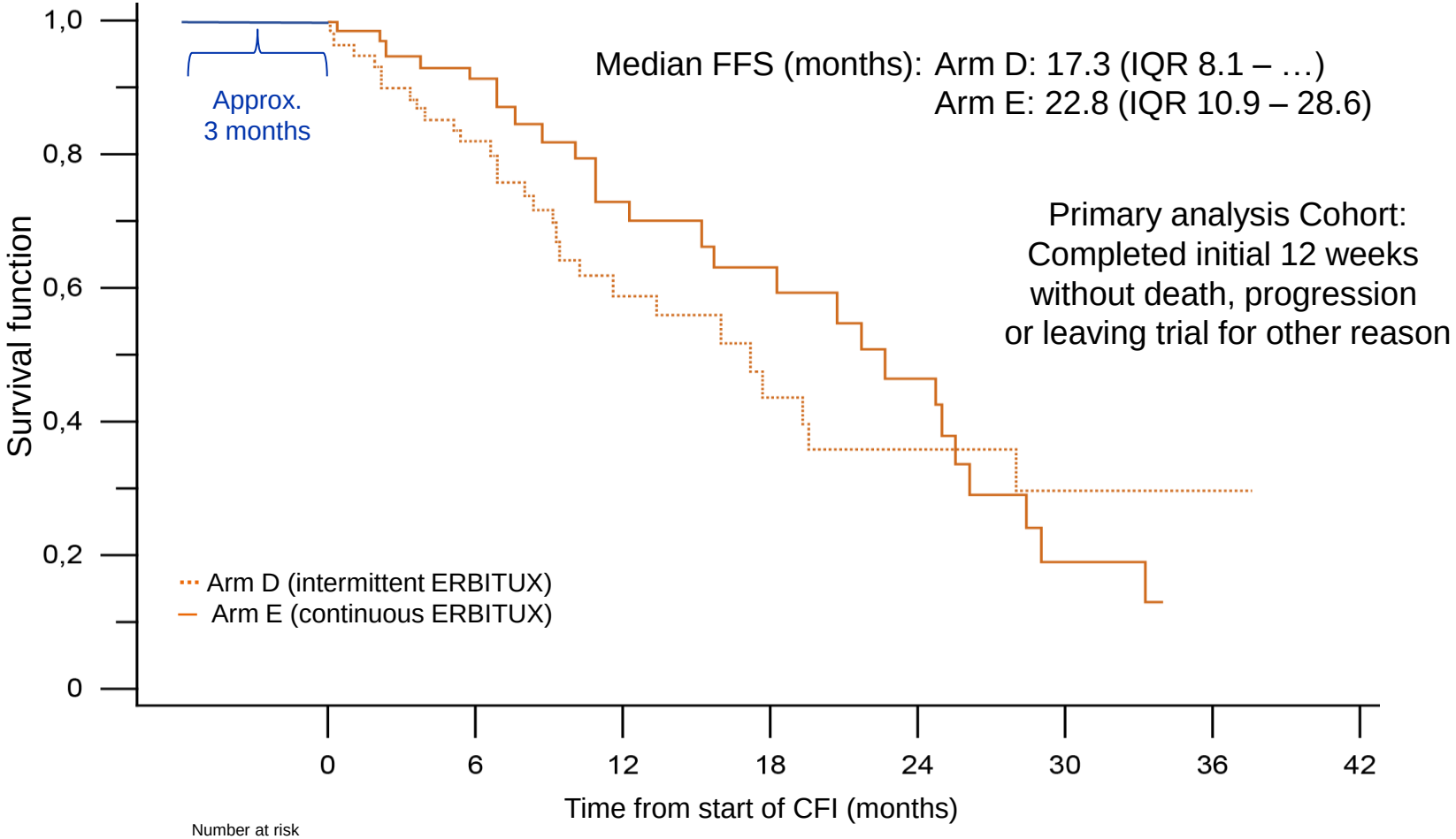




OS from start of first chemotherapy-free interval

KRAS wt patients: Primary analysis cohort

Wasan et al., ESMO 2011, # 6006 ; Lancet Oncology 2014



Number at risk

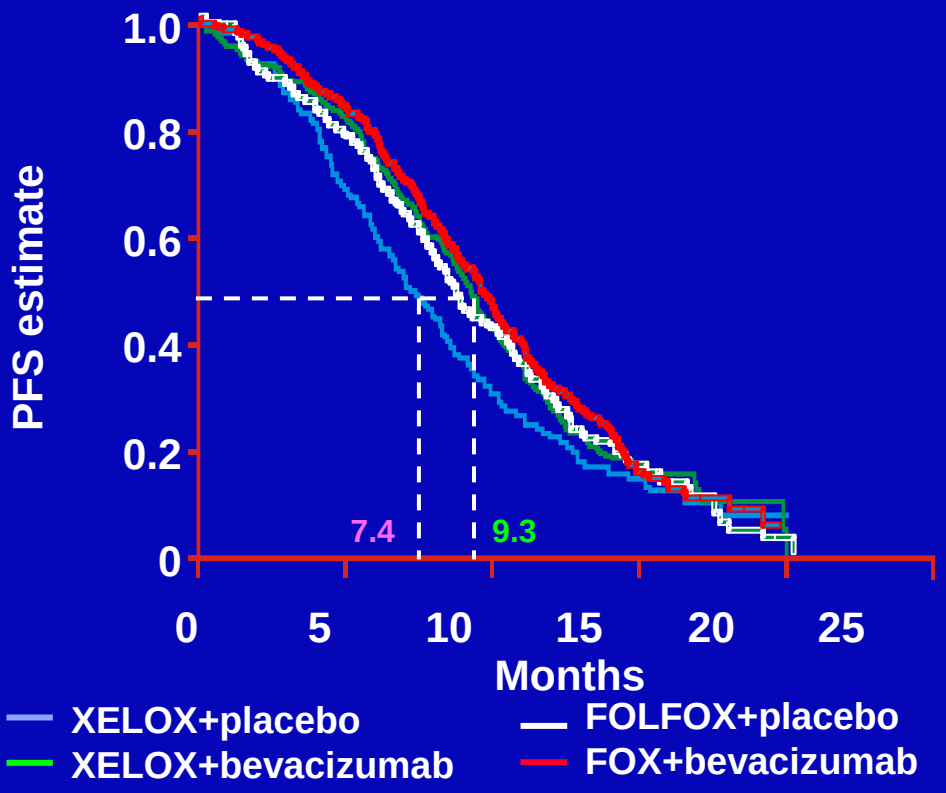
Arm D	65	46	22	11	6	5	2	0
Arm E	67	46	23	18	11	4	0	0

VEGF in 1st line mCRC

Regimen	RR	PFS	OS
Less active regimens (FU/FA, Cape, IFL)	+10% *	+ 3-4 mo HR 0.5-0.63 *	+ 1-4 mo (sig. IFL,only)
NO16966 FOLFOX# (N=700)	equal	8.6 vs 9.4 HR 0.83 P=0.19	20.3 vs. 21.2 HR 0.94 P=n.s.
FOLFOX/ FOLFIRI (N=376)	48 vs. 54%	8.4 vs. 9.2 HR 0.88 n.s.	20.6 vs. 20.6 HR 1.18 n.s.
FOLFIRI	No data	No data	No data

Passardi et al. ASCO 2013 Cassidy et al. ASCO 2007; Saltz et al. JCO 2008

NO16966 PFS CTx +/- bevacizumab : XELOX and FOLFOX subgroups



	FOLFOX	FOLFOX+ Bev	XELOX	XELOX +Bev
N Pat	351	349	350	350
PFS mo	8.6	9.4	7.4	9.3
HR	0.89		0.77	
97.5% CI	0.73 - 1.08		0.63 – 0.94	
p-value	0.19		0.0026	
OS (mo)	20.3	21.2	19.2	21.4
HR	0.94		0.84	
97.5% CI	0.75 to 1.16		0.68 – 1.04	
P-value	n.s.		n.s.	

Cassidy et al. ASCO 2007; Saltz et al. JCO 2008

PFS in Phase III PFS data VEGF TKI or Bevacizumab

Failure		Breakthrough	
FOLFOX	+ PTK	FOLFOX	+ Bev
7.6	**7.7**	**8.6**	**9.4**
HR 0.88 P=0.118		**HR 0.89 P= 0.19**	
Confirm I Hecht JCO 2011		*NO16966 Saltz et al. JCO 2008*	

FINANCIAL TIMES
DEUTSCHLAND
WWW.FTD.DE | 57/12 | DIENSTAG, 22. MÄRZ 2005 | C50937 | DEUTSCHLAND 1,70€

Frankfurter Allgemeine
ZEITUNG FÜR DEUTSCHLAND

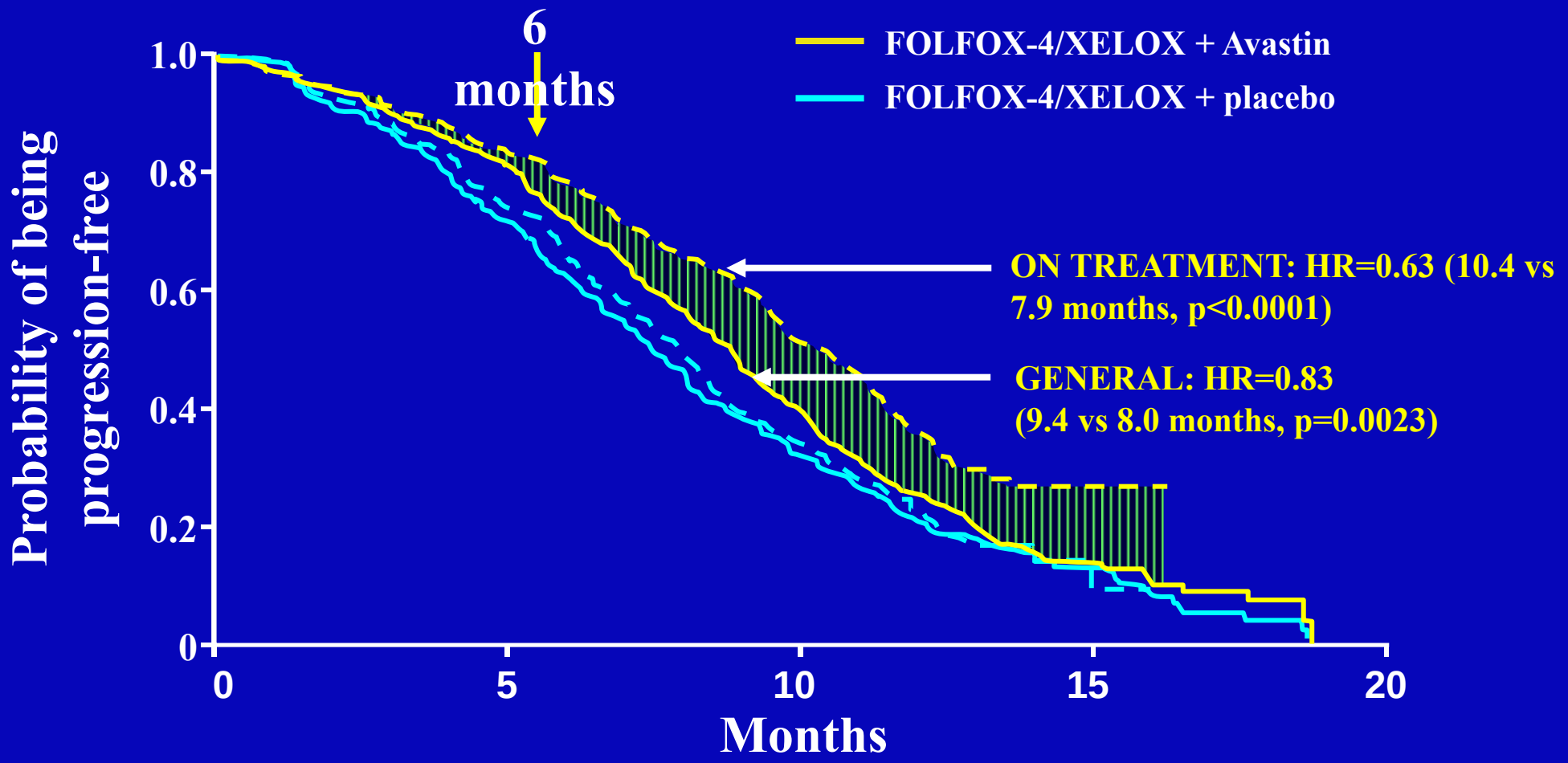
PTK/ZK doesn‘t work

PTK/ZK nutzt nichts

Es sollte die Chemotherapie bei Krebs ersetzen, das neue Medikament PTK/ZK von Schering. Versuche haben aber ergeben, daß es keine besseren Ergebnisse bringt. UNTERNEHMEN 15

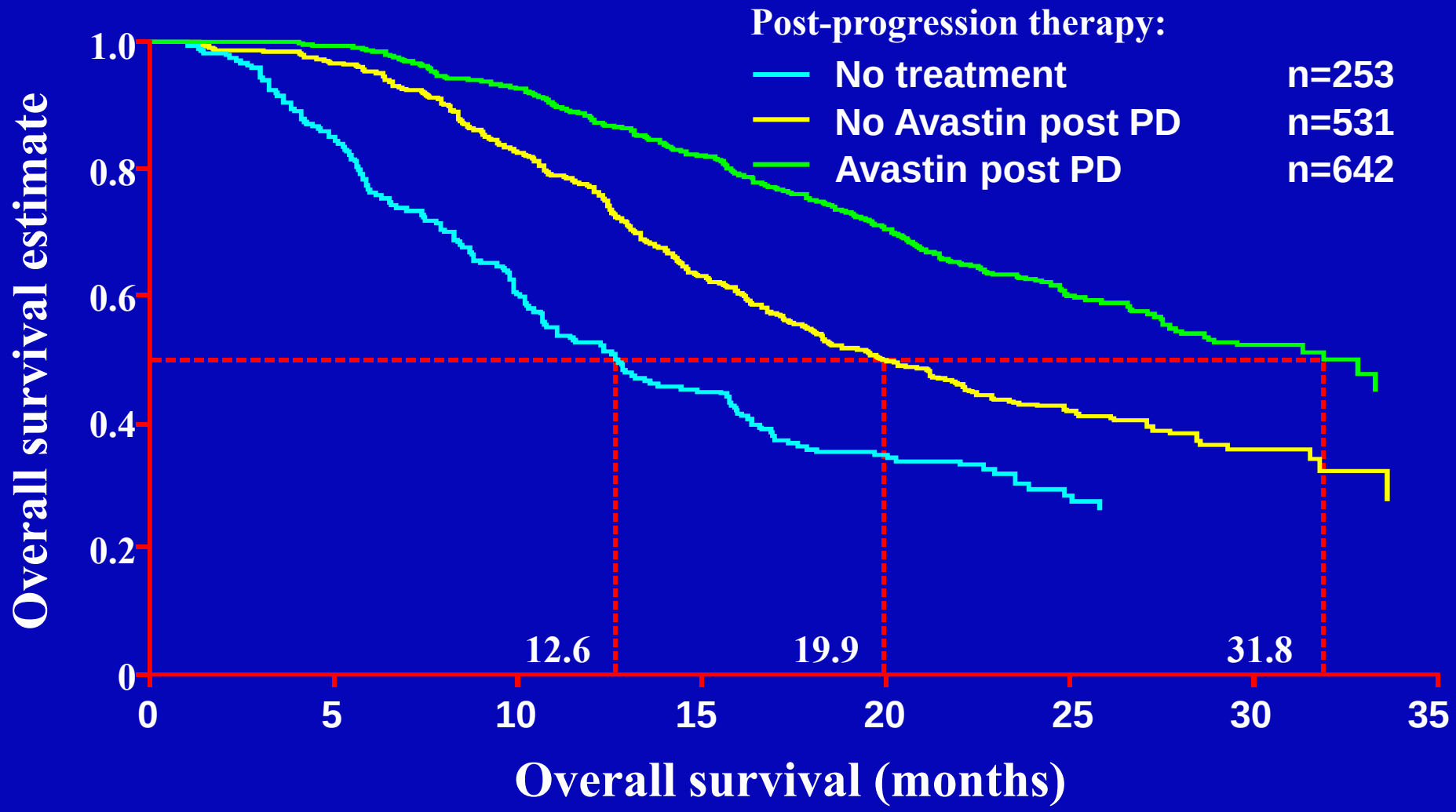
Alstom baut Arbeitsplätze ab

NO16966: strong benefit from treatment until progression



Saltz, et al. ASCO 2007

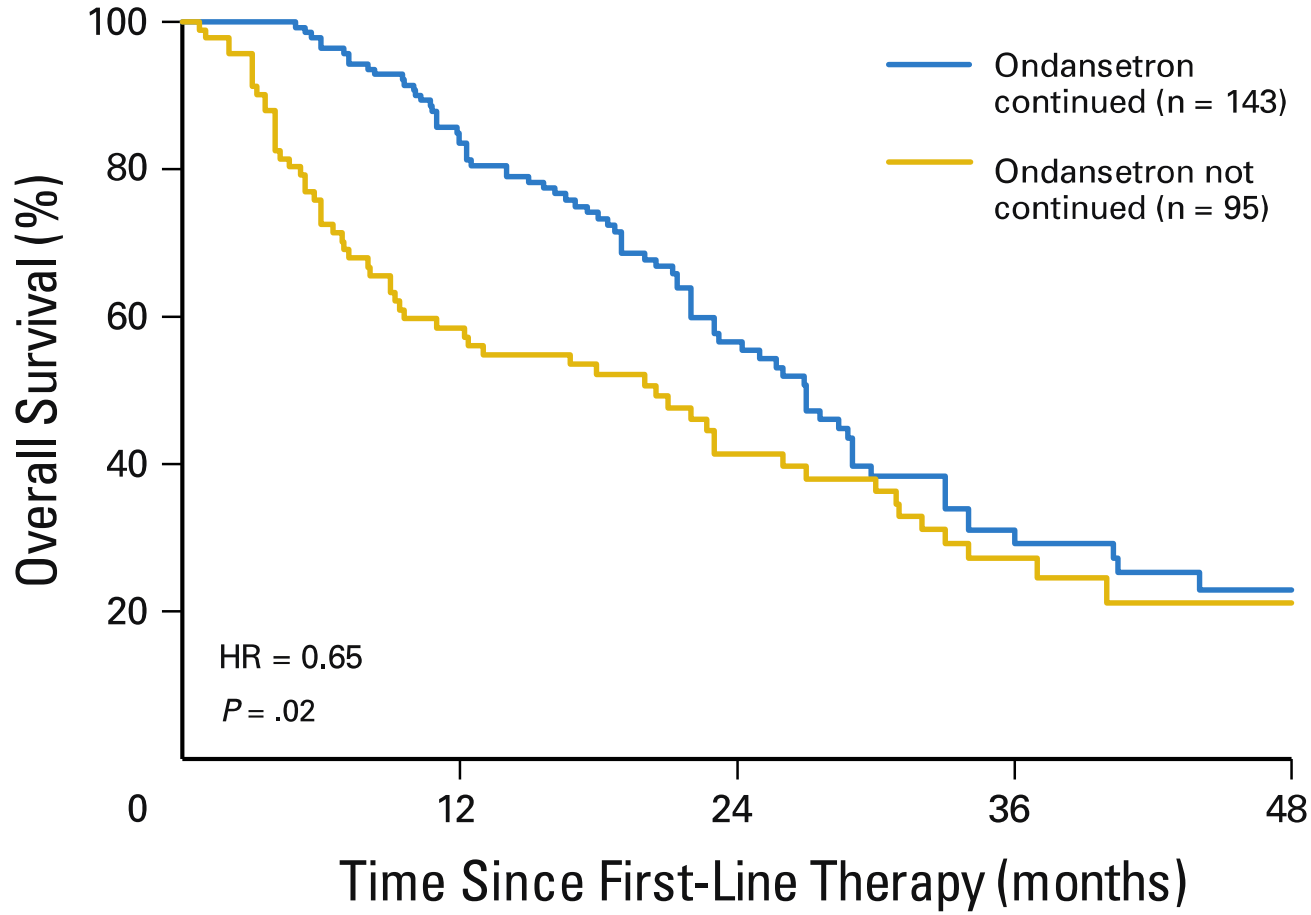
BRITE: Avastin increases survival post first-progression



PD = progressive disease

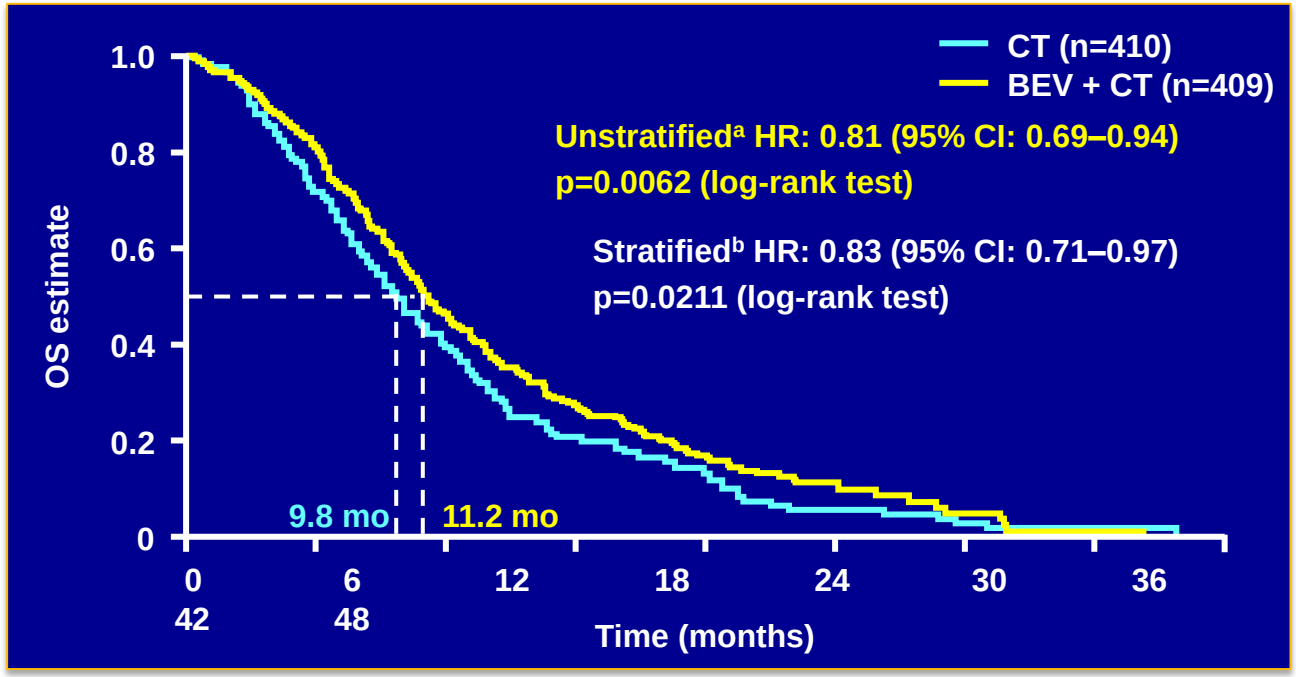
Grothey, et al. ASCO 2007

Hidden Biases in an Observational Study of Bevacizumab Beyond Progression
- Ondansetron beyond progression -



Kopetz et al. JCO 2009

Overall survival : Bevacizumab beyond PD in mCRC



Overall survival composite from 1st and 2nd line treatment

22.5 - 9.8 = 12.7 mo

1st line

23.9 – 11.2 = 12.7 mo

9.8 mo

2nd line

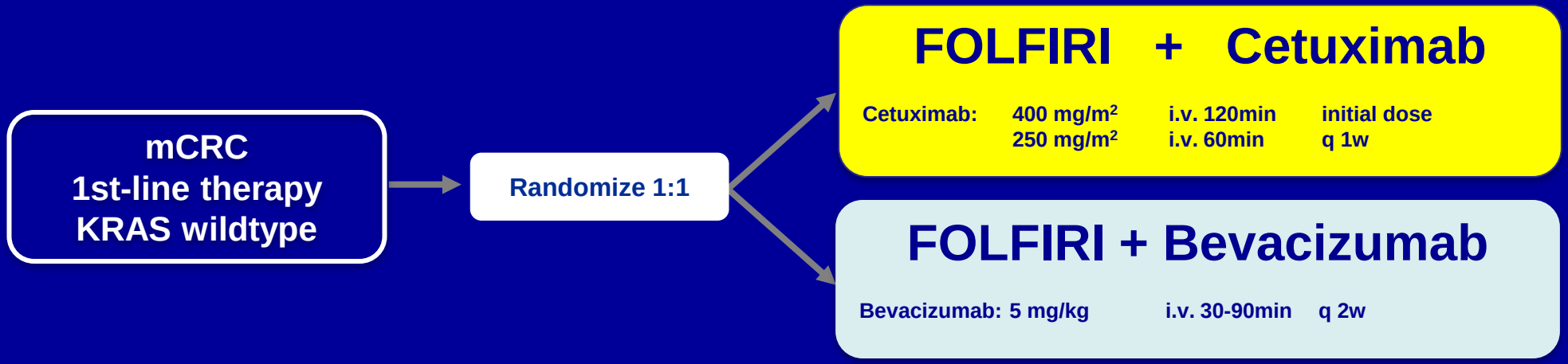
11.2 mo

22.5 mo

∂ 1.4 mo

23.9 mo

1st line Head to Head comparison EGFR vs. VEGF

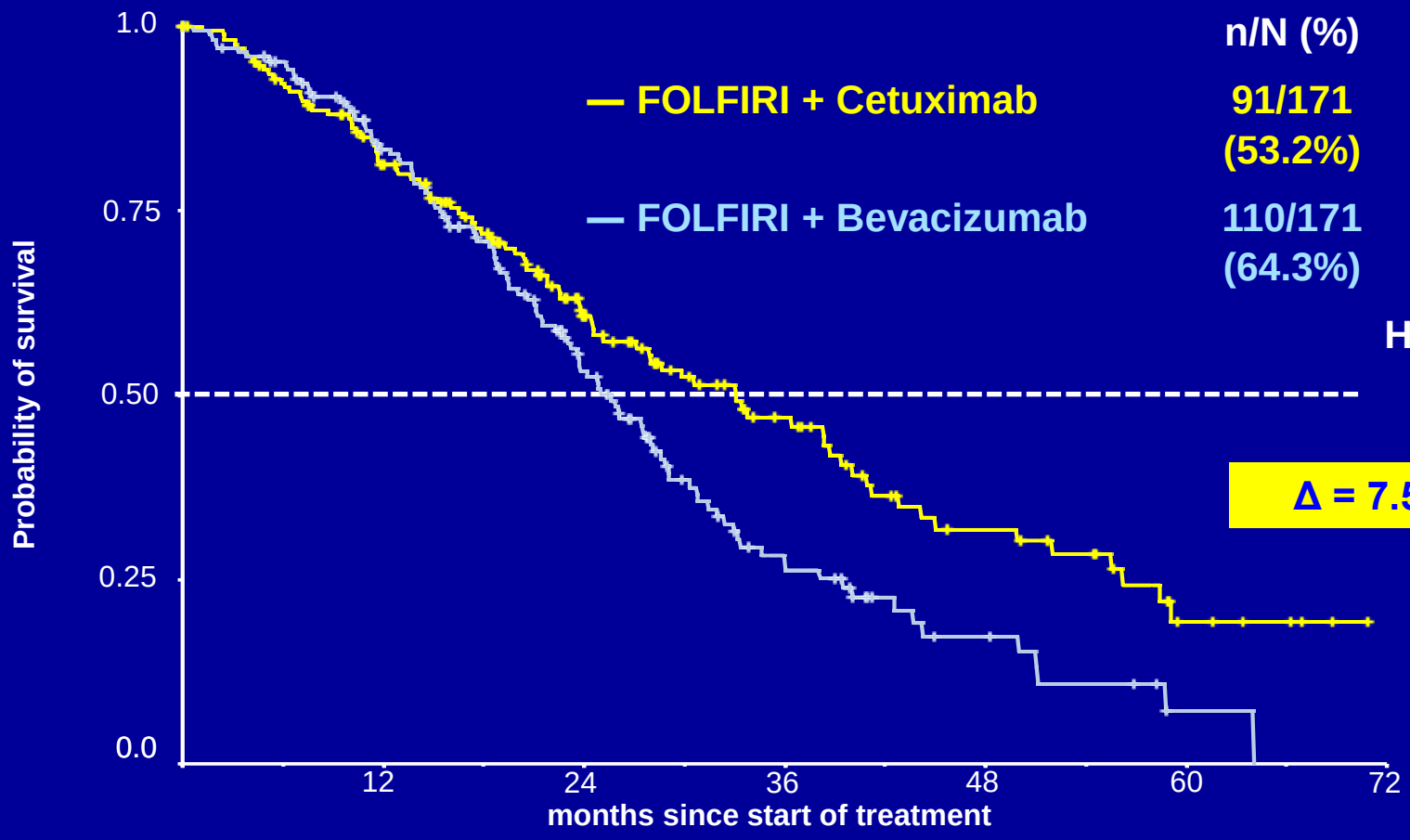


FOLFIRI q2w: 5-FU: 400 mg/m² (i.v. bolus);
folinic acid: 400mg/m²
irinotecan: 180 mg/m²
5-FU: 2,400 mg/m² (i.v. 46h)

- **Primary objective: Overall response rate (ORR)**
- Designed to detect a difference of 12% in ORR induced by FOLFIRI + cetuximab (62%) as compared to FOLFIRI + bevacizumab (50%)
- 284 evaluable patients per arm needed to achieve 80% power for an one-sided Fisher‘s exact test at an alpha level of 2.5%

all analyzed in the ITT population

Overall survival
RAS* wild-type



	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	91/171 (53.2%)	33.1	24.5 – 39.4
— FOLFIRI + Bevacizumab	110/171 (64.3%)	25.6	22.7 – 28.6

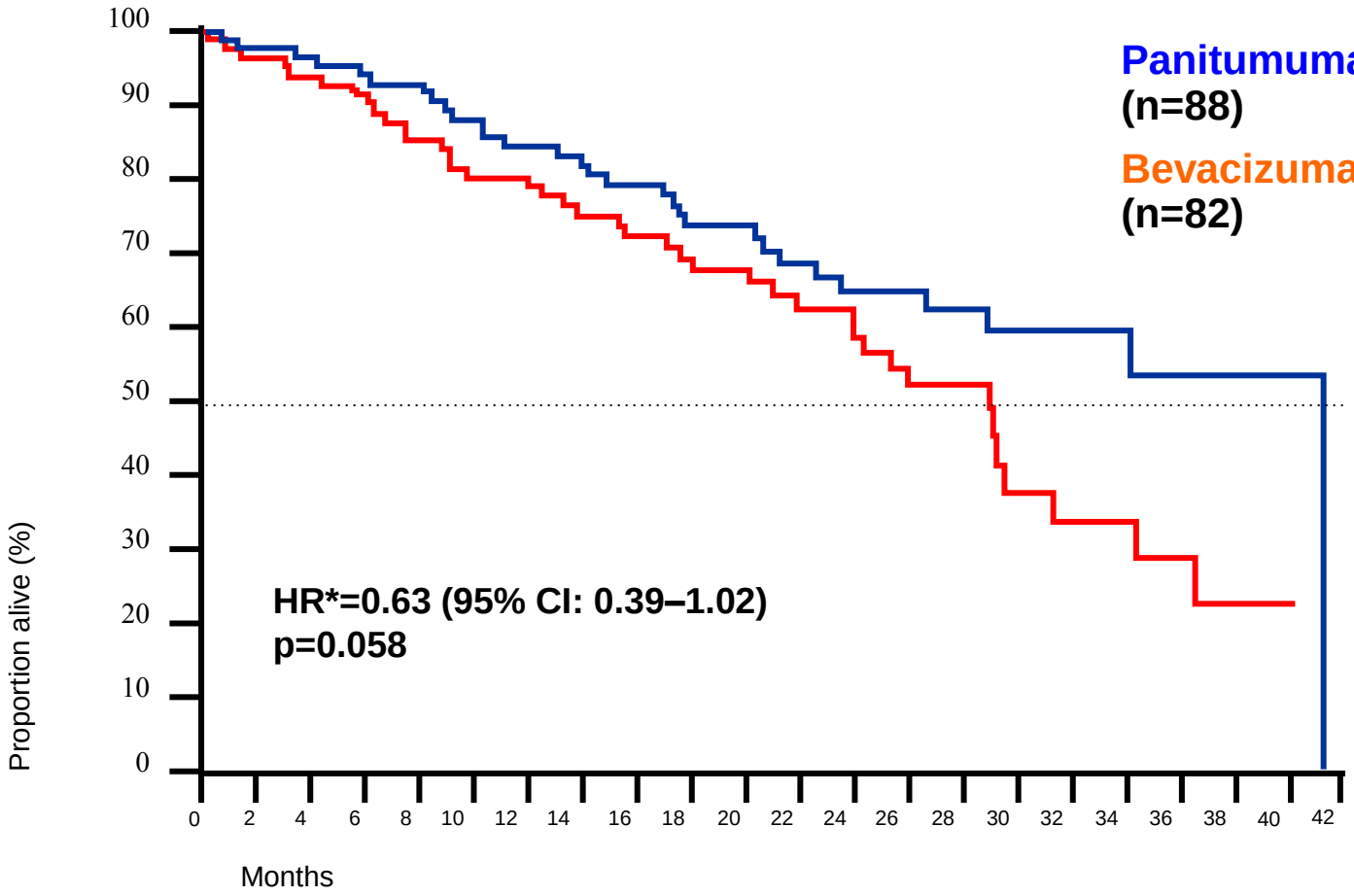
HR 0.70 (95% CI: 0.53 – 0.92)
p (log-rank)= 0.011

Δ = 7.5 months

No. at risk						
	171	128	71	39	20	6
	171	127	68	26	9	1

* KRAS and NRAS exon 2, 3 and 4 wild-type

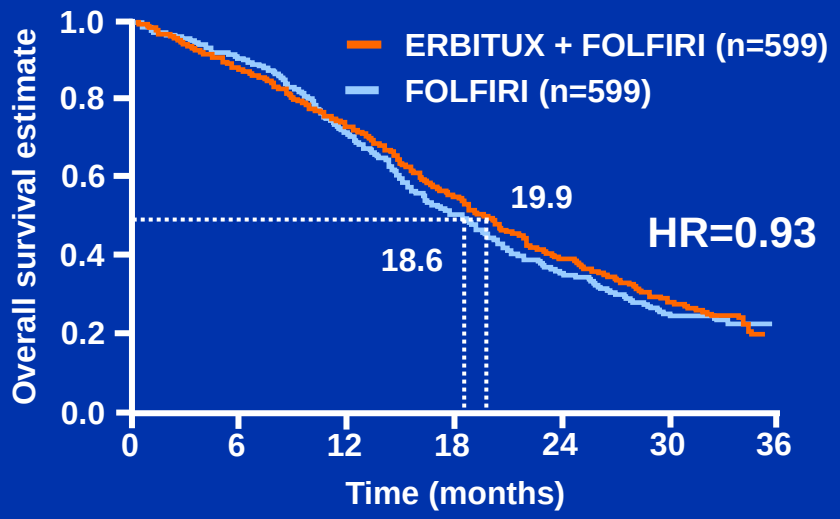
PEAK study: Overall survival
Panitumumab vs. Bevacizumab in RAS wt mCRC: WT RAS (exon 2,3,4 KRAS/NRAS)



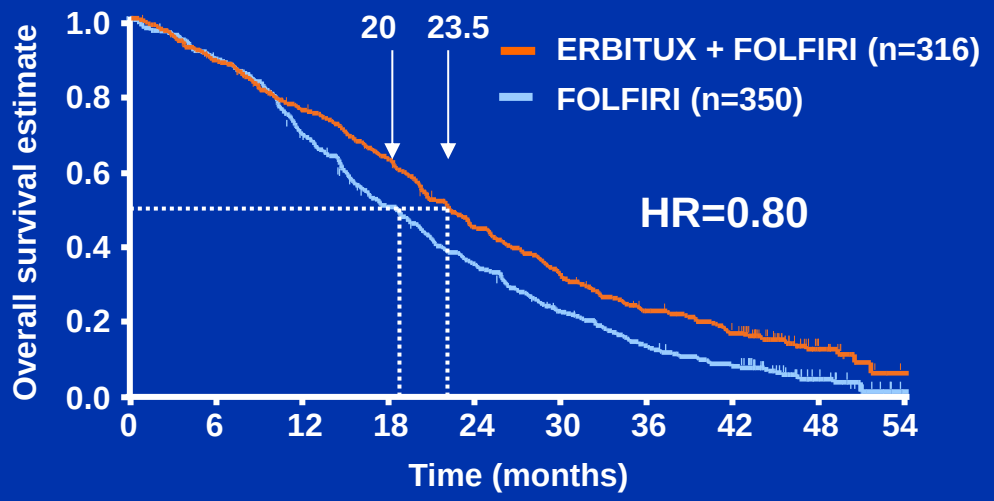
mFOLFOX6 +	Events n (%)	Median (95% CI) months
Panitumumab + (n=88)	30 (34)	41.3 (28.8–41.3)
Bevacizumab + (n=82)	40 (49)	28.9 (23.9–31.3)

Schwartzberg L, et al. JCO 2014

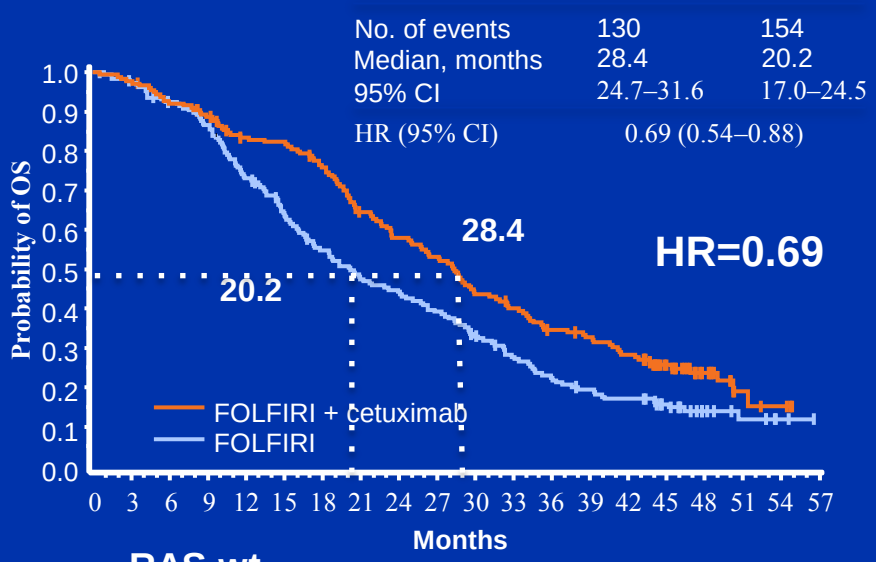
Using biomarkers to optimize clinical outcome



Overall patient population



KRAS exon 2 wild-type (wt) population



RAS wt
(KRAS exon 2,3,4 and NRAS exon 2,3,4)

Group 2 + 3

non-resectable metastases, asymptomatic and less aggressive disease

Van Cutsem E…Köhne CH al. N Engl J Med 2009;360:1408–1417;
Van Cutsem E, Köhne CH al. J Clin Oncol 2010;28 (Suppl. 15):Abstract No. 3570

Ciardiello…….,Köhne et al. ASCO 2014

Influence of KRAS and RAS mutational status on survival
Randomised trials of EGFR antibodies – 1st line

Trial	Therapy	OS (mo) KRAS		OS (mo) RAS wt		OS (mo) RAS mut	
		CTx	+EGFR	CTx	+EGFR	CTX	+EGFR
CRYSTAL *(n=666)*	*FOLFIRI +/- Cetux**	20.0	**23.5**	20.2	**28.4**	**17.7**	16.4
PRIME *(n=656)*	*FOLFOX +/- Pani**	19,4	**23.8**	20.2	**26.0**	**19.2**	15.6
OPUS *(n=197)*	*FOLFOX +/- Cetux**	18,5	(22.8)	17.8	**19.8**	**17.8**	13.5

Van Cutsem, Ciardiello, Köhne et al. ASCO 2014
Douillard et al. NEJM 2014
Bokemeyer, Köhne et al. 2014 ASCO 2014

The later EGRF antibodies are given the shorter the survival

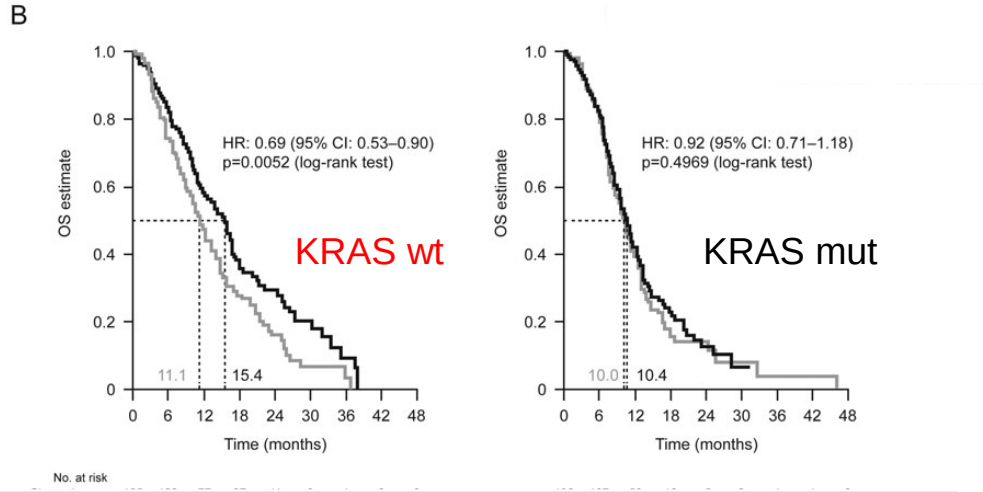
Study		1st line Regimen	2nd line CTx plus		PFS (1st line) (mo)	OS (mo)
			VEGF	EGFR		
TML	*Positive selection: Patients suitable for 2nd line Tx*	Chemo + Bev	100%	0%	n.a.	23.9
TRIBE	*1st line studies*	FOLFIRI + Bev	n.a.		9.7	25.8
FIRE-3#		FOLFIRI + Bev	17.3%	41.4%	10.3	25.6
FIRE-3		FOLFIRI + Cet	46.6%	15.2%	10.0	33.1

Falcone A. et al. ASCO 2013; Bennouna J, et al. Lancet Oncol 2013; Stintzing, Heinemann et al. ASCO 2013

RAS wt only

PFS and OS subgroup analysis of TML study
Efficacy of Chemo ± bevacizumab in 2nd line according to K-ras mutational status

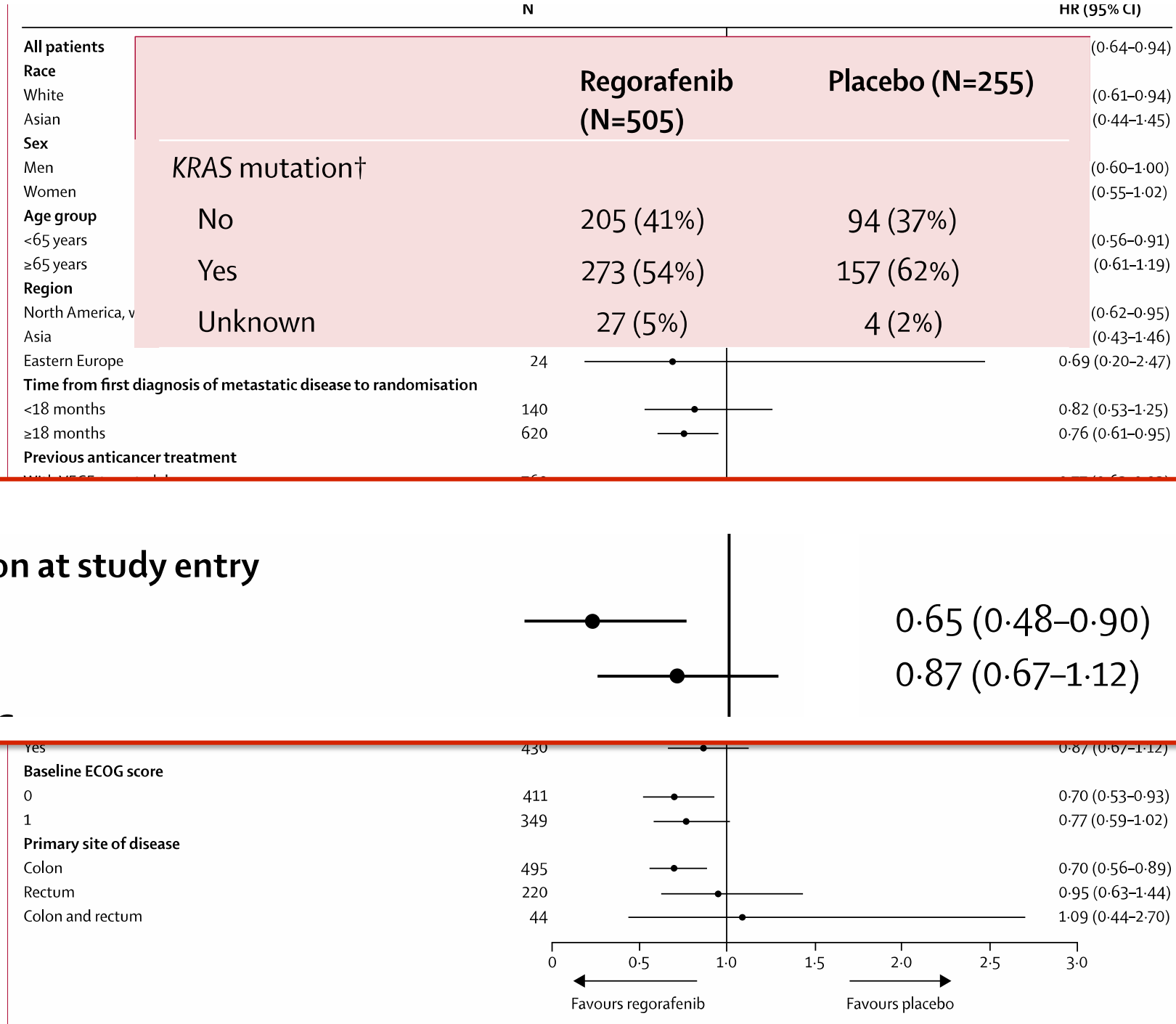
Overall survival free survival



	OS	
	KRAS wt	KRAS mut
CTx	**11.1**	10.0
CTx + Bev	**15.4**	10.4
HR	**0.69**	0.92
P-value	**.0052**	0.497

Kubicka et al. Ann Oncol 2014

CORRECT: BSC +/- Regorafenib Overall survival



	Regorafenib (N=505)	Placebo (N=255)
KRAS mutation†		
No	205 (41%)	94 (37%)
Yes	273 (54%)	157 (62%)
Unknown	27 (5%)	4 (2%)

***KRAS* mutation at study entry**	
No	0·65 (0·48–0·90)
Yes	0·87 (0·67–1·12)

Pooled analysis of Bevacizumab efficacy

	Overall survival		
	HR	95% CI	P-value
KRAS wt N=364	**0.70**	0.54-0.91	**0.007**
KRAS mut N=166	0.85	0.60-1.22	0.38

Hurwitz et al. The Oncologist 2013

Conclusions on EGFR or VEGFR in 1st line

- **RAS wt and RAS mut are 2 kinds of diseases**
- **The value of EGFR antibodies in 1st line to prolong survival in RAS wt disease is without doubt**
- **The efficacy of VEGF antibodies in 1st line RAS mut disease needs to be established**

Balance Risk and Survival benefit for choice of 1st line mCRC

VEGF	Study	All pts
IFL ± Bev [1)]	*Hurwitz*	+
Cape ± Bev [2)]	*Cunningham*	trend
FOLFOX ± Bev [3)]	*NO16966*	-
FOLFIRI ± Bev	*n.a.*	*n.a.*
EGFR		**(K)RAS wt**
FOLFIRI ± Cet[4)]	*CRYSTAL*	+
FOLFOX ± Pan[5)]	*PRIME*	+
FOLFOX ± Cet[6)]	*OPUS*	trend
CTx ± Cet[7)]	*Chinese*	+
CapeOx	*COIN*	-
bolusFU/Ox Nordic	*NORDIC*	-

FOLFIRI [8)]	FIRE3	(K)RAS wt
Bevacizumab		
Cetuximab		+
FOLFOX [9)]	**PEAK**	**(K)RAS wt**
Bevacizumab		
Panitumumab		(+)

1)Hurwitz et al. 2)Cunningham et al. and AGIC 3)NO16966 4)CRYSTAL 5)PRIME 6)OPUS 7)Ye 8) FIRE 9) PEAK

Sequencing Biologicals in mCRC

Line of Therapy		RAS wt ~48%	RAS mut ~48%	BRAF mut ~5%
1st line	Antibody +	**EGFR +**	**Clinical trials**	
	Chemotherapy	FOLFIRI FOLFOX FOLFOXIRI	FOLFOXIRI FOLFIRI FOLFOX	
2nd line	Antibody +	**VEGF +**		
	Chemotherapy	FOLFIRI / FOLFOX		
3rd / 4th Line	Antibody / TKI	**EGFR +**	**Regorafenib**	
	Chemotherapy	Irinotecan containing	non	
	TKI	**Regorafinib**	Clinical trial	

No need to wait for CLGB C80405 results
Head-to-Head Comparisons VEGF / EGFR

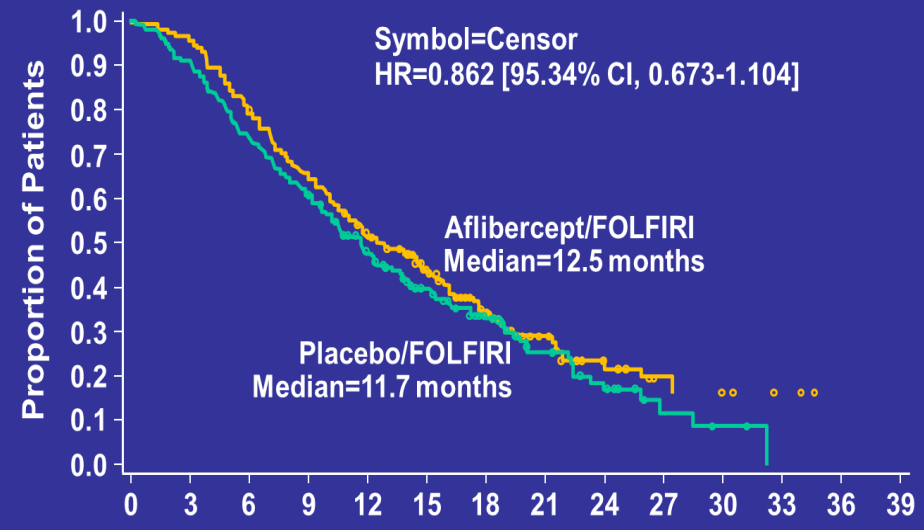
Trial	n	Chemo Backbone	Targeted Therapy
FIRE-3	**592**	**FOLFIRI**	**Cetuximab** **Bevacizumab**
PEAK	**285**	**FOLFOX**	**Panitumumab** **Bevacizumab**
CALGB C80405	**1177**	**FOLFOX (~2/3) or FOLFIRI (~1/3)**	**Cetuximab** **Bevacizumab**
SPIRITT 2nd-line	**182**	**FOLFIRI**	**Panitumumab** **Bevacizumab**

FIRE-3 is already and will be in the future the largest trial on FOLFIRI
CALGB 80405 will mostly add evidence on FOLFOX

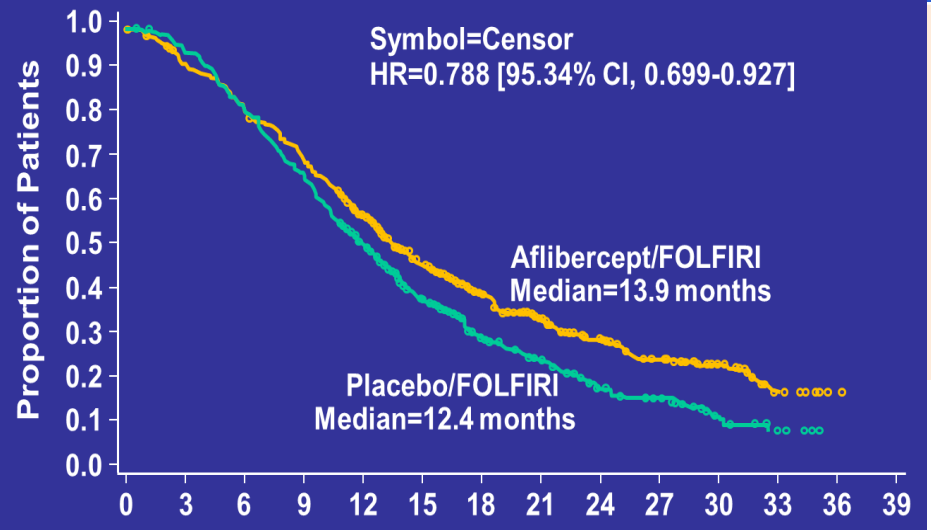
VEGF Inhibition in 2nd or later line therapy

	2nd line VEGF			„Last“ line multi VEGF TKI
	TML 18147	E3200	VELOUR	CORRECT
Bev in 1st line	all pts.			all pts (+ EGFR if RASwt)
2nd line Chemoth				CC
VEGF				

Prior Bevacizumab



No Prior Bevacizumab



Conclusions

- ✓ **Patients with RAS wt tumors benefit from EGFR therapy**
- ✓ **Group 1:**
  - **EGFR antibodies prolong survival in LLD CRC and induce more R0 resection**
- ✓ **Group 2+3:**
  - **In 1st line metastatic CRC EGFR antibodies prolong OS in 3 out of 4 randomised trials with FOLFIRI or FOLFOX**
  - **Compared to Bevacizumab combinations (FOLFIRI or FOLFOX) prolong survival in 1st line**

VOLUME 25 · NUMBER 29 · OCTOBER 10 2007

JOURNAL OF CLINICAL ONCOLOGY

Surrogate End Points for Median Overall Survival in Metastatic Colorectal Cancer: Literature-Based Analysis From 39 Randomized Controlled Trials of First-Line Chemotherapy

Patricia A. Tang, Søren M. Bentzen, Eric X. Chen, and Lillian L. Siu

PFS and OS

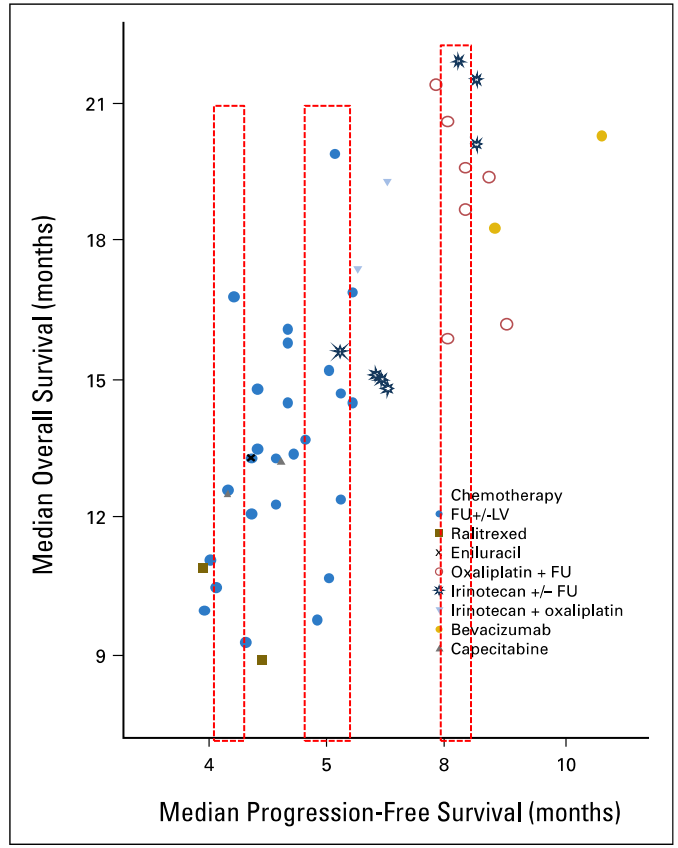
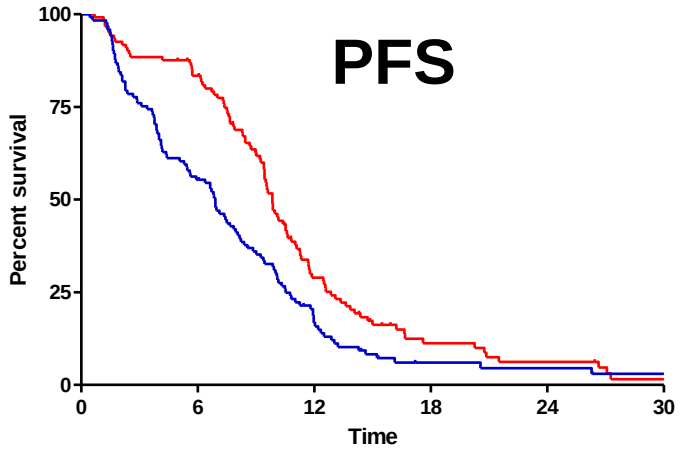
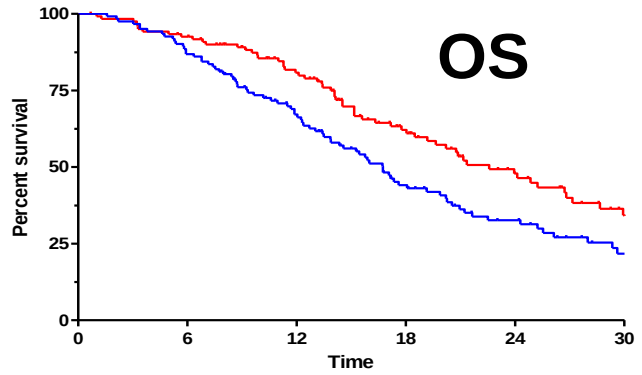


Fig 1. Correlation between median progression-free survival and median overall survival. FU, fluorouracil; LV, leucovorin.

FOLFIRI vs. FOLFOXIRI

	FOLFIRI (122 pts)	FOLFOXIRI (122 pts)
RR	**34%**	**60%**
PD	**24%**	**11%**
R0	**6%* (7 pts)**	**15%* (18 pts)**
Pts with liver mets only	**N=42**	**N=39**
R0	**12%**	**36%**





Falcone et al.
JCO 2007/ASCO 2007

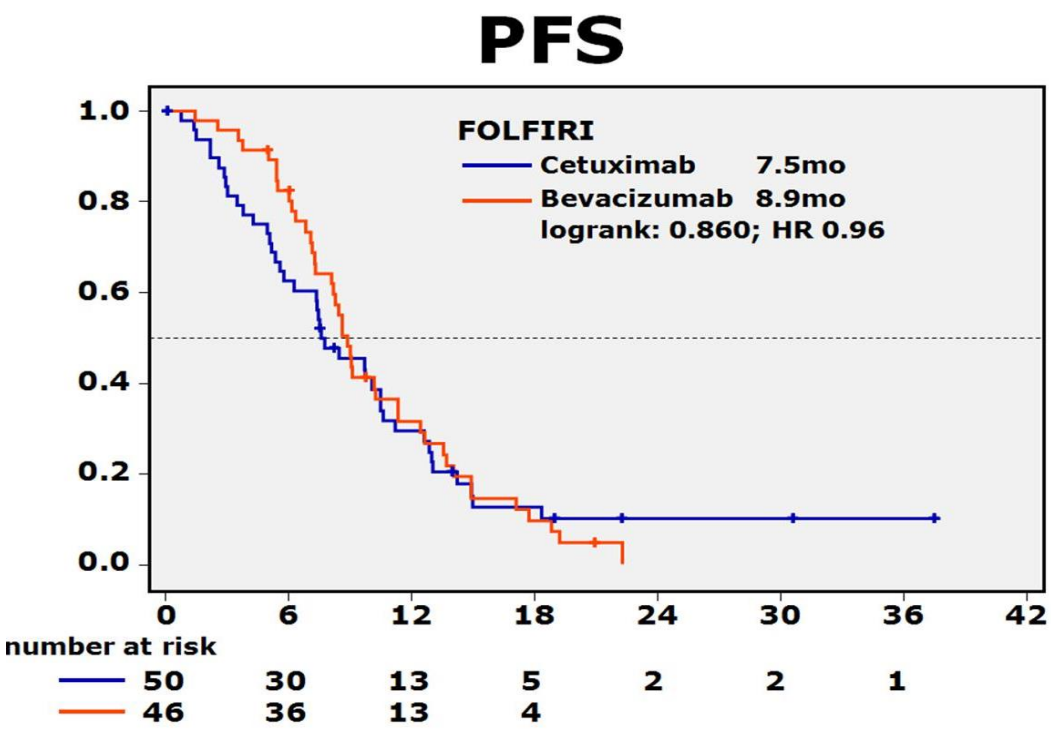
FOLFIRI vs. FOFOXIRI

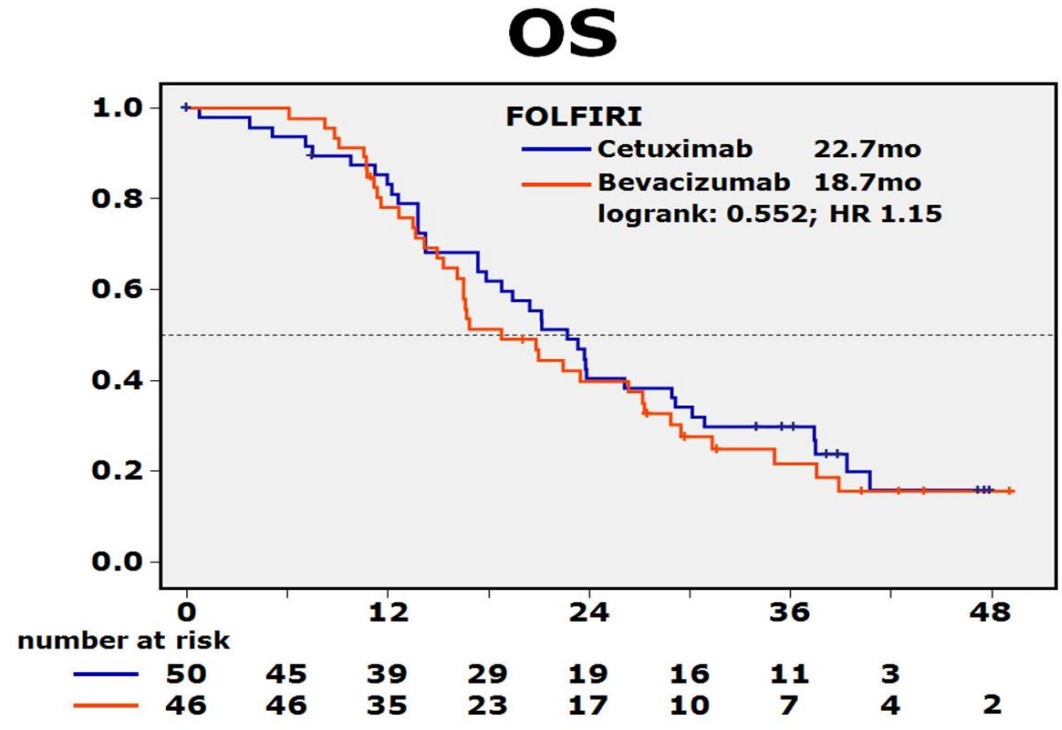
Regimen	N	RR	PFS	OS	Author
FOLFIRI	122	41%	6.9	16.7	Falcone
FOLFOXIRI	122	66%	9.9	23.6	JCO 2007
FOLFIRI+Bev	256	53%	9.7	25.8	Falcone
FOLFOXIRI+Bev	252	65%	12.2	31.0	ASCO 2013

- FOLFOXIRI more effective than FOLFIRI
- Role of bevacizumab?
- Promising regimen for BRAF mut
- FOLFIRI if prior adjuvant FOLFOX?

VEGF in (K)RAS mut disease?
FIRE3 (KRAS mt)

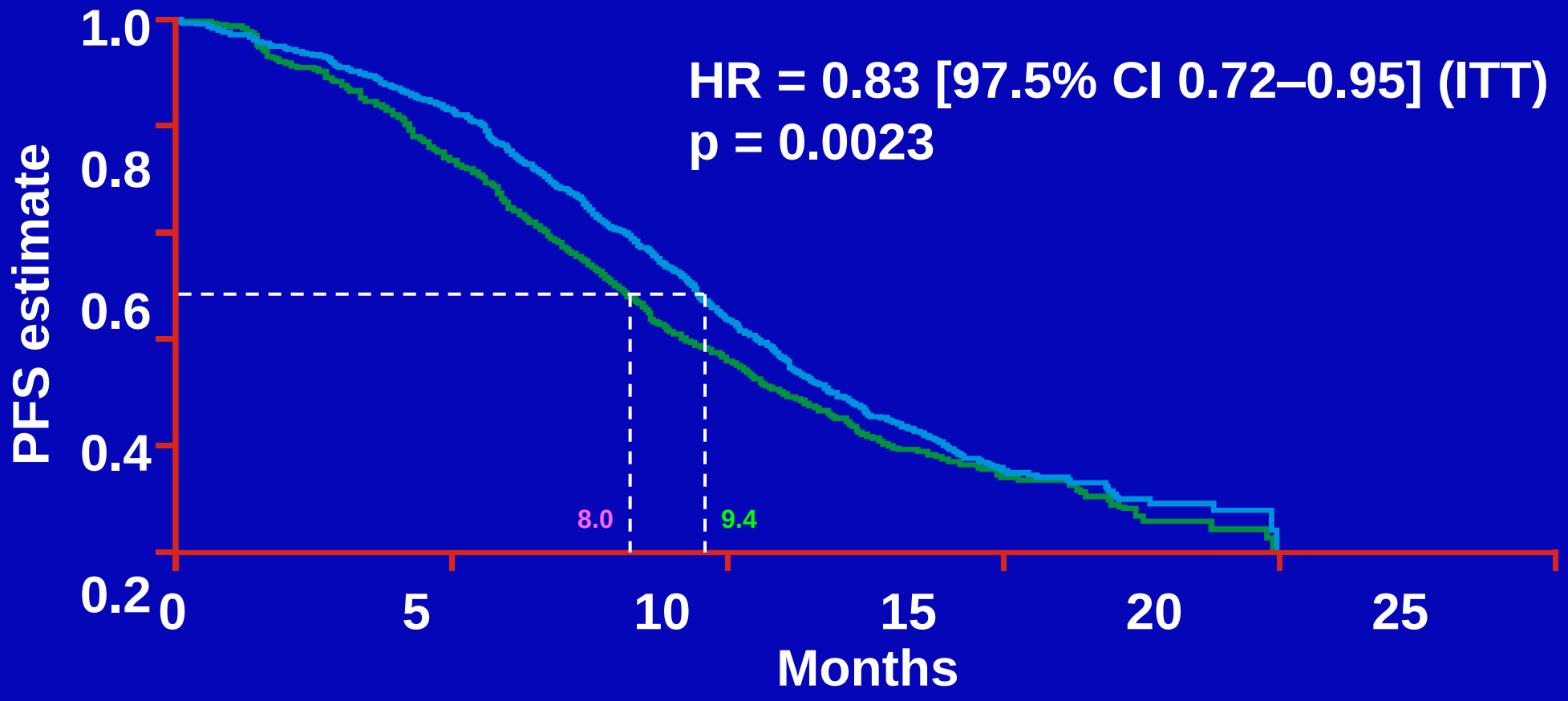
Stintzing et al. Ann Oncol 2012





	FOLFIRI + cetuximab	FOLFIRI + bevacizumab	p-value*
response rate (%) 95% CI	43.9 (28.7-59.1)	47.8 (33.4-62.3)	0.83

FOLFOX or XELOX +/- bevacizumab
Progression free survival (NO16966)

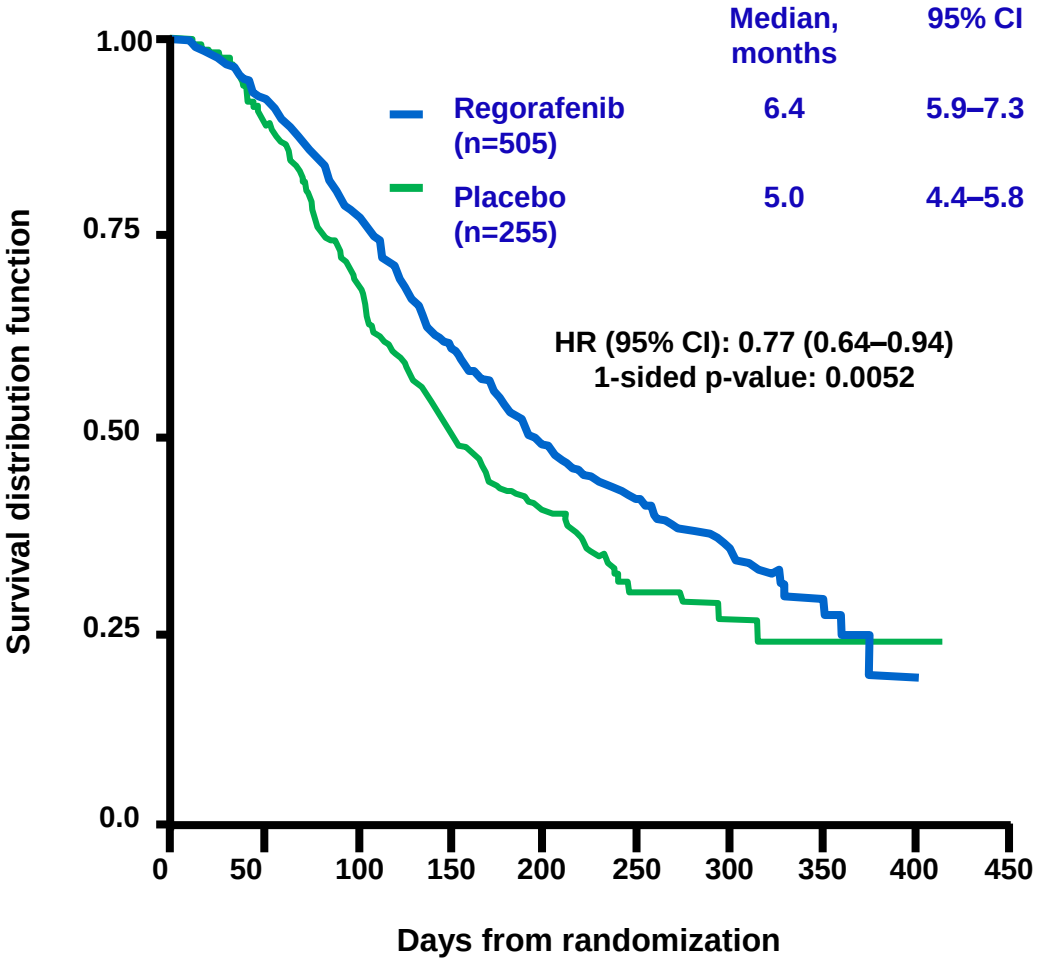


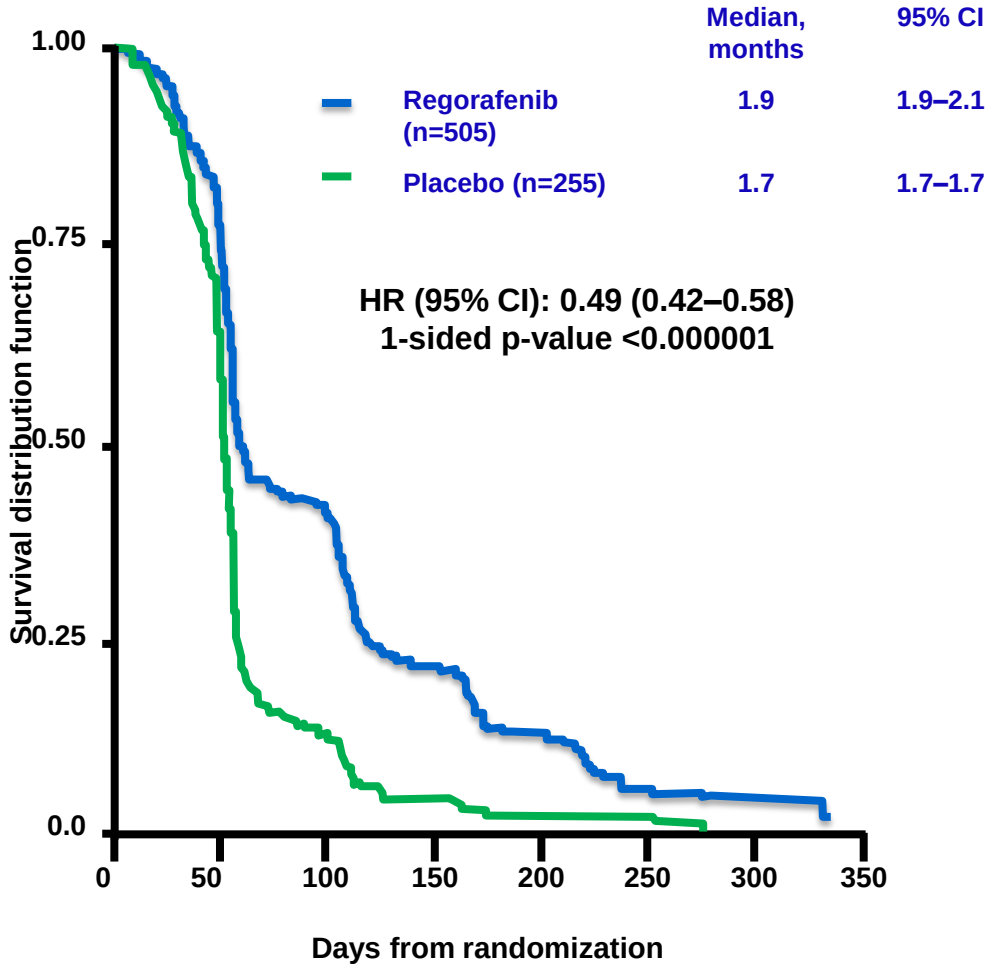
Saltz et al. JCO 2008

END

Discussion slides

CORRECT: BSC +/- Regorafenib
OS and PFS





*** RR = 1.0% vs .04%**

Grothey A, et al. ASCO GI 2012 (Abstract No. LBA385)

Group 0

Resectable metastases

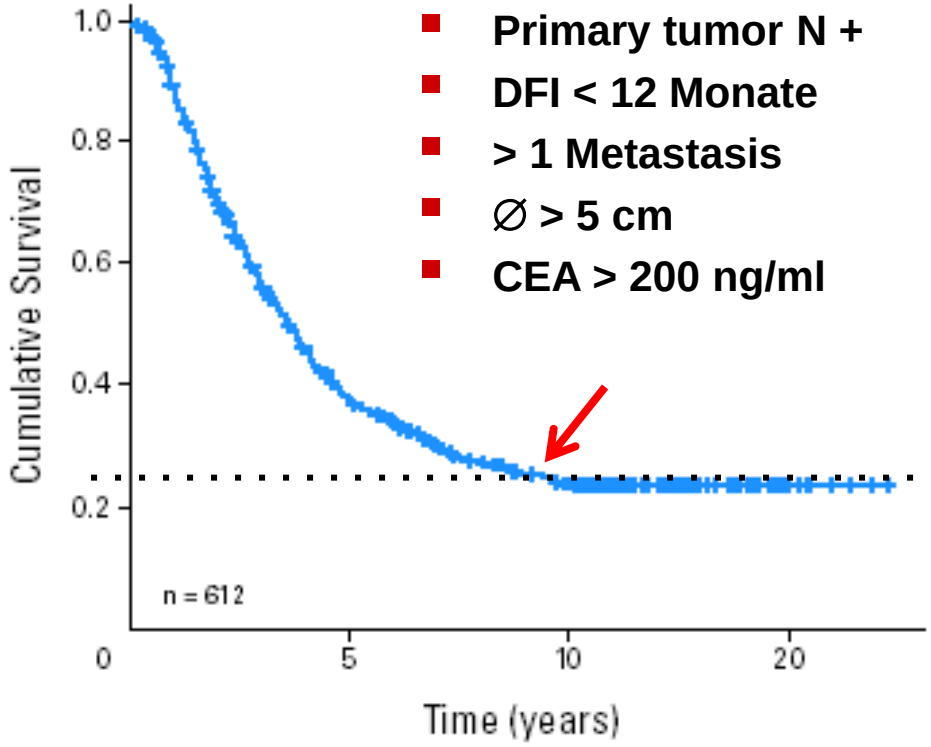
VOLUME 25 · NUMBER 29 · OCTOBER 10 2007

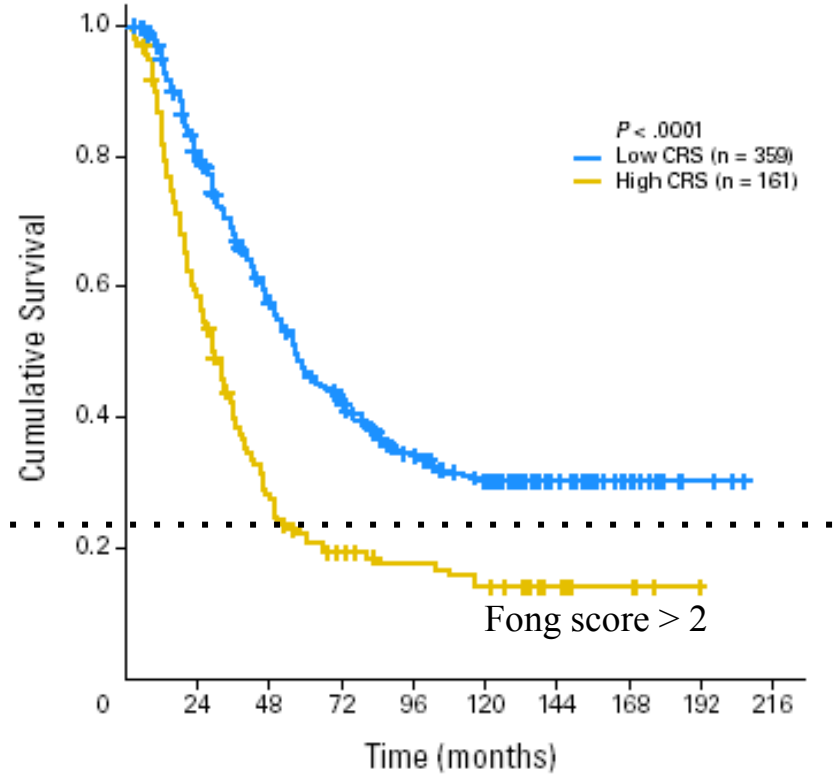
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Actual 10-Year Survival After Resection of Colorectal Liver Metastases Defines Cure

James S. Tomlinson, William R. Jarnagin, Ronald P. DeMatteo, Yuman Fong, Peter Kornprat, Mithat Gonen, Nancy Kemeny, Murray F. Brennan, Leslie H. Blumgart, and Michael D'Angelica

- **Primary tumor N +**
- **DFI < 12 Monate**
- **> 1 Metastasis**
- **∅ > 5 cm**
- **CEA > 200 ng/ml**



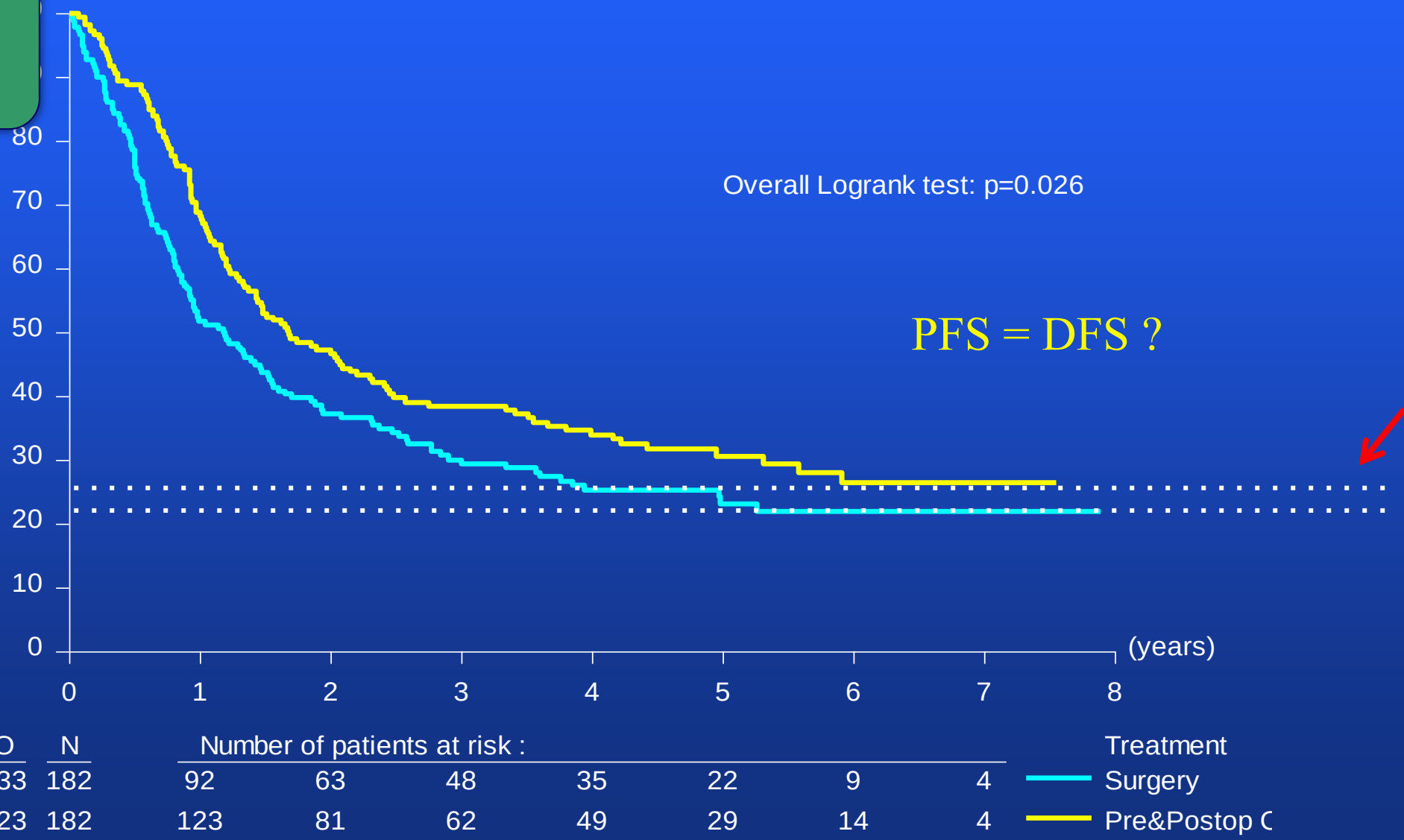


Disease specific survival (DSS)

EORTC 40983: PFS irrespective of resection (usual definition), all patients, updated May25, 2009

Group 0

Resectable metastases



Group 0

Resectable metastases

A randomised clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in KRAS wild-type patients with operable metastases from colorectal cancer

The New EPOC study

CANCER RESEARCH UK

Operable (including borderline operable) colorectal liver metastases

R

Arm A (control)
Chemotherapy 12 weeks
Liver resection
Chemotherapy 12 weeks

≈54%

≈2/3 FOLFOX

Arm B (experimental)
Chemotherapy + cetuximab 12 weeks
Liver resection
Chemotherapy + cetuximab 12 weeks

RR 58%

UNIVERSITY OF Southampton
Clinical Trials Unit

Primrose et al.

PRESENTED AT: ASCO Annual '13 Meeting

Evaluation of ORR

ORR	FOLFIRI + Cetuximab %	FOLFIRI + Cetuximab 95%-CI	FOLFIRI + Bevacizumab %	FOLFIRI + Bevacizumab 95%-CI	Odds ratio	p
KRAS exon 2 WT ITT population (N= 592)	62.0	56.2 – 67.5	58.0	52.1 – 63.7	1.18 0.85-1.64	0.183*
RAS WT (N= 342)	65.5	57.9 – 72.6	59.6	51.9 – 67.1	1.28 0.83-1.99	0.32**
RAS MT (N= 65)	38.2	22.2 – 56.4	58.1	39.1 – 75.5	0.45 0.17-1.21	0.14**
KRAS exon 2 MT and RAS MT (N= 178)	38.0	28.1 – 48.8	51.2	40.1 – 62.1	0.59 0.32-1.06	0.097**

p = *one-sided Fisher´s exact test
** two-sided Fisher's exact test

Consider STEPs for treatment in metastatic CRC

- **S**trategy (curative vs. palliative)
- **T**umor biology (aggressive vs. indolent)
- **E**GFR dependency (wt vs. mut)
- **P**atient

Influence of KRAS and RAS mutational status on survival
Randomised trials of EGFR antibodies – 1st line

Trial	Therapy	OS (mo) KRAS		OS (mo) RAS wt		OS (mo) RAS mut	
		CTx	+EGFR	CTx	+EGFR	CTX	+EGFR
CRYSTAL *(n=666)*	*FOLFIRI +/- Cetux**	20.0	**23.5**	ASCO	**ASCO**	17.7	16.4
PRIME *(n=656)*	*FOLFOX +/- Pani**	19,4	**23.8**	20.2	**26.0**	**19.2**	15.6
OPUS *(n=197)*	*FOLFOX +/- Cetux**	18,5	(22.8)	17.8	**19.8**	**17.8**	13.5

Influence of KRAS and RAS mutational status on survival
Randomised trials of EGFR antibodies – 1st line

Trial	Therapy	OS (mo) KRAS		OS (mo) RAS wt		OS (mo) RAS mut	
		+VEGF	+EGFR	+Bev	+EGFR	+VEGF	+EGFR
FIRE 3 *(n=592)*	*FOLFIRI*	25.0	**28.7**	25.6	**33.1**	**20.6**	20.3
CALGB (≈400)	*FOLFIRI*	na	na	na	na	-	-
PEAK *(n=285)*	*FOLFOX +/- Pani**	25,4	**NR**	28.9	**41.3**	-	-
CALGB (≈800)	*FOLFOX*	na	na	na	na	-	-

Evaluation of PFS

PFS	FOLFIRI + Cetuximab		FOLFIRI + Bevacizumab		Hazard ratio	p
	months	95%-CI	months	95%-CI		
KRAS exon 2 WT ITT population (N= 592)	10.0	8.8 – 10.8	10.3	9.8 – 11.3	1.06 (0.88 – 1.26)	0.547
RAS WT (N= 342)	10.4	9.5 – 12.2	10.2	9.3 – 11.5	0.93 (0.74 – 1.17)	0.54
RAS MT (N= 65)	6.1	5.3 – 8.5	12.2	9.7 – 13.9	2.22 (1.28 – 3.86)	0.004
KRAS exon 2 MT and RAS MT (N= 178)	7.5	6.1 – 9.0	10.1	8.9 – 12.2	1.31 (0.98 – 1.78)	0.085

p = log-rank test

Evaluation of OS

PFS	FOLFIRI + Cetuximab		FOLFIRI + Bevacizumab		Hazard ratio	p
	months	95%-CI	months	95%-CI		
KRAS exon 2 WT ITT population (N= 592)	28.7	24.0 – 36.6	25.0	22.7 – 27.6	0.77 (0.62 – 0.96)	0.017
RAS WT (N= 342)	33.1	24.5 – 39.4	25.6	22.7 – 28.6	0.70 (0.53 – 0.92)	0.011
RAS MT (N= 65)	16.4	15.9 – 27.6	20.6	17.0 – 28.4	1.20 (0.64 – 2.28)	0.57
KRAS exon 2 MT and RAS MT (N= 178)	20.3	16.4 – 23.4	20.6	17.0 – 26.7	1.09 (0.78 – 1.52)	0.60

p = log-rank test

OS in Trials with 1st-line Bev

Study		1st line Regimen	2nd line CTx plus		PFS (1st line) (mo)	OS (mo)
			VEGF	EGFR		
TRIBE	*1st line studies*	FOLFIRI + Bev	n.a.		9.7	25.8
FIRE-3#		FOLFIRI + Bev	17.3%	41.4%	10.3	25.0
TML	*Positive selection: Patients suitable for 2nd line Tx*	Chemo + Bev	100%	0%	n.a.	23.9

Best what is acheivable with Bev beyond progression in positively selected subgroup (no PD within 3 months of 1st line therapy and survived 1st line Tx)

Falcone A. et al. ASCO 2013; Bennouna J, et al. Lancet Oncol 2013; Stintzing, Heinemann et al. ASCO 2013

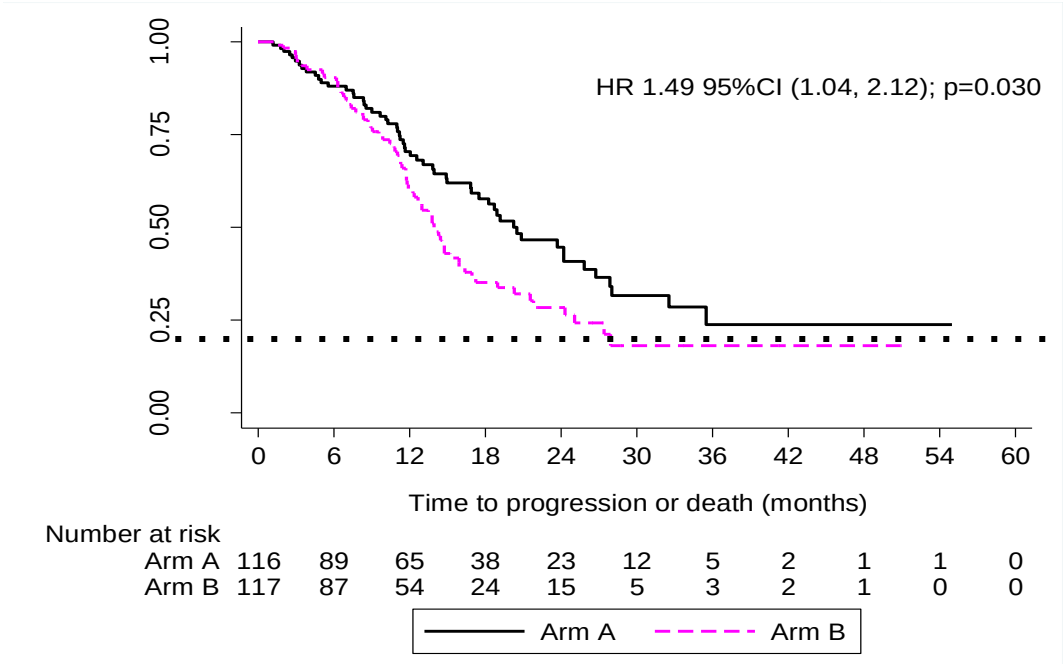
KRAS codon 12/13 wt only

Group 0

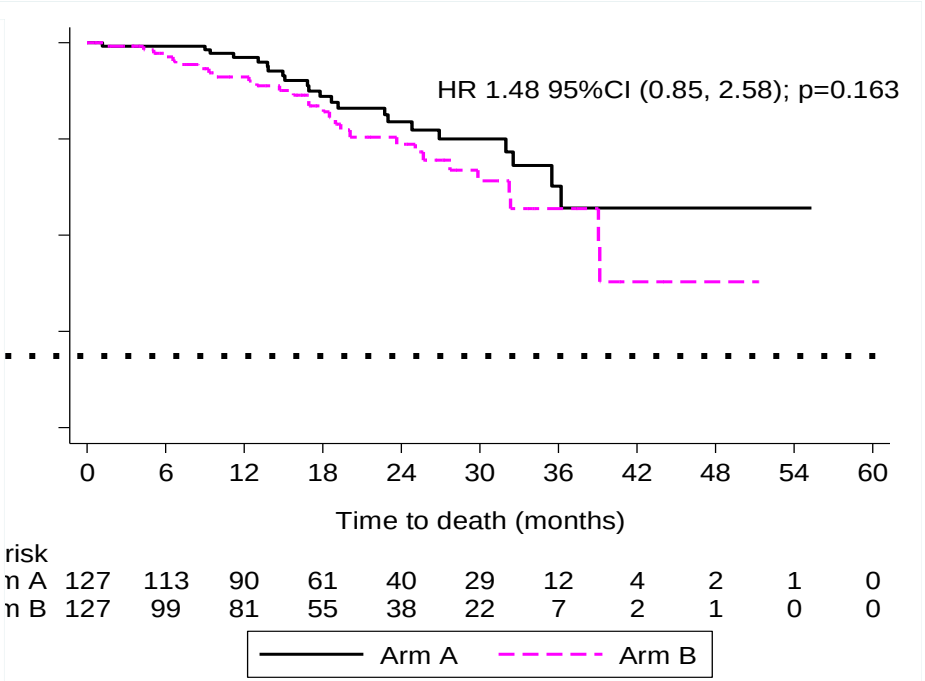
Resectable metastases

PFS and OS all randomised KRAS wt

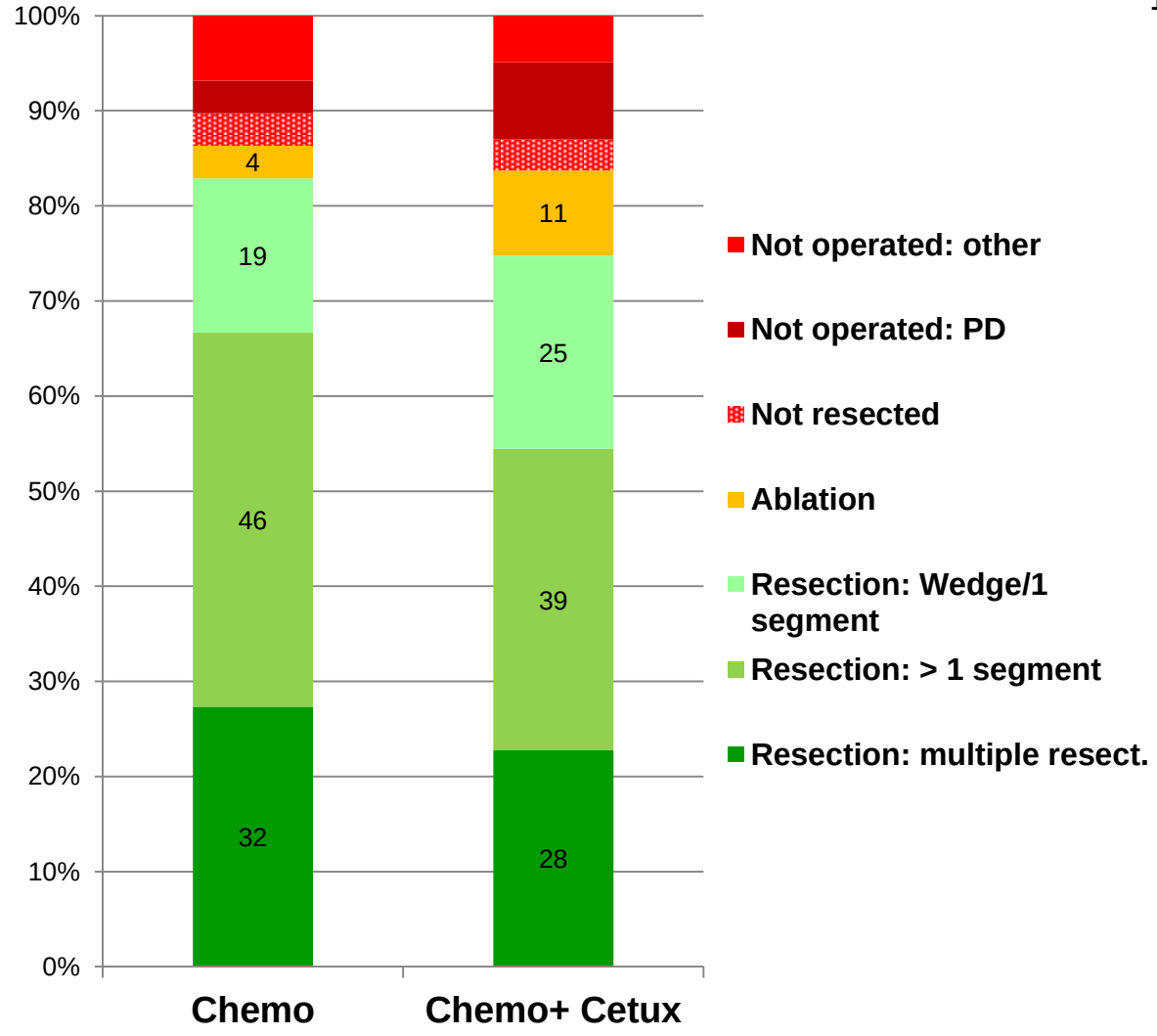
PFS primary endpoint

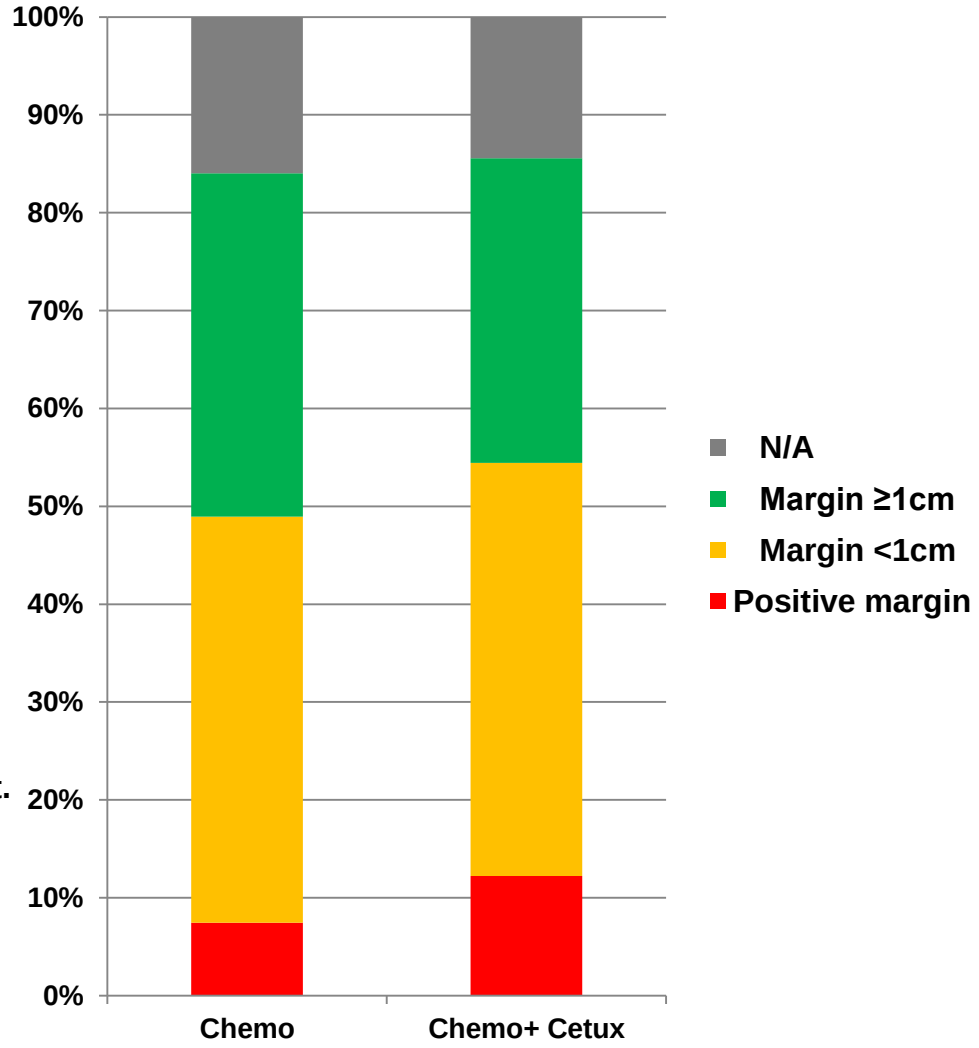


OS



Group 0 Resectable metastases





2nd-line treatment

	FOLFIRI + Cetuximab N= 297	FOLFIRI + Bevacizumab N= 295
Alive after 1st-line therapy	87.5% (260/297)	84.7% (250/295)
Any 2nd-line therapy	78.5% (204/260)	76.4% (191/250)
2nd-line substances, %	n=204 (100)	n=191 (100)
Fluoropyrimidine %	91.7	85.3
Oxaliplatin %	63.7	62.8
Irinotecan %	15.7	15.7
Bevacizumab %	46.6	17.3
Anti-EGFR mAB %	15.2	41.4

Treatment with a substance not being part of 1st-line therapy

FIRE-3: 2nd line regimens (patients alive after 1st line therapy)

2nd line substances, %		Cetuximab + FOLFIRI n=204	Bevacizumab + FOLFIRI n=191
Chemotherapy alone	Fluoropyrimidine	6.4	5.8
	Oxaliplatin-based	26.0	30.4
Bevacizumab + chemotherapy	Fluoropyrimidine	4.4	4.7
	Oxaliplatin-based	29.4	11.5
	Irinotecan-based	12.4	0.5
Anti-EGFR mAb + chemotherapy	Irinotecan-based	2.0	15.2
	Oxaliplatin-based	6.4	18.3
Anti-EGFR mAb alone		4.9	5.8
Others		8.3	7.9

Modest D, et al. WCGC 2013 (Abstract No. O-0029)

FIRE-3: 2nd line regimens (patients alive after 1st line therapy)

2nd line substances, %		Cetuximab + FOLFIRI n=204	Bevacizumab + FOLFIRI n=191
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Bevacizumab + chemotherapy	Fluoropyrimidine	4.4	4.7
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	Irinotecan-based	12.4	0.5
Anti-EGFR mAb + chemotherapy	Irinotecan-based	2.0	15.2
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Others		8.3	7.9

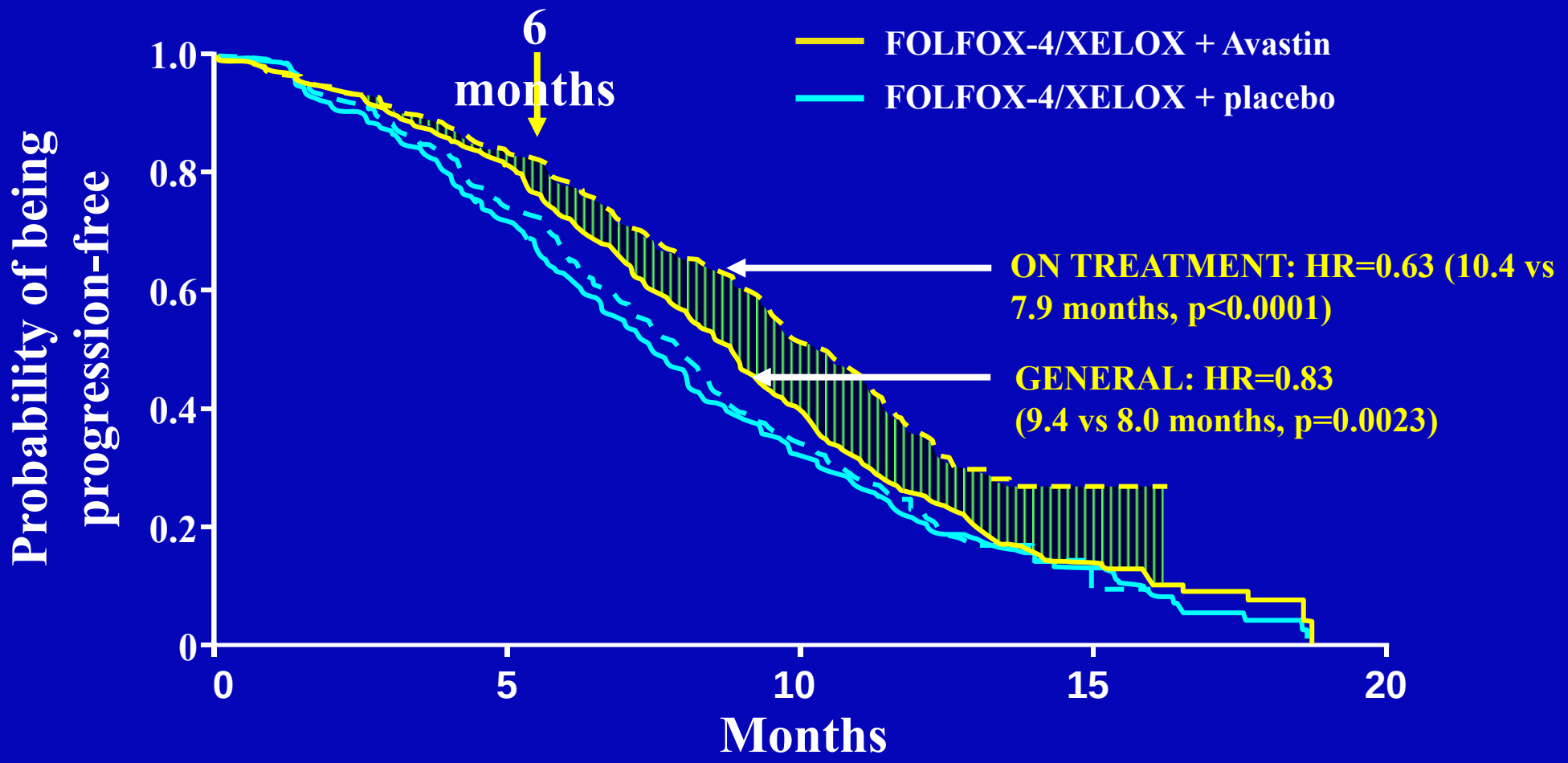
Modest D, et al. WCGC 2013 (Abstract No. O-0029)

Optimized treatment decisions

Consider STEPs for treatment in mCRC

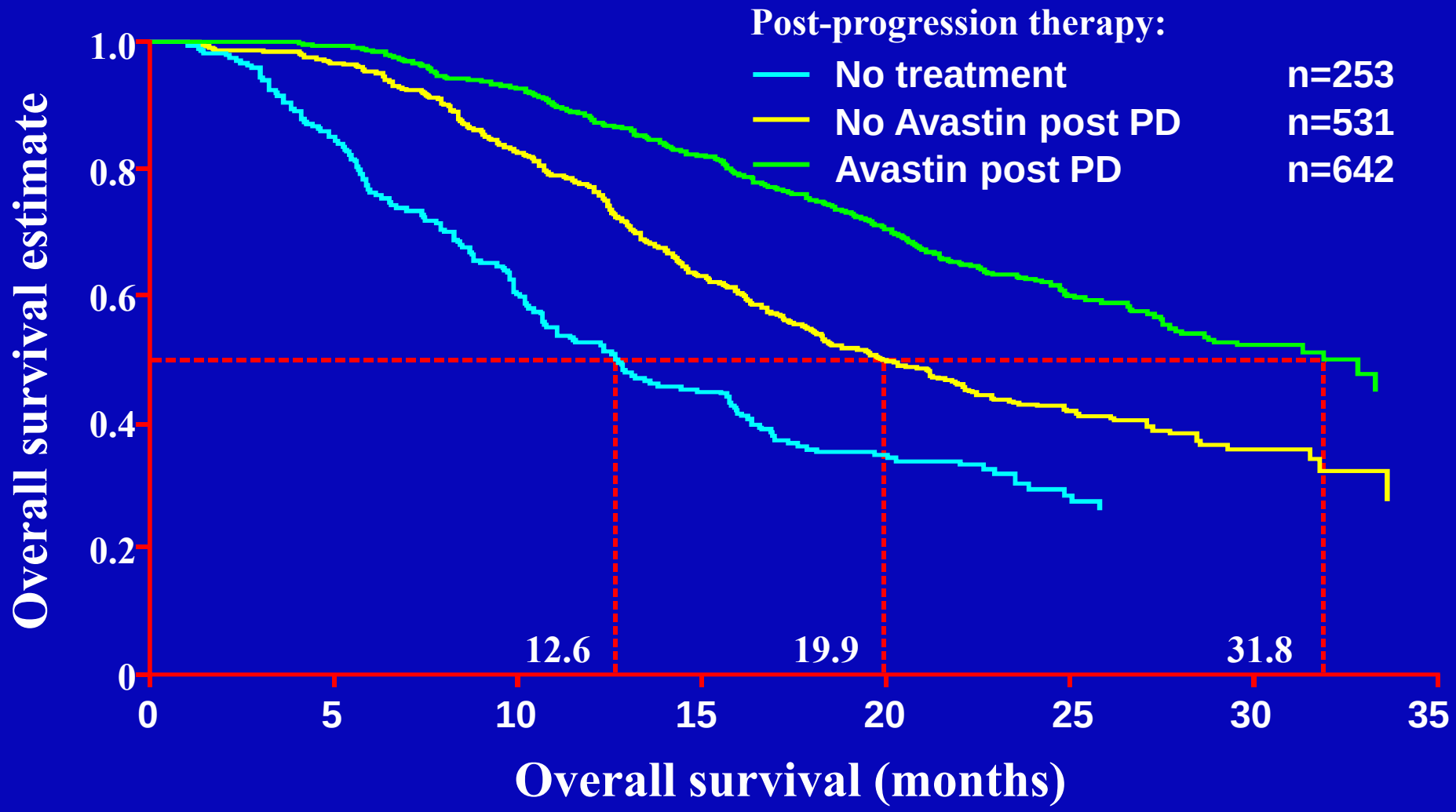
- **S**trategy — curative vs. palliative
- **T**umor biology — aggressive vs. indolent
- **E**GFR dependency — wt vs. mut
- **P**atient

NO16966: strong benefit from treatment until progression



Saltz, et al. ASCO 2007

BRITE: Avastin increases survival post first-progression

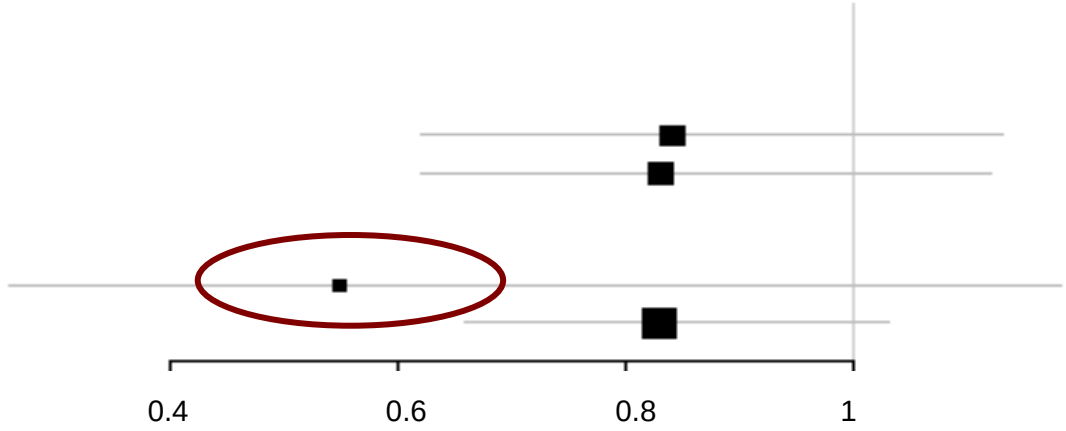


PD = progressive disease

Grothey, et al. ASCO 2007

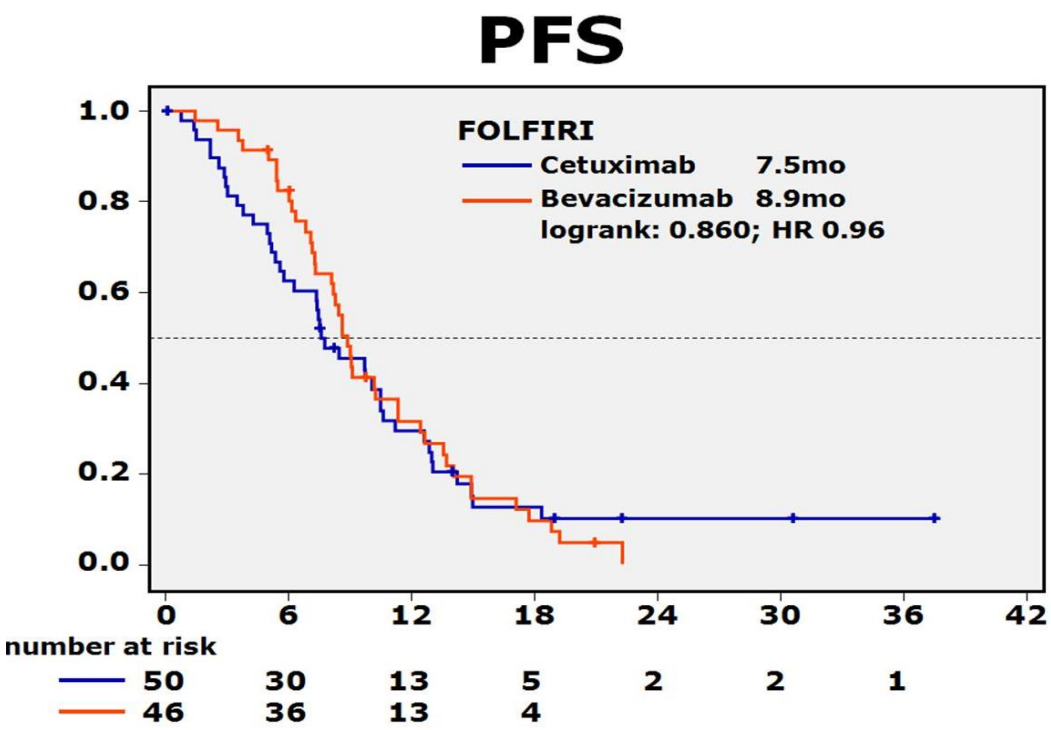
Subgroup analyses of PFS – molecular characteristics

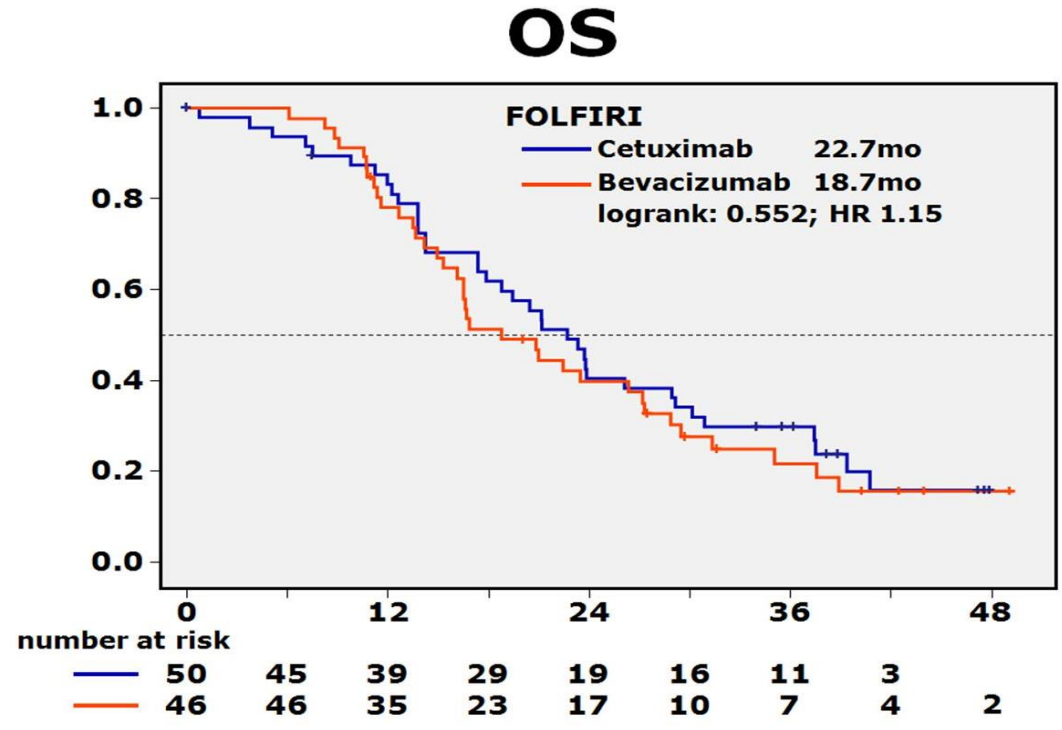
Factor	N	HR	p
KRAS status			
mut	200	0.84	0.973
wt	193	0.83	
BRAF status			
mut	28	0.55	0.323
wt	365	0.83	



VEGF in (K)RAS mut disease?
FIRE3 (KRAS mt)

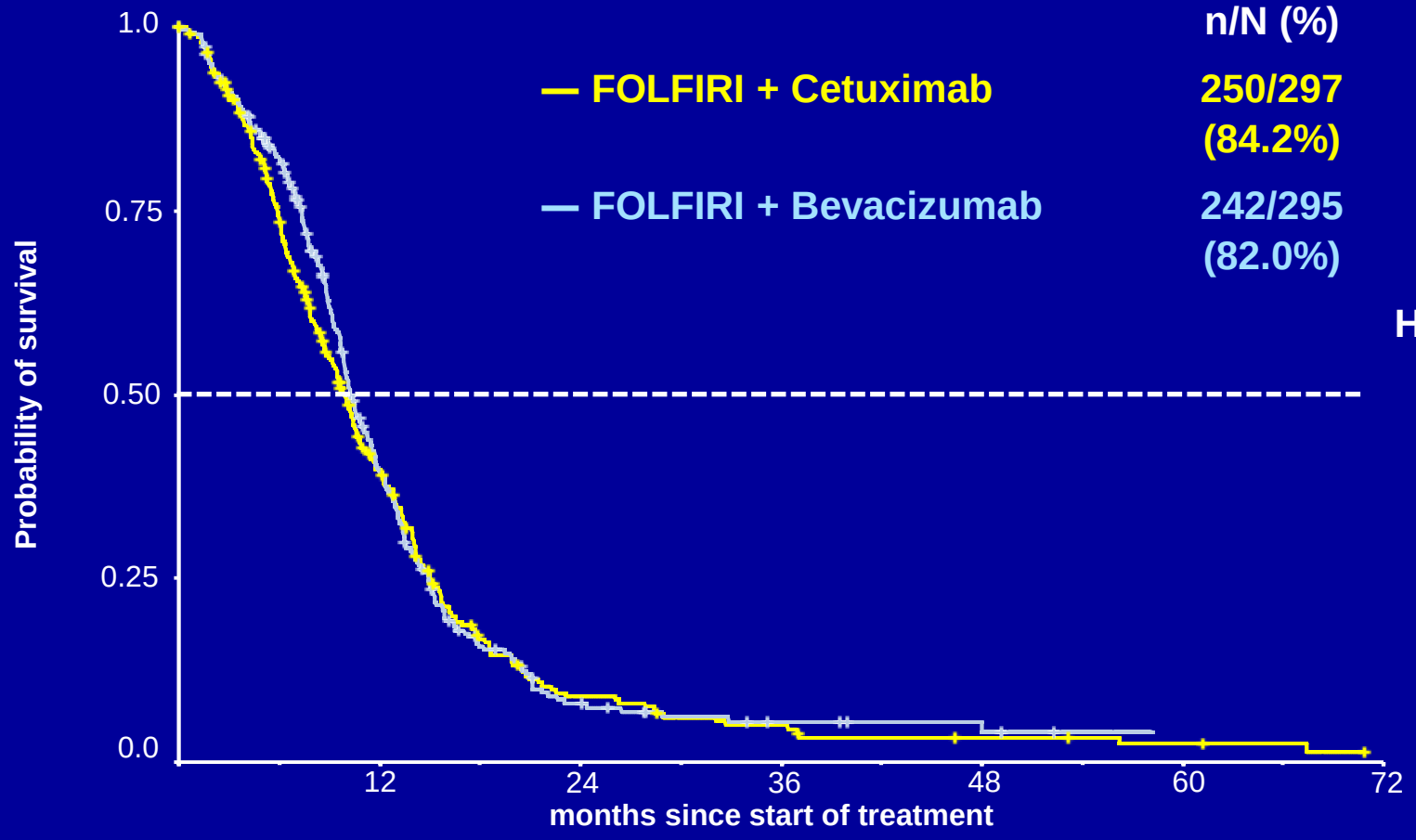
Stintzing et al. Ann Oncol 2012





	FOLFIRI + cetuximab	FOLFIRI + bevacizumab	p-value*
response rate (%) 95% CI	43.9 (28.7-59.1)	47.8 (33.4-62.3)	0.83

Progression-free survival



	Events n/N (%)	Median (months)	95% CI
— FOLFIRI + Cetuximab	250/297 (84.2%)	10.0	8.8 – 10.8
— FOLFIRI + Bevacizumab	242/295 (82.0%)	10.3	9.8 – 11.3

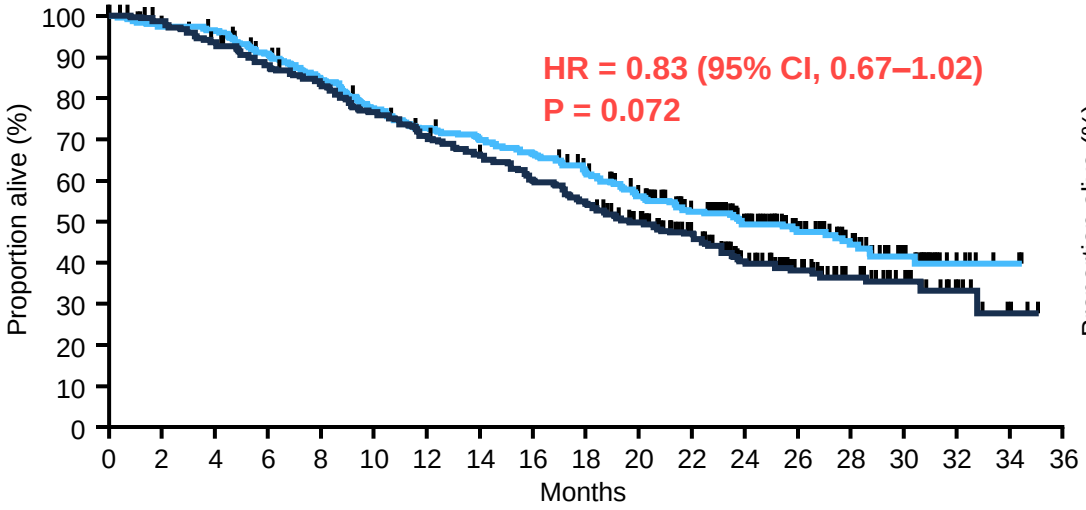
HR 1.06 (95% CI: 0.88 – 1.26)
p (log-rank)= 0.547

No. at risk						
	297	100	19	10	5	3
	295	99	15	6	4	

PRIME *RAS/RAF OS* analysis*
Refinement of patient population by WT *RAS* status

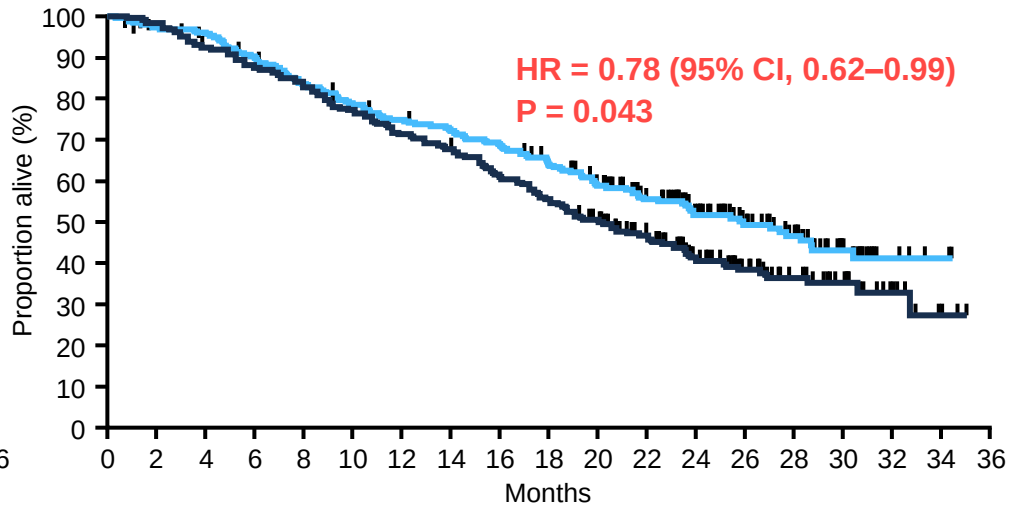
Overall survival

Original WT *KRAS* exon 2 testing



	Events n (%)	Median (95% CI) months
Panitumumab + FOLFOX4 (n = 325)	165 (51)	**23.9** (20.3–28.3)
FOLFOX4 (n = 331)	190 (57)	**19.7** (17.6–22.6)

WT *RAS*

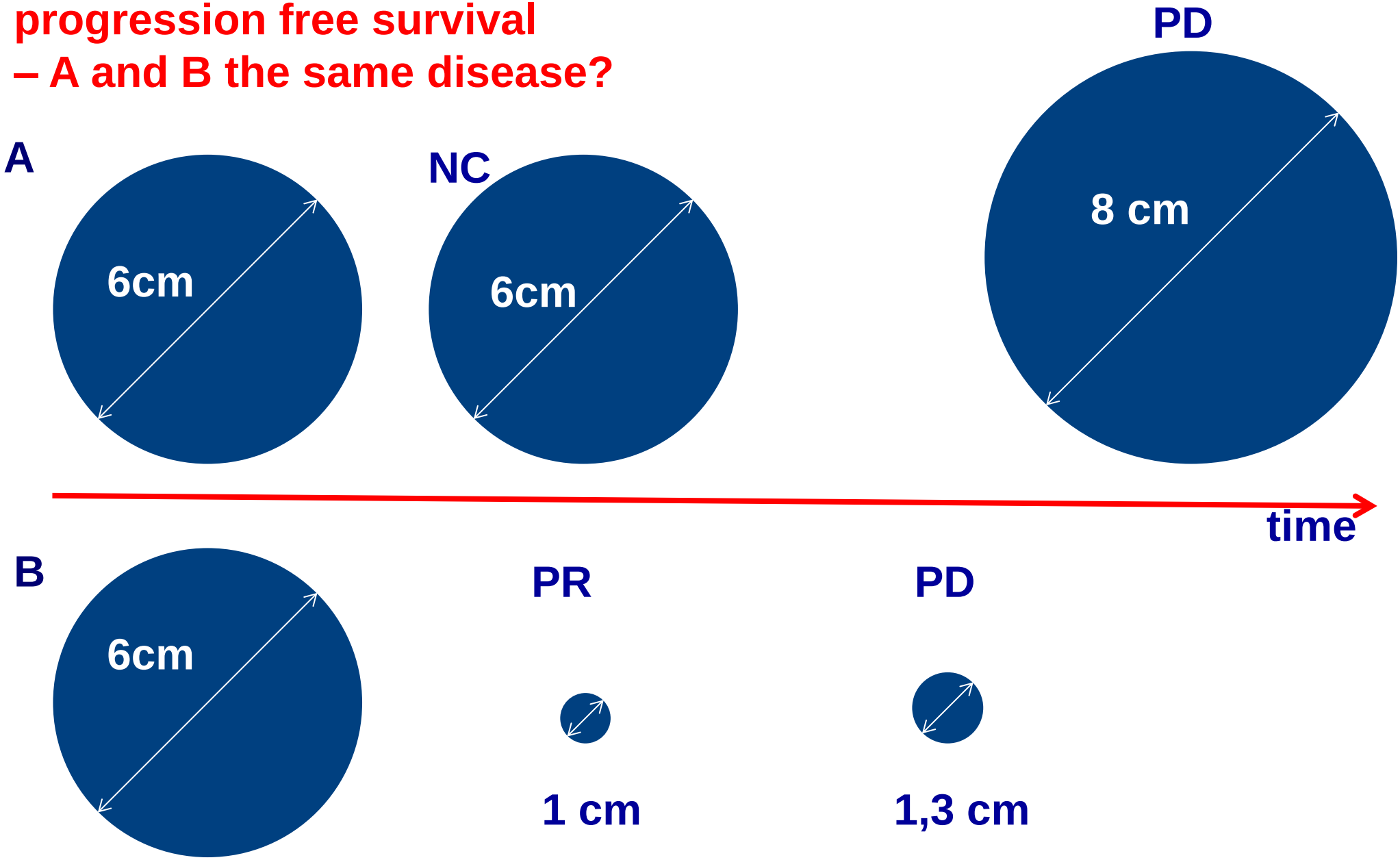


	Events n (%)	Median (95% CI) months
Panitumumab + FOLFOX4 (n = 259)	128 (49)	**26.0** (21.7–30.4)
FOLFOX4 (n = 253)	148 (58)	**20.2** (17.7–23.1)

1. Douillard JY, et al. J Clin Oncol 2010;28:4697–705;
2. Douillard JY et al New Engl J Medicine Sept 12 2013.

*Predefined retrospective analysis;
7 patients harbouring Codon 59 mutations were not excluded from this analysis.

Response to chemotherapy and progression free survival – A and B the same disease?



Conclusions EGFR or VEGFR in 1st line

- **The value of cetuximab in 1st line to prolong survival in RAS wt disease is without doubt**

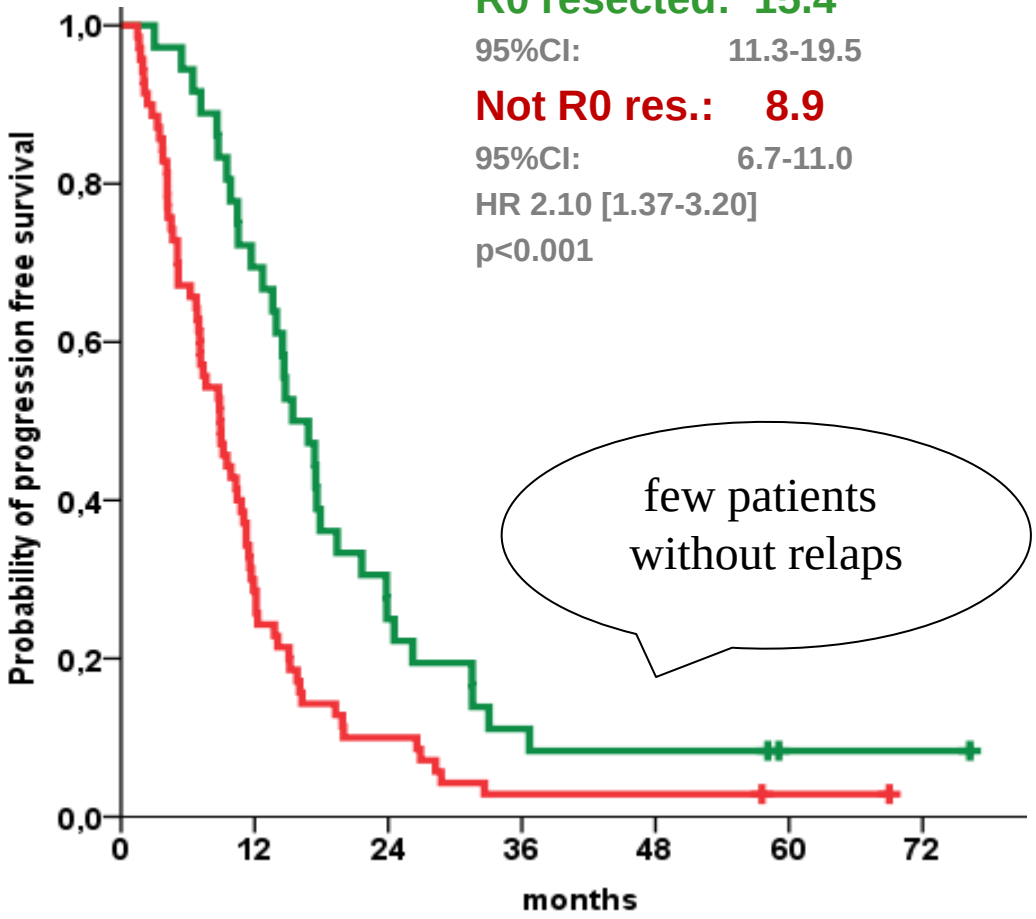
- **The efficacy of VEGF antibodies in 1st line RAS mut disease needs to be established**

Group 1

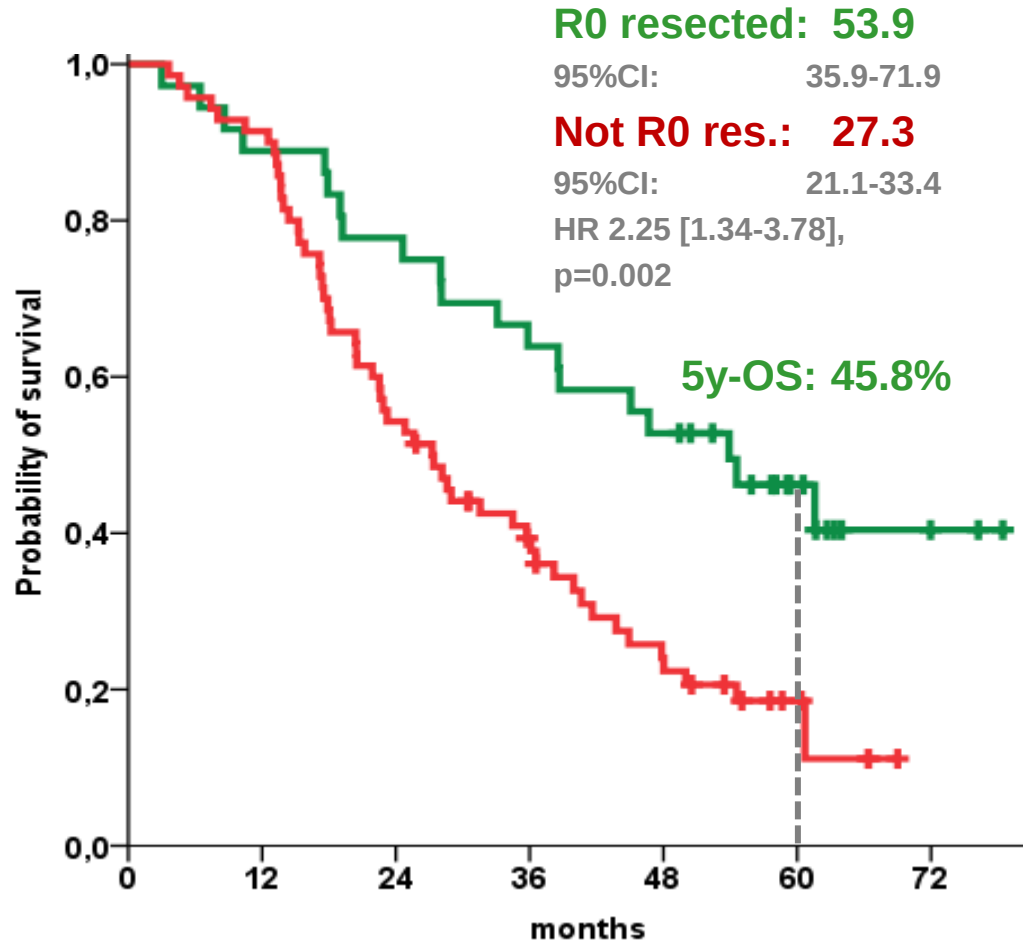
Potentially resectable metastases

CELIM: R0 Resection as a surgical „maintenance therapy“ in the continuum of care

Progression free survival



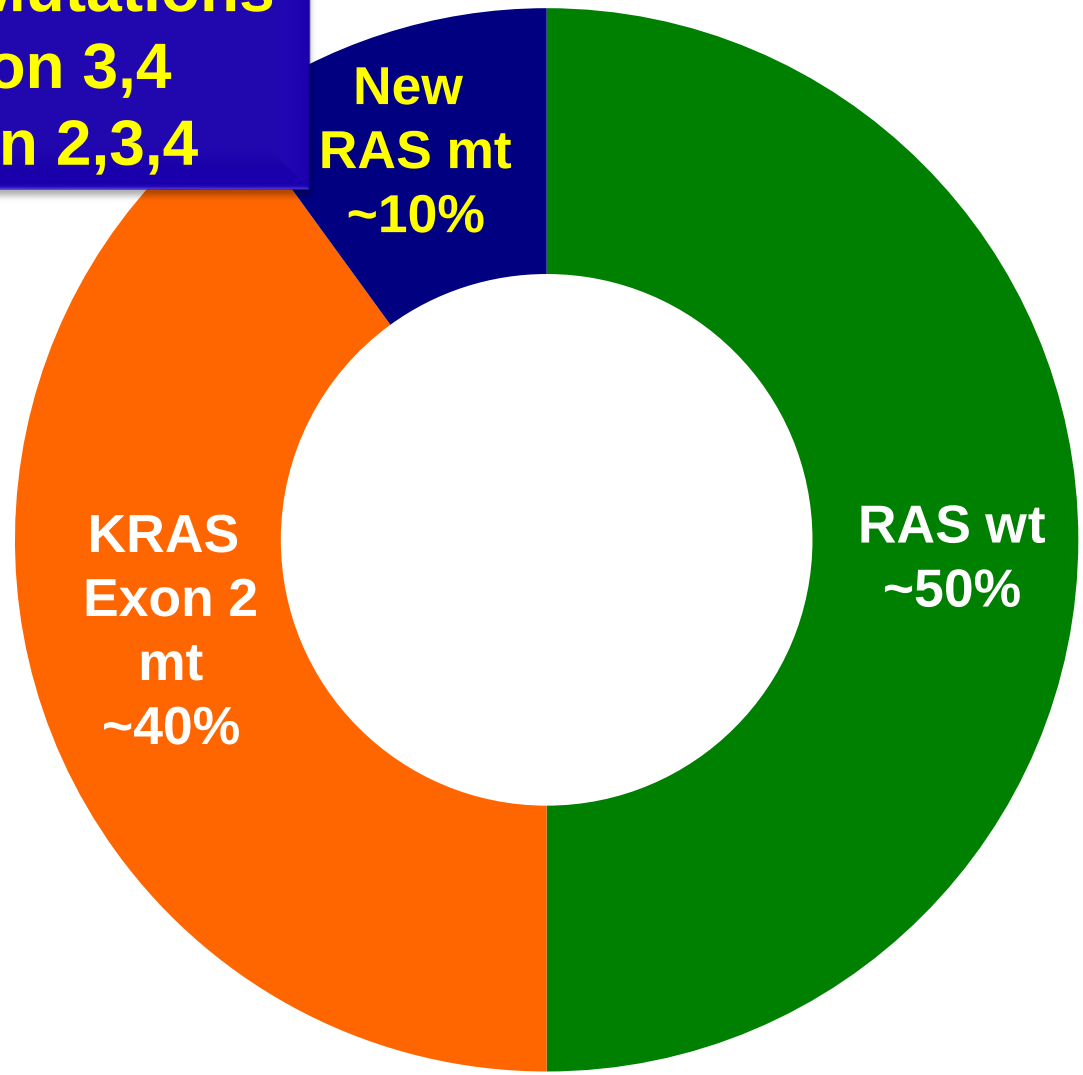
Overall survival



Update CELIM 12/2012, ASCO 2013

Distribution of mutations in mCRC

Rare KRAS Mutations
KRAS exon 3,4
NRAS exon 2,3,4



VEGF Inhibition in 2nd or later line therapy

	2nd line VEGF			„Last“ line multi VEGF TKI
	TML 18147	E3200	VELOUR	CORRECT
Bev in 1st line	all pts.	no pts	yes / no	all pts (+ EGFR if KRASwt)
2nd line Chemotherapy	FOLFIRI or FOLFOX	FOLFOX	FOLFIRI	Last line BSC
VEGF inhibitor	bevacizumab	bevacizumab	aflibercept	regorafenib
OS	11.2 v 9.8 mo HR 0.81 p=0.0062	12.9 v 10.8 mo HR 0.75 p=0.0011	13.5 v 12.1 mo HR 0.82 p=0.003	6.4 vs. 5.0 mo HR 0.77 P=0.0052

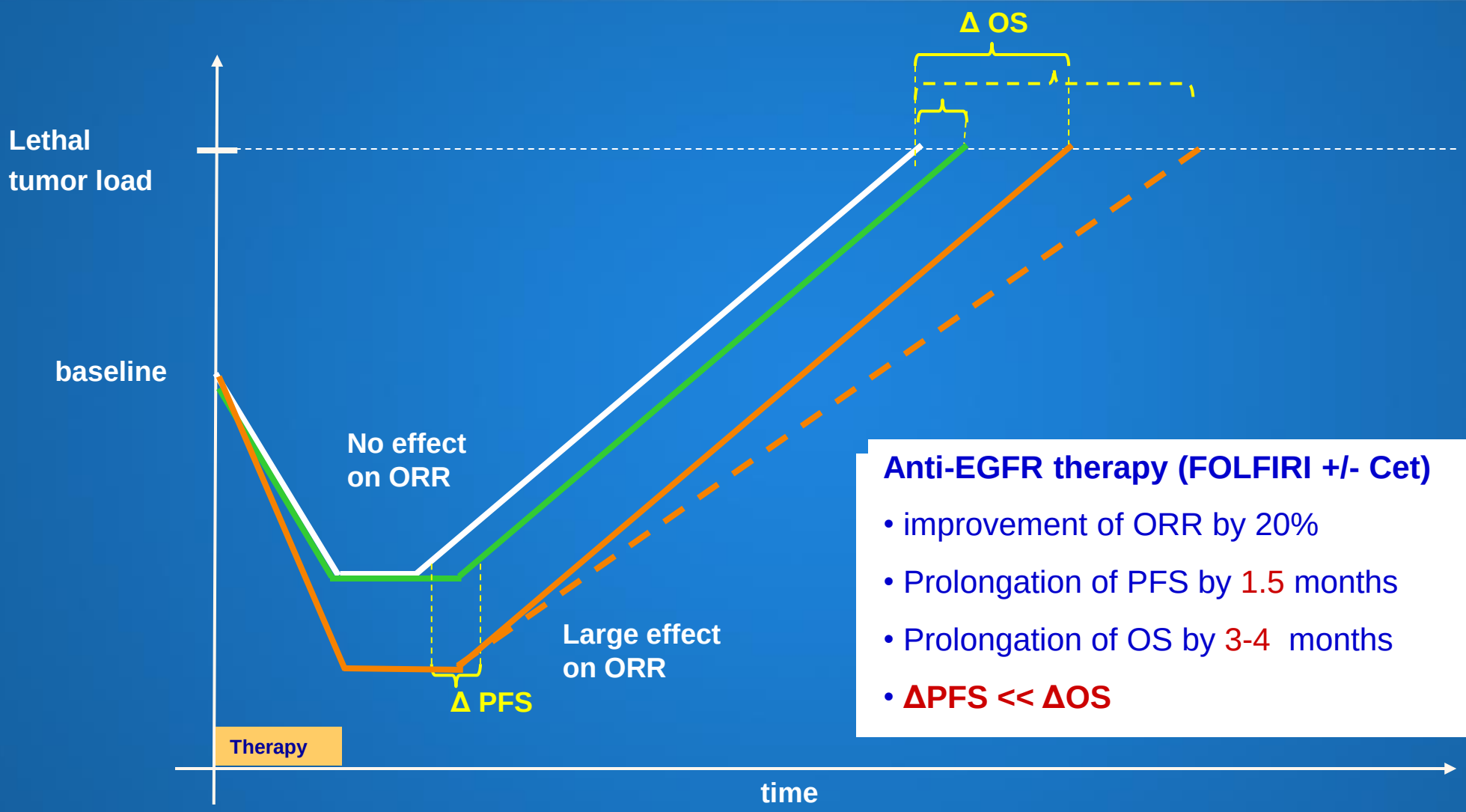
Overall survival with VEGF antibodies in 1st line or 2nd line mCRC

VEGF	Study	All pts
VEGF in 1st line		
IFL ± Bev [1)]	*Hurwitz*	+
Cape ± Bev [2)]	*Cunningham*	-
FOLFOX ± Bev [3)]	*NO16966*	-
FOLFIRI ± Bev	*n.a.*	*n.a.*
VEGF in 2nd line (RAS wt only?)		
CTx +/- Bev	*TML*	+
FOLFOX +/-Bev	*E3200*	+
FOLFIRI +/- Aflibercept	*VELOUR*	+
VEGF in 3nd line (RAS wt only?)		
Regorafenib	*CORRECT*	+

Consider STEPs for treatment in metastatic CRC

- **S**trategy (curative vs. palliative)
- **T**umor biology (aggressive vs. indolent)
- **E**GFR dependency (wt vs. mut)
- **P**atient

Effect of PFS-increase on OS



Anti-EGFR therapy (FOLFIRI +/- Cet)

- improvement of ORR by 20%
- Prolongation of PFS by 1.5 months
- Prolongation of OS by 3-4 months
- **ΔPFS << ΔOS**

According to Saltz et al. JCO 2008

Group 1

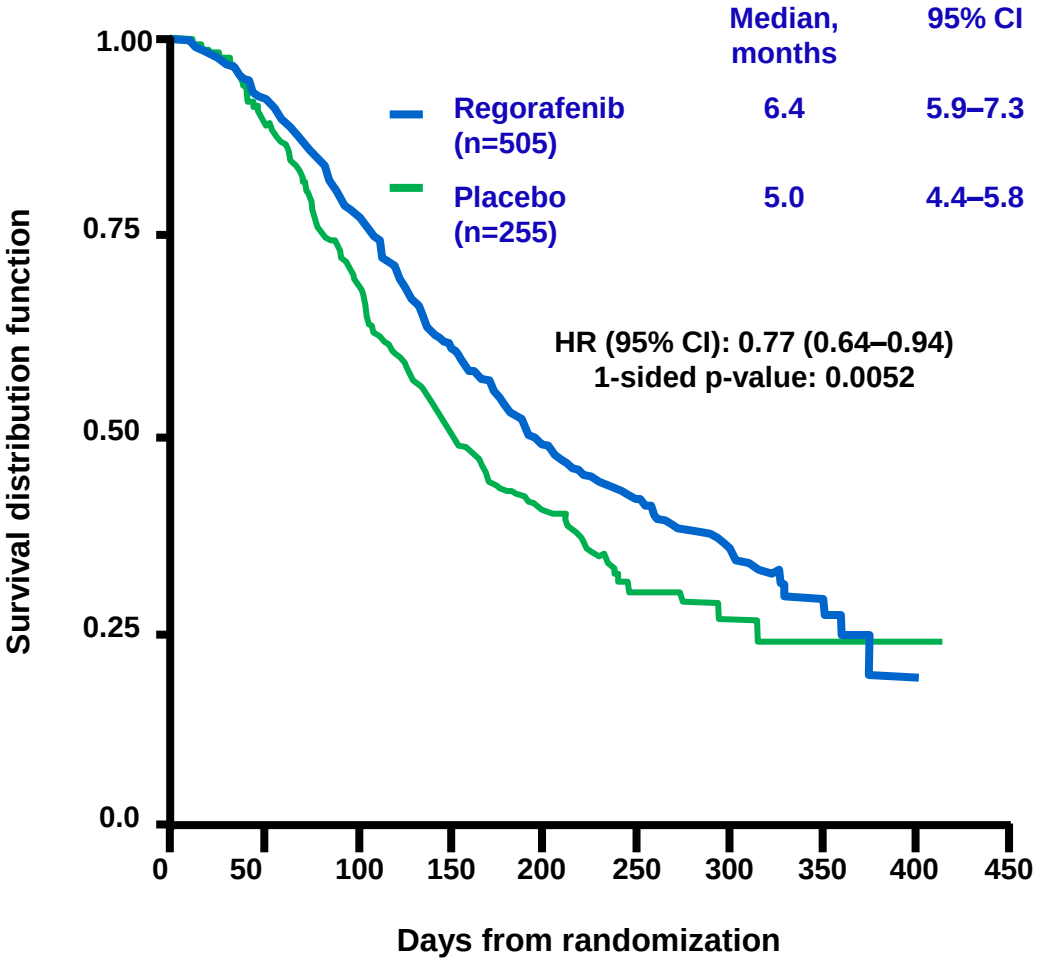
Potentially resectable metastases

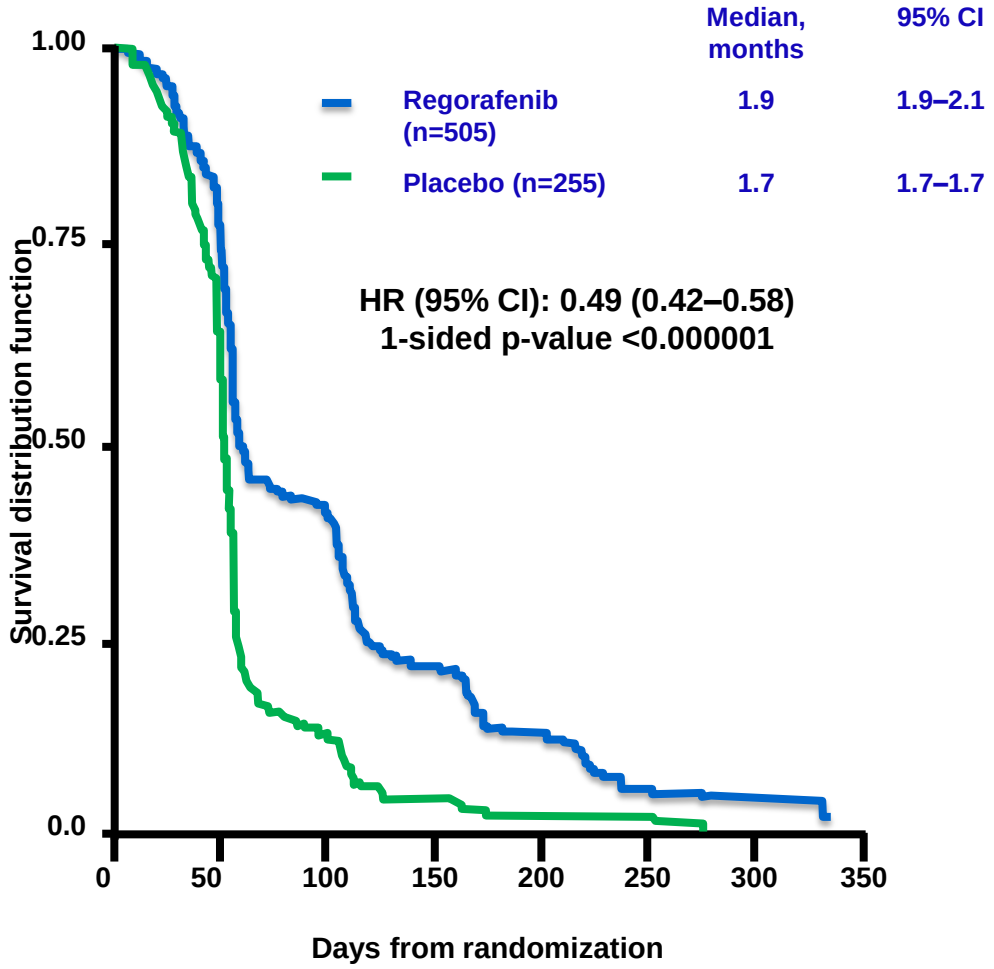
Randomized trials in patients with non resectable k-ras exon 2 wt CRC LLD Chemotherapy +/- Cetuximab

	Chinese study		CELIM
	CT N=68	CT + Cet N=70	CT + Cet N=67
RR	40%	57%	70%
R0 resection	7%	**26%**	**33%**
OS all pts (mo)	21.0	**30.9**	**35.7**
OS resected pts (mo)	36.0	**46.4**	**53.9**
OS non resected pts (mo)	19.6	25.7	27.3

Ye et al. JCO 2013; Folprecht...Köhne Lancet Oncol 2010

CORRECT: BSC +/- Regorafenib
OS and PFS





*** RR = 1.0% vs .04%**

Grothey A, et al. ASCO GI 2012 (Abstract No. LBA385)