September 28th 2018

The Evolving Management of Metastatic Colorectal Cancer

Mt Tremblant

Mark Vincent

MB ChB, FRCPC, MRCP(UK)

Professor

Dept. of Oncology

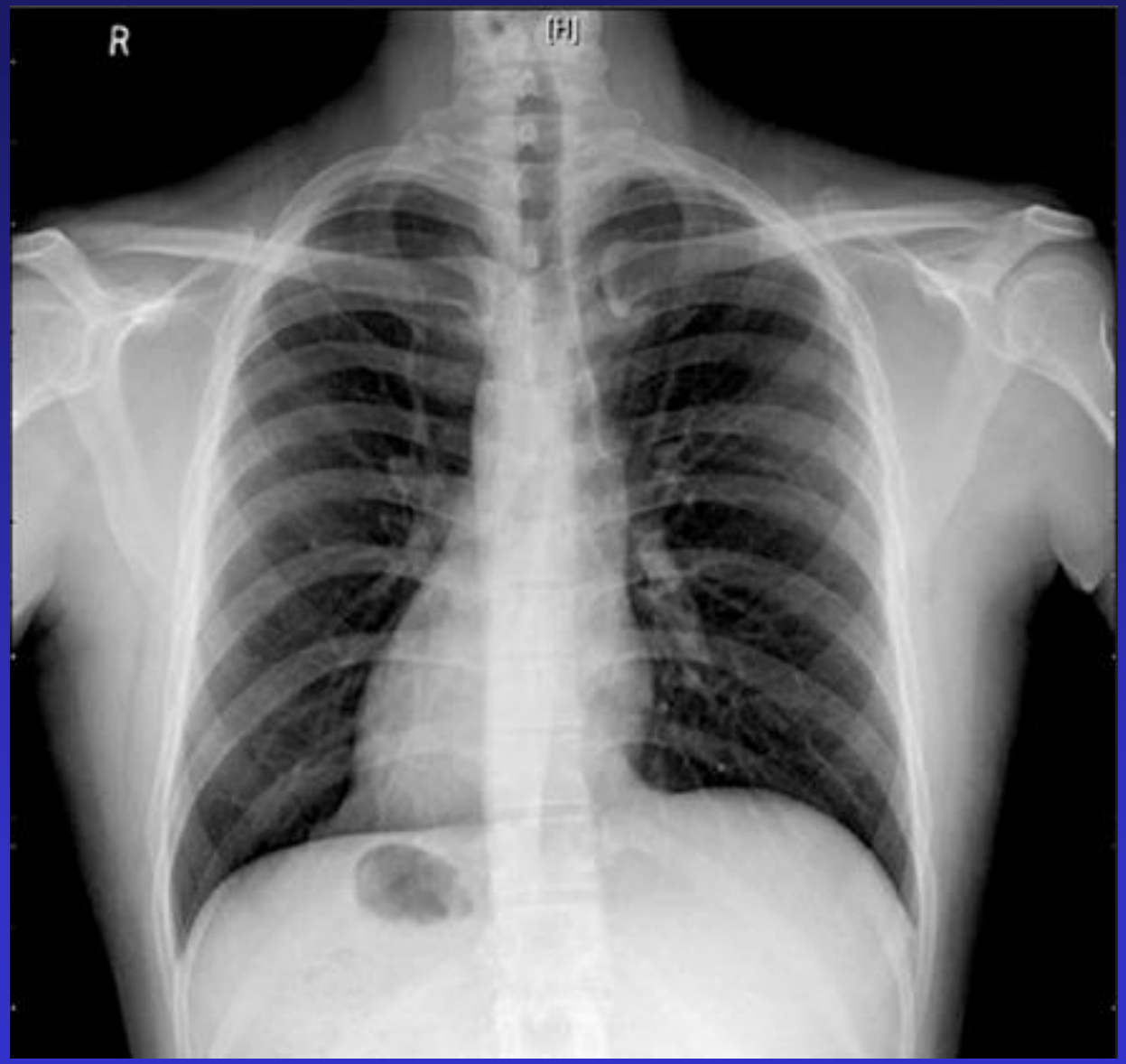
Staff Medical Oncologist

Thoracic & GI MDT

London Regional Cancer Program

"London, from the River Thames
James Hamilton. c1840

Good Afternoon



Disclosures

Research Support/P.I.	Roche, Astra-Zeneca, Sanofi-Aventis
Employee	N/A
Consultant	Lilly
Major Stockholder	N/A
Speakers Bureau	Lilly, Boehringer-Ingelheim, Merck, Astra-Zeneca
Honoraria	Amgen, Astra-Zeneca, BMS, Roche, Lilly, Boehringer-Ingelheim, Sanofi-Aventis, Merck, Novartis, Pfizer, Taiho.
Scientific Advisory Board	N/A
Ownership	Sarissa Inc
Board of Directors	Aptose BioSciences Inc

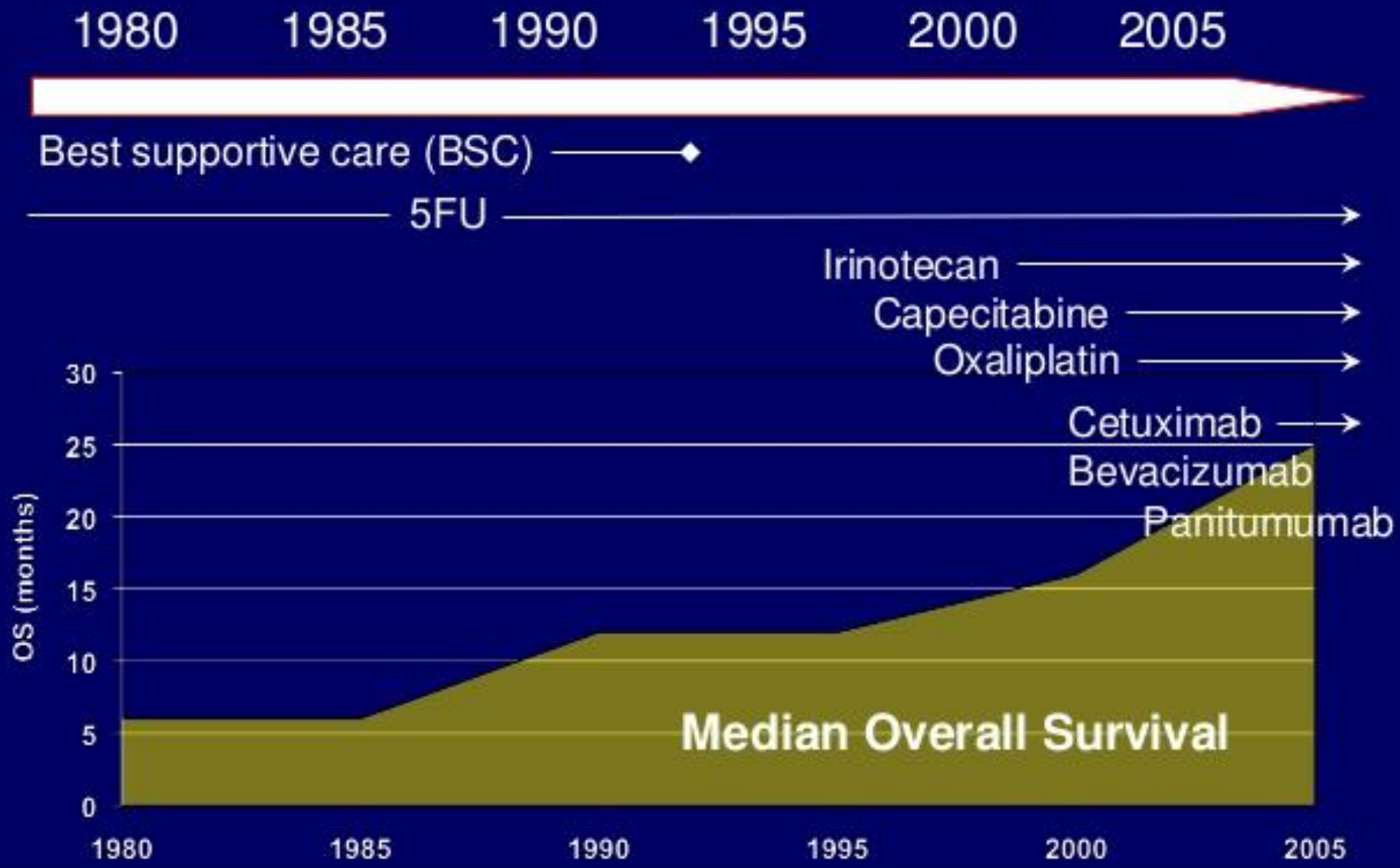
Learning Objectives

- Use of EGFR inhibitors in untreated pts with mCRC and CCO funding
- Prognostic and predictive value of primary tumor location
- Canadian Colorectal Cancer Sidedness Guidelines
- Biomarker role and impact in treatment selection for mCRC

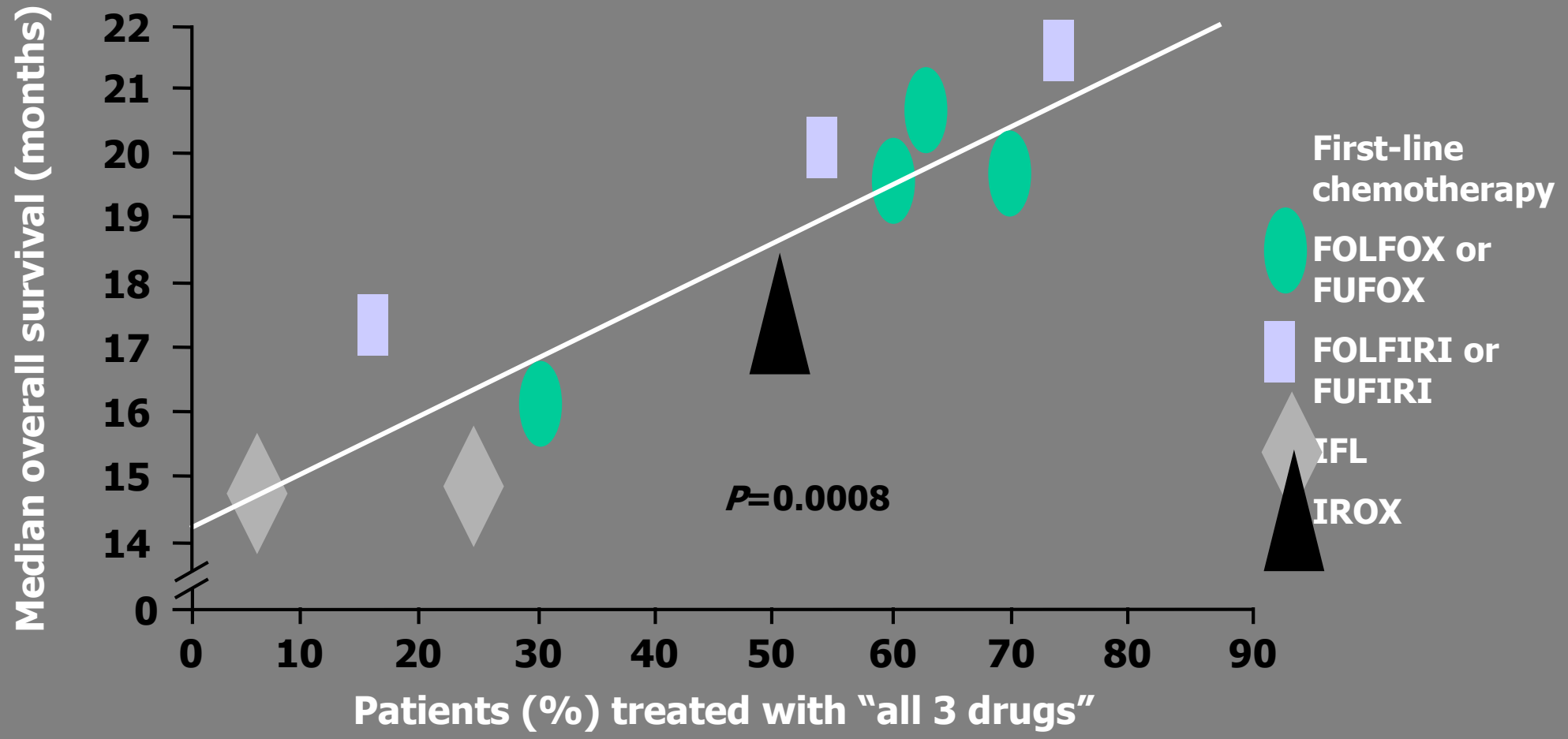
TOPIC ONE

The Evolution of Treatment in mCRC

Advances in the Treatment of Stage IV CRC:



THE VALUE OF CYTOTOXIC CHEMOTHERAPY: Correlation Between Exposure to "All-Three-Drugs" and Median Overall Survival



Grothey et al. *J Clin Oncol*. 2004; 22:1209.

Colorectal Cancer: 20 Years Later

meta-analysis 1992 — 80405 results

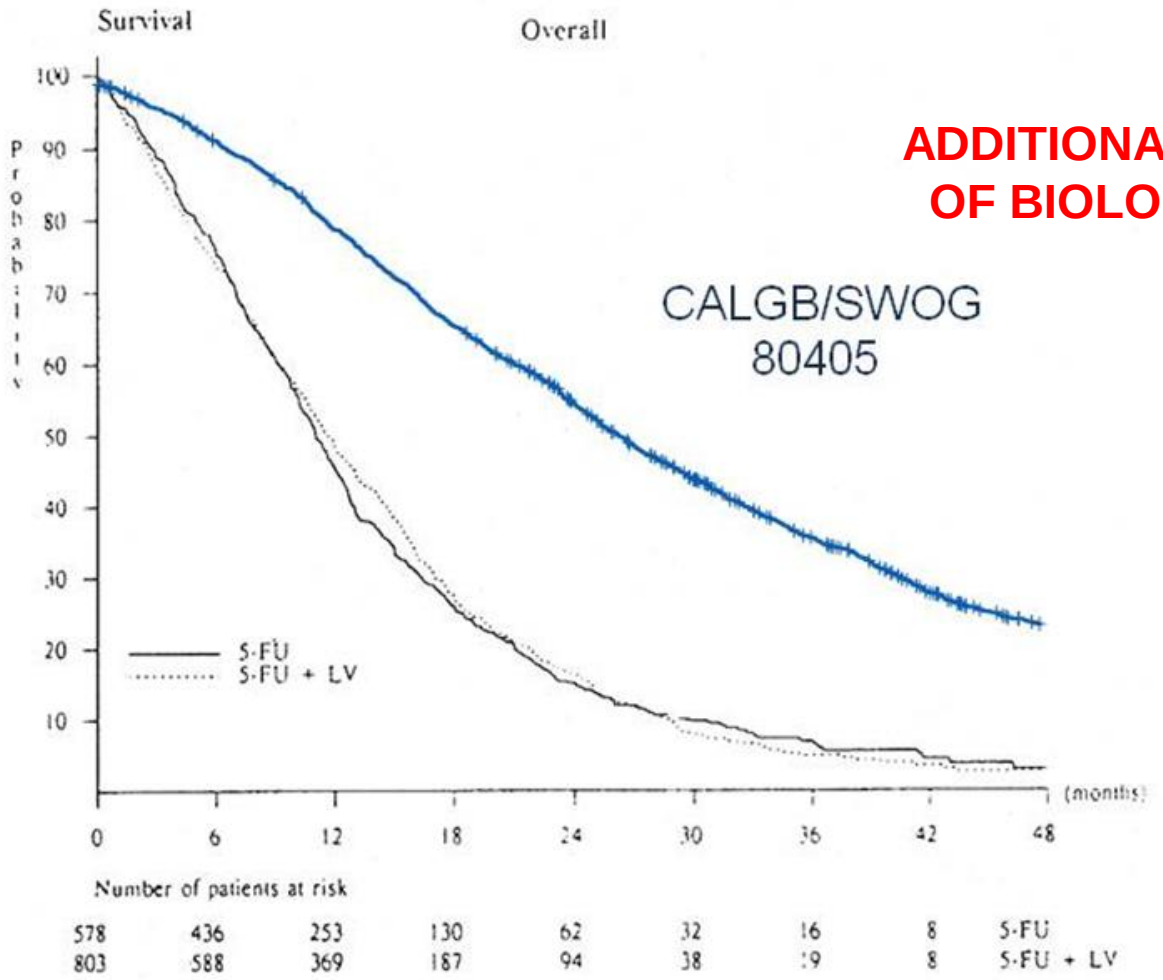


Fig 2. Overall survival.

J Clin Oncol, 1992

ADDITIONAL VALUE OF BIOLOGICALS

CALGB/SWOG 80405

Federally Funded Research

TOPIC TWO

Factors Influencing Treatment Selection

PATIENT-FACTORS INFLUENCING Rx

- ECOG PS and Age
- Prior adjuvant FOLFOX
- Possible C/I to VEGF(R)-based Rx
- DYPD status (determines fluoropyrimidine tolerance)
- Goals and values
- Drug plan and perhaps home province
- Cognition and co-morbidities

DISEASE-RELATED FACTORS INFLUENCING Rx

- Genetic status of the primary tumour: RAS, RAF, MSI
- Sidedness (Left vs Right)?
- Whether metastases are potentially resectable
- Primary in or out
- Primary in the rectum or colon

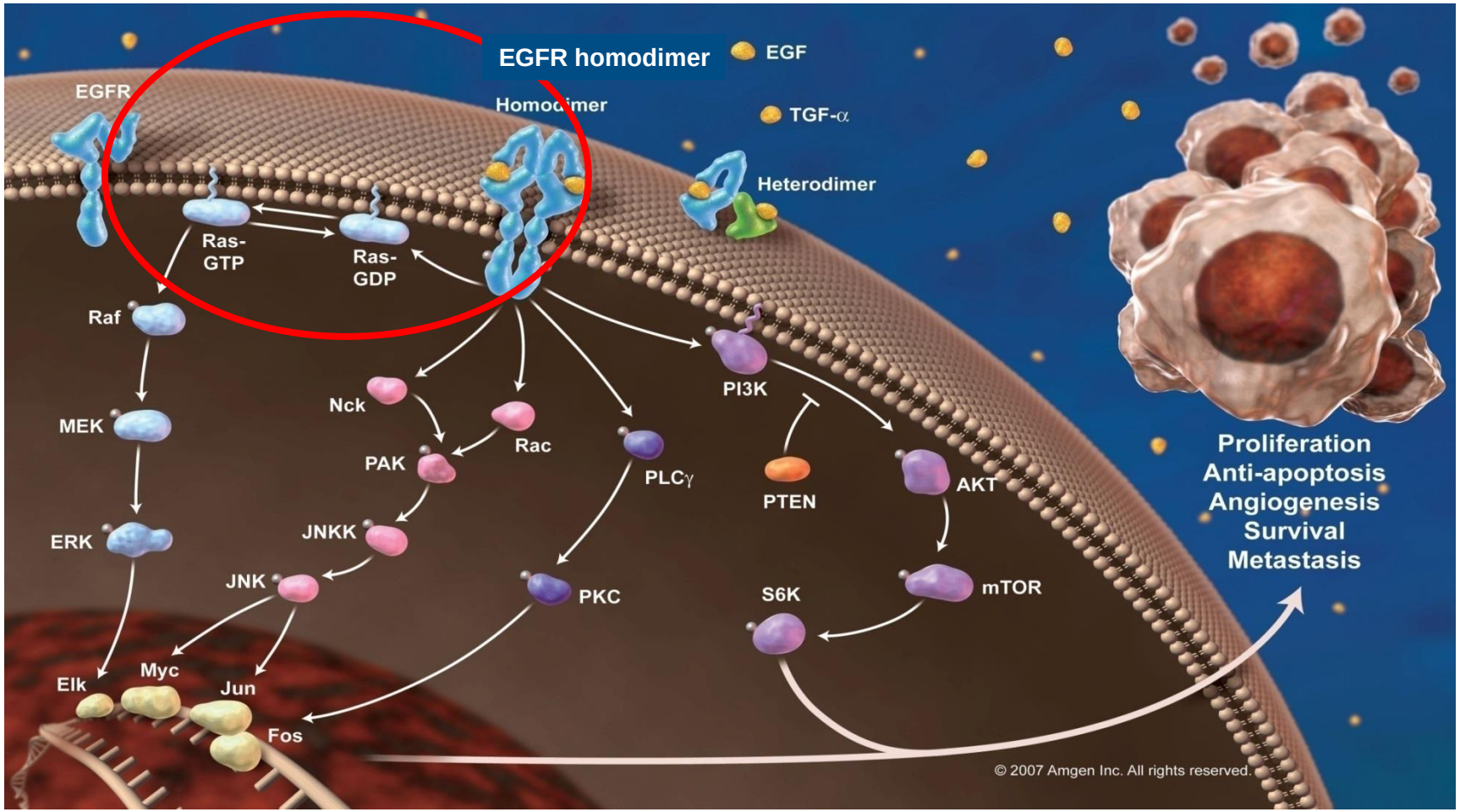
OTHER FACTORS INFLUENCING Rx

- Availability of a clinical trial
- Cost of drugs to the system (e.g. oxaliplatin now a ‘we don’t care’ drug)

TOPIC THREE

RAS and RAF

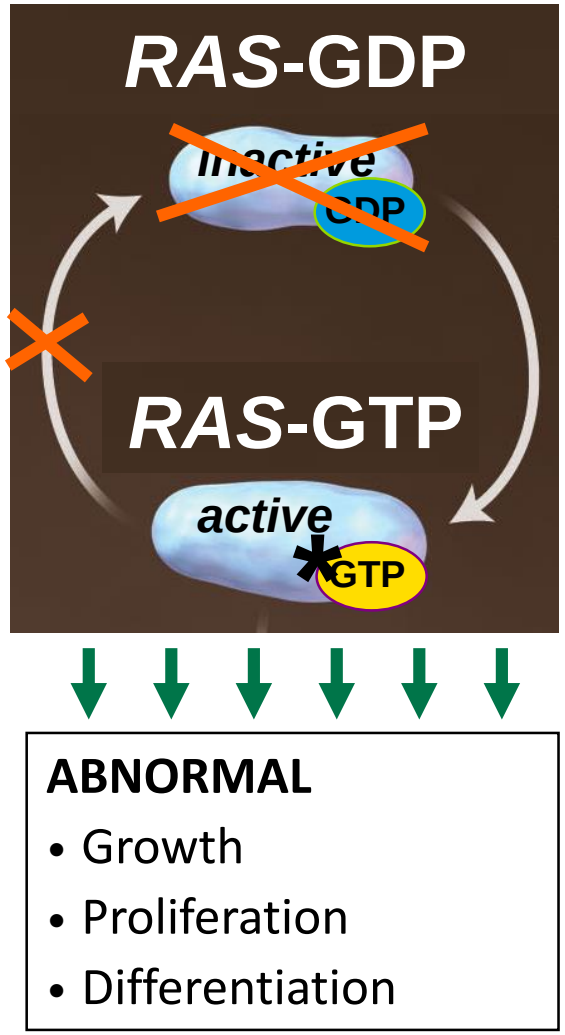
EGFR Activation May Involve Downstream Signaling Pathways That Include *RAS*



Berg M, et al. *Discov Med* 2012;14:207-14; Di Fiore F, et al. *Br J Cancer* 2010;103:1765-72; Han W, et al. *Cancer Lett* 2012;318:124-34; Herbst RS, et al. *Cancer* 2002;94:1593-1611.

Mutated *RAS* May Lead to Uncontrolled Cell Signaling and Cancer

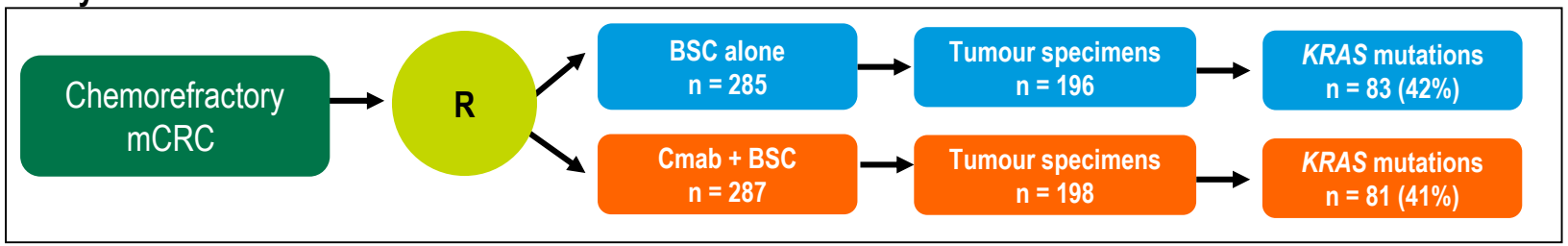
- Mutations in *KRAS* or *NRAS* are found in approximately 53% of CRCs[1]
- Specific mutations in *RAS* genes result in constitutively active proteins
- Patients with *KRAS* or *NRAS* mutations do not benefit from EGFR inhibition[1-3]



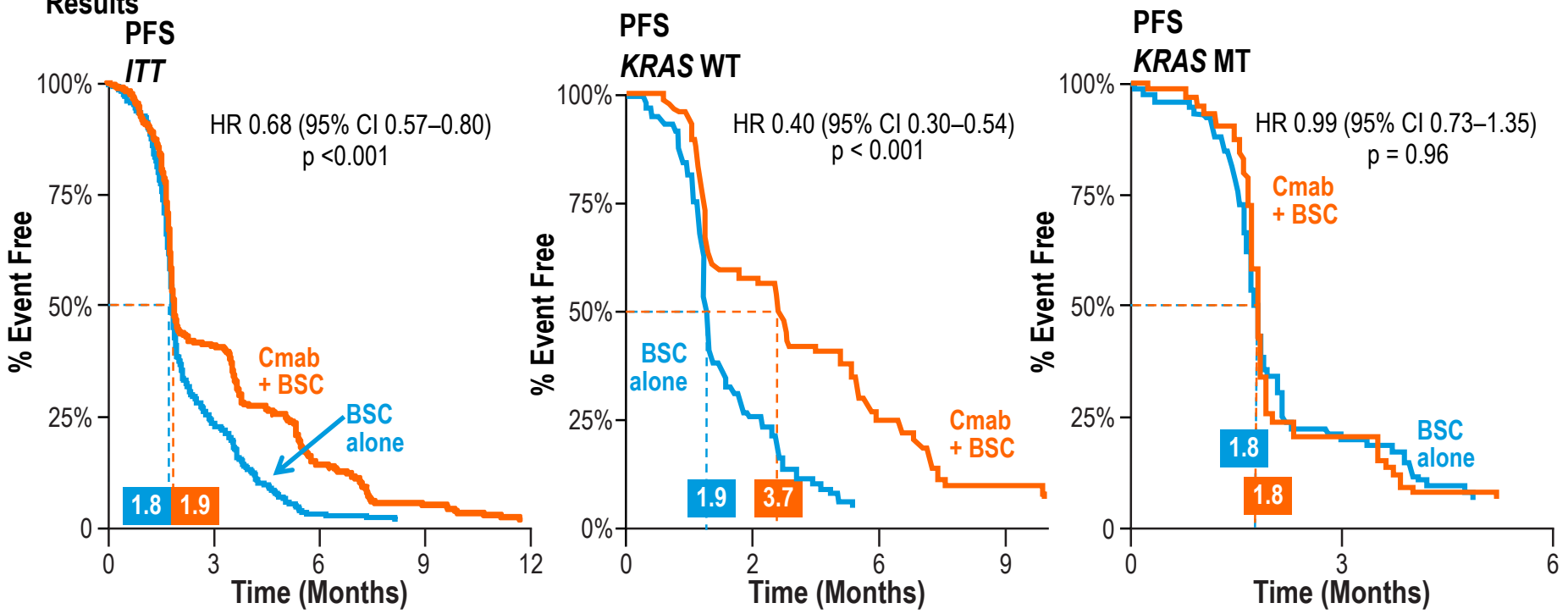
1. Sorich MJ, et al. *Ann Oncol* 2015;26 13-21; 2. Amado RG, et al. *J Clin Oncol* 2008;26:1626-1634;
3. Karapetis CS, et al. *N Engl J Med* 2008;359:1757-1765.

NCIC CO.17 Trial
Cetuximab and *KRAS* exon 2 Status

Study Schema



Results



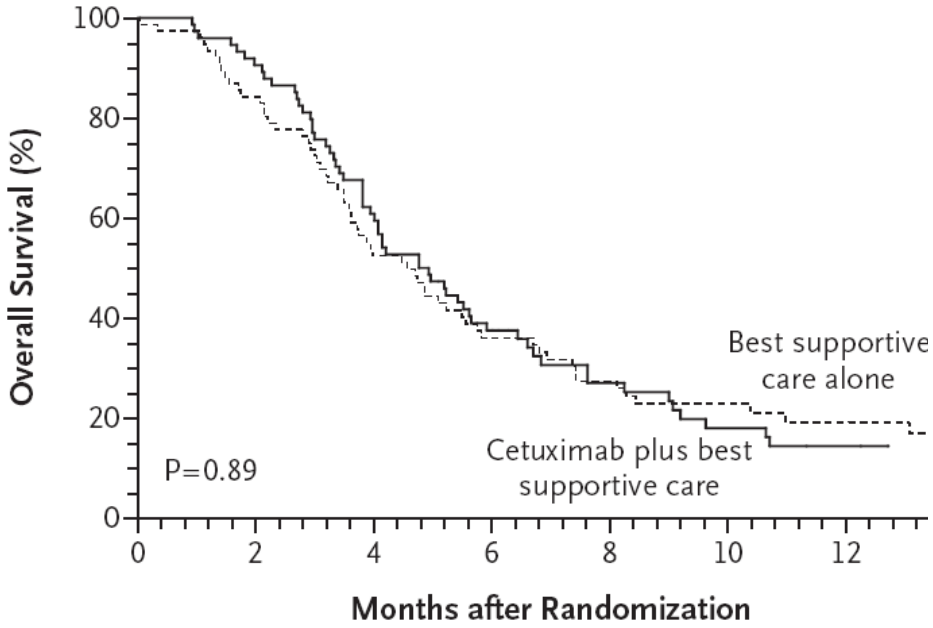
Adapted from Jonker et al. *N Engl J Med* 2008;357:2040-2048.
Cmab = Cetuximab; NCIC = National Cancer Institute of Canada

Adapted from Karapetis C, et al. *N Engl J Med* 2008;359:1757-1765.

KRAS Mutational Status Associated with Outcome: Predictive Biomarker (but not Prognostic) – NCIC CO.17

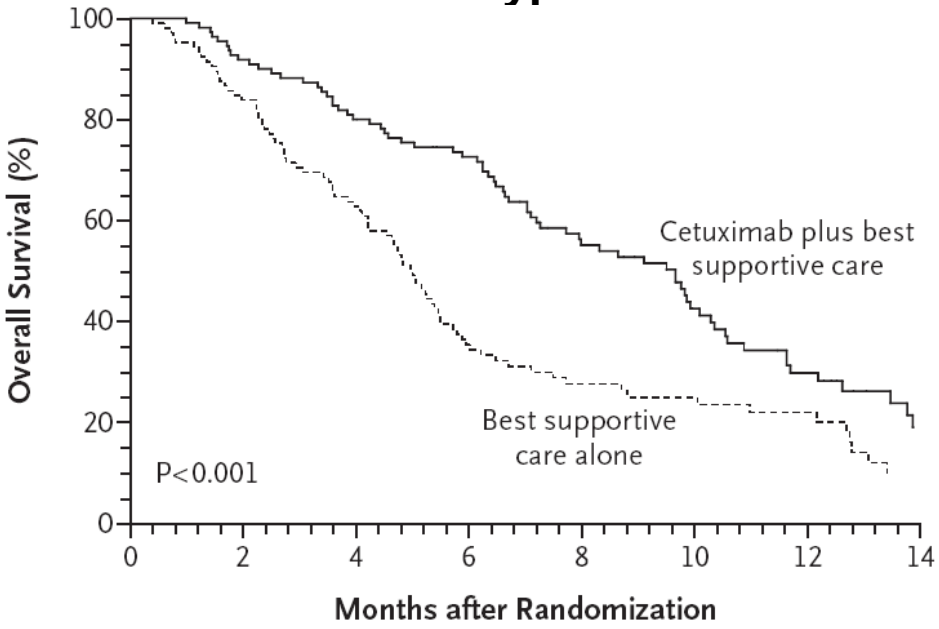
Overall Survival

Mutant



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

Wild type

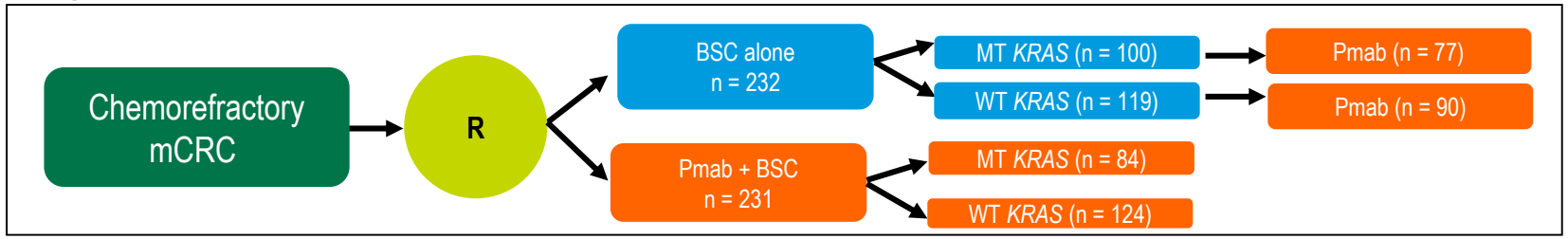


Study arm	Median OS (months)	95% CI
Cetuximab + BSC	9.5	7.7 – 10.3
BSC alone	4.8	4.2 – 5.5

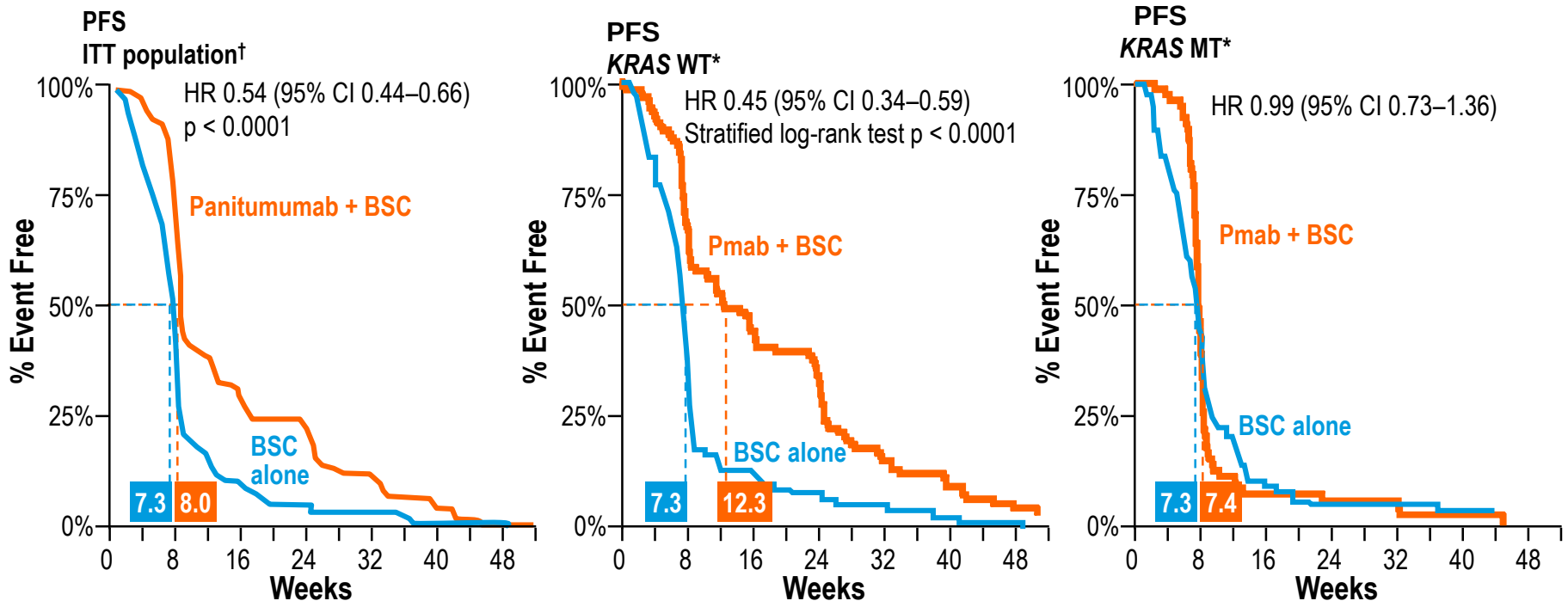
Adapted from Karapetis CS, *et al: N Engl J Med* 2008; 359(17):1757-65.

408 Study
Panitumumab and *KRAS* Exon 2 Status

Study Schema



Results



BSC = Best supportive care; MT = Mutant; Pmab = Panitumumab; WT = Wild type

*Adapted from from Amado RG, et al. *J Clin Oncol* 2008;26:1626-1634.
†Adapted from Van Cutsem, et al. *J Clin Oncol* 2007;25:1658-1664.

KRAS Exon 2 Status Predicts Response to EGFR Inhibitors in Most Studies

NORDIC VII is the only study in which the results with regard to *KRAS* status were not clear in patients with wild-type tumours.

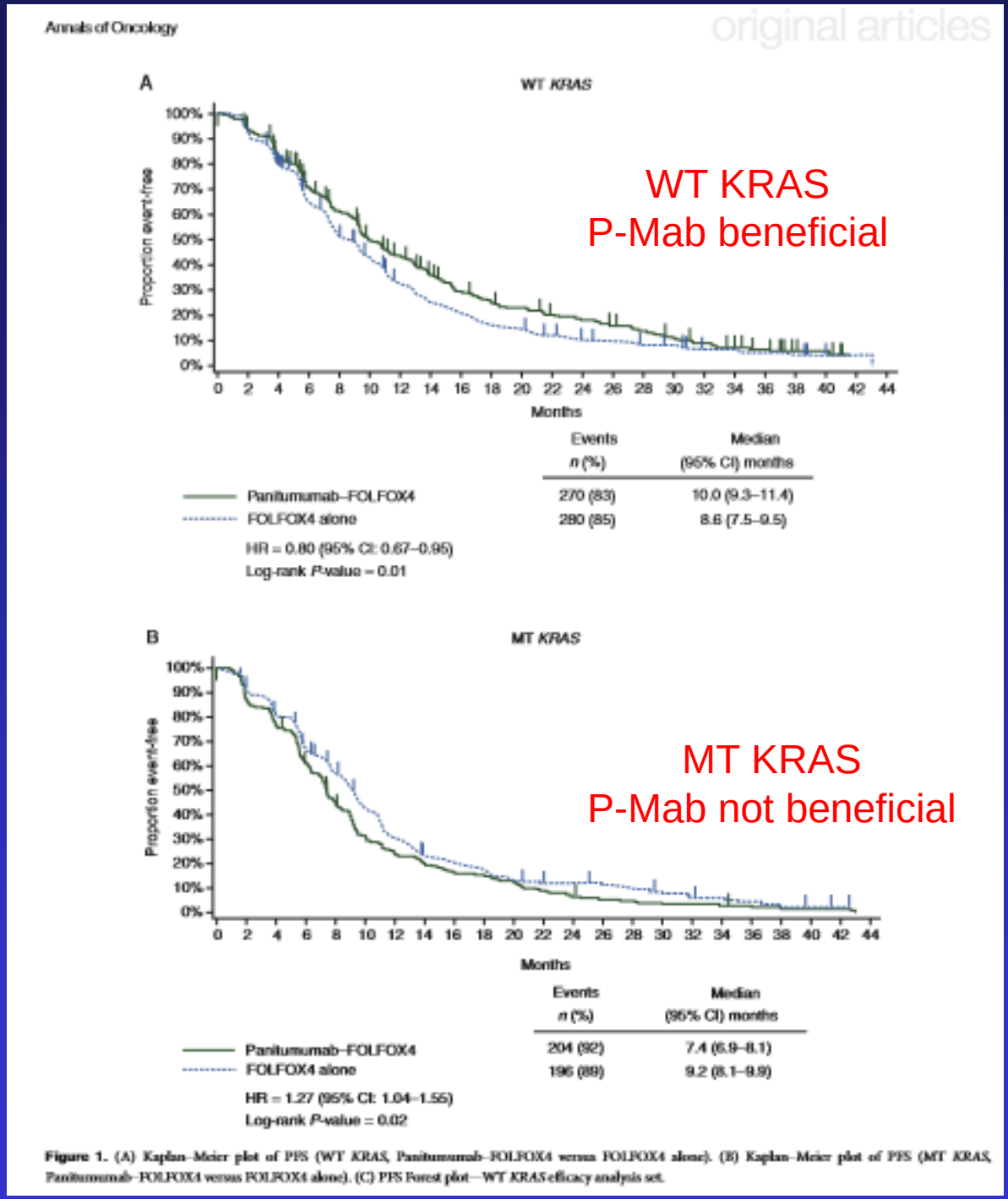
Study		n	Key Results	Improved Outcomes in *KRAS* WT patients
First-line	CRYSTAL[1]	1,198	FOLFIRI + cetuximab > FOLFIRI	✔
	COIN[2]	1,630	5-FU/capecitabine + oxaliplatin + cetuximab > 5-FU/capecitabine + oxaliplatin	✔
	PRIME[3]	1,183	FOLFOX4 + panitumumab > FOLFOX4	✔
	NORDIC VII[4]	566	FLOX = FLOX + cetuximab	✗
Second-line	EPIC[5,6]	1,298	Irinotecan + cetuximab > Irinotecan	✔
	181[7]	1,186	FOLFIRI + panitumumab > FOLFIRI	✔
Third-line	NCIC CO.17[8,9]	572	Cetuximab + BSC > BSC	✔
	408[10, 11]	463	Panitumumab + BSC > BSC	✔
	FIRE-3[12]	592	Cetuximab + FOLFIRI > Bevacizumab + FOLFIRI	✔
	CALGB/SWOG 80405	526	Cetuximab + Chemo = Bevacizumab + Chemo	✔

BSC = Best supportive care; FLOX = Fluorouracil (5-FU), leucovorin (LV), and oxaliplatin; FOLFIRI = 5-FU/LV + irinotecan; FOLFOX = 5-FU + LV + oxaliplatin

1. Van Cutsem E, et al. *J Clin Oncol* 2011;29:2011; 2. Maughan TS, et al. *Lancet* 2011;377:2103-2114; 3. Douillard JY, et al. *J Clin Oncol* 2010;28:4697-4705; 4. Tveit K, et al. *J Clin Oncol* 2012;30:1755-62;
5. Sobrero AF, et al. *J Clin Oncol* 2008;26:2311-2319; 6. Langer C, et al. *Ann Oncol* 2008;19(suppl 8) (Abstr 385P); 7. Peeters M, et al. *J Clin Oncol* 2010;28:4706-4713; 8. Karapetis C, et al. *N Engl J Med* 2008;359:1757-1765; 9. Jonker DJ, et al. *N Engl J Med* 2007;357:2040-2048;
10. Van Cutsem E, et al. *J Clin Oncol* 2007;25:1658-1664; 11. Amado RG, et al. *J Clin Oncol* 2008;26:1626-1634. 12. Heinemann V, et al. *Lancet Oncol* 2014;15:1065-1075. 13. Venook A. ASCO 2014. *J Clin Oncol* 2014;32:5s(suppl). Abstr LBA3; 14. Lenz H. *Ann Oncol* 2014;25 (suppl 4). Abstr 501O.

PFS the primary endpoint: met

PRIME: ANALYSIS A/C to KRAS STATUS



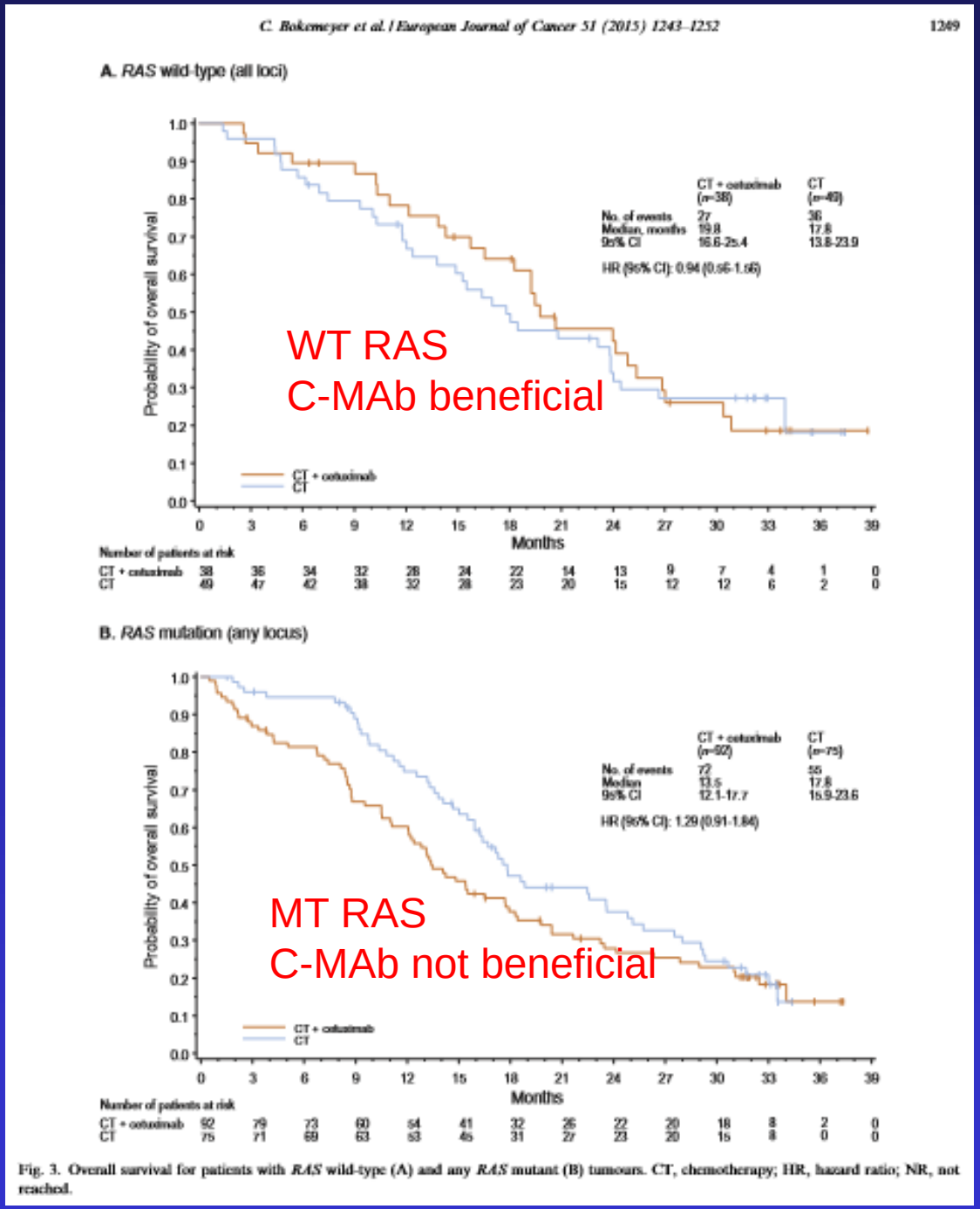
WT KRAS
P-Mab beneficial

MT KRAS
P-Mab not beneficial

PRIME: FOLFOX ± P-MAb

Overall Survival

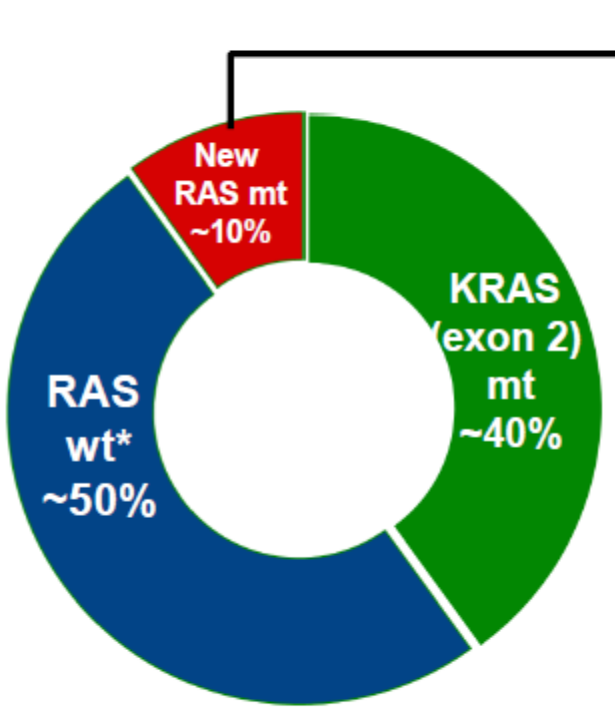
THE SAME PATTERN SEEN WITH CETUXIMAB



OPUS: FOLFOX ± C-MAb

EXPANDED RAS ANALYSIS

Beyond KRAS (exon 2): Additional RAS mutations in mCRC



New' RAS mutations within the KRAS (exon 2) wt population

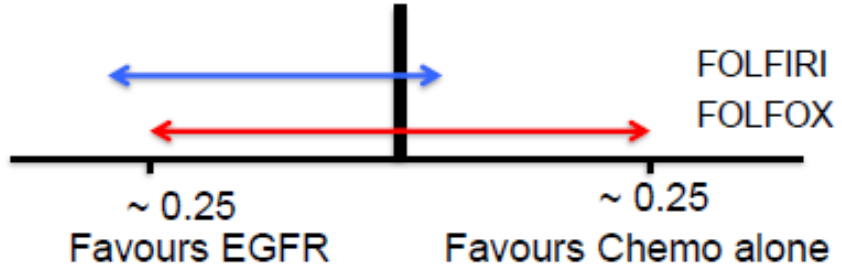
	EXON 2	EXON 3	EXON 4
KRAS	★★ 12 13 wt	★★ 59 61	★★ 117 146
NRAS	★★ 12 13	★★ 59 61	★★ 117 146

*Wt at KRAS exons 2, 3, 4 and NRAS exons 2, 3, 4

MEASURING EXPANDED RAS PROVIDES MORE BENEFIT FROM EGFR MABS THAN KRAS

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

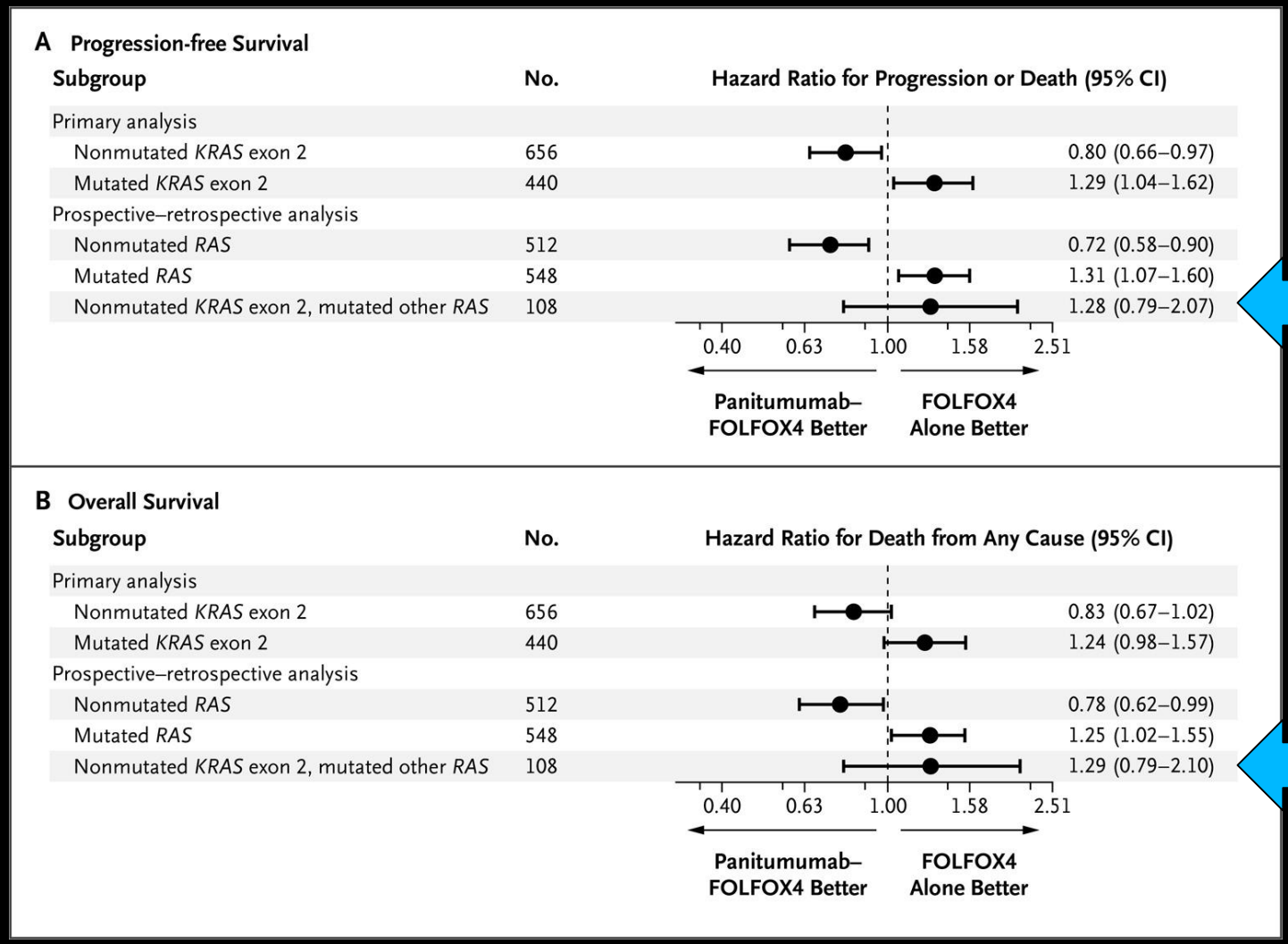
Trial	Therapy	OS (mo) KRAS*wt*		OS (mo) RAS*wt*		OS (mo) RAS*mut*	
		CTx	+EGFR	CTx	+EGFR	CTX	+EGFR
CRYSTAL *(n=666)*	*FOLFIRI +/- Cetux**	**HR 0.80** *0.67-0.95*		**HR 0.69** *0.54-0.88*		HR 1.05 *0.85-1.25*	
PRIME *(n=656)*	*FOLFOX +/- Pani**	**HR 0.83** *0.67-1.02*		**HR 0.78** *0.62-0.99*		**HR 1.25** *1.02-1.55*	
OPUS *(n=197)*	*FOLFOX +/- Cetux**	**HR 0.86** *0.60-1.22*		**HR 0.83** *0.49-1.42*		**HR 1.35** *0.95-1.92*	



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

PRIME

Hazard Ratio for Disease Progression or Death and Hazard Ratio for Death from Any Cause, According to *KRAS* and *RAS* Mutation Status.



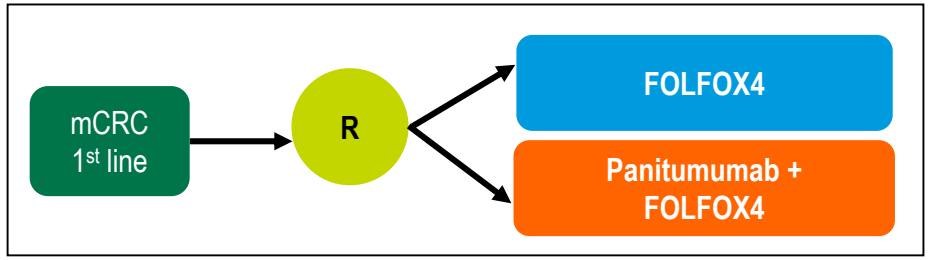
Douillard J-Y et al. N Engl J Med 2013;369:1023-1034

The NEW ENGLAND JOURNAL of MEDICINE

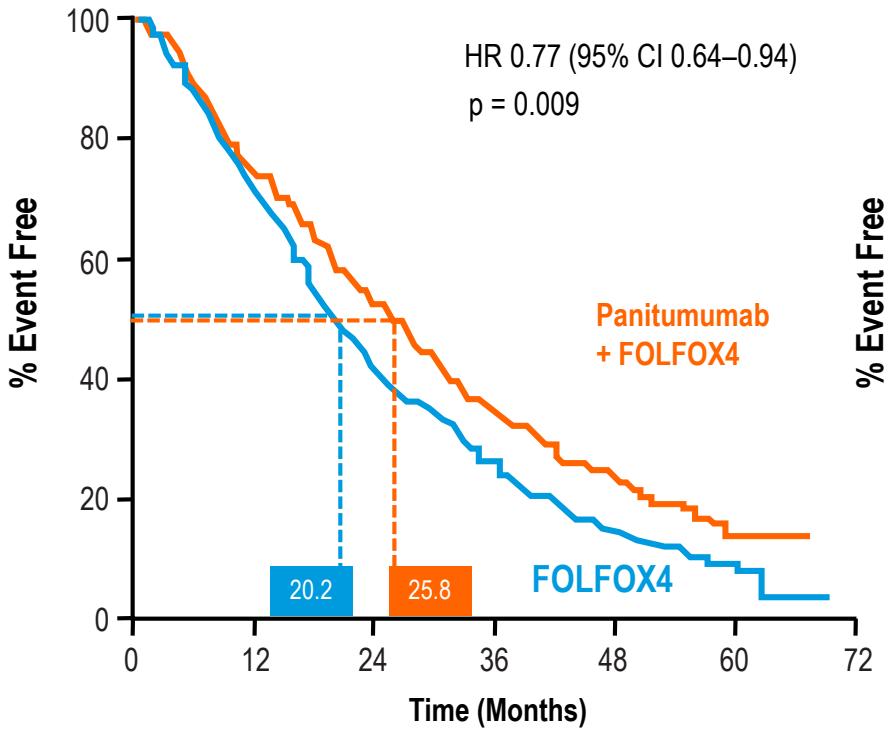
PRIME Phase III Study

RAS Status†: Panitumumab + FOLFOX4 vs. FOLFOX Alone (Updated Analysis‡)

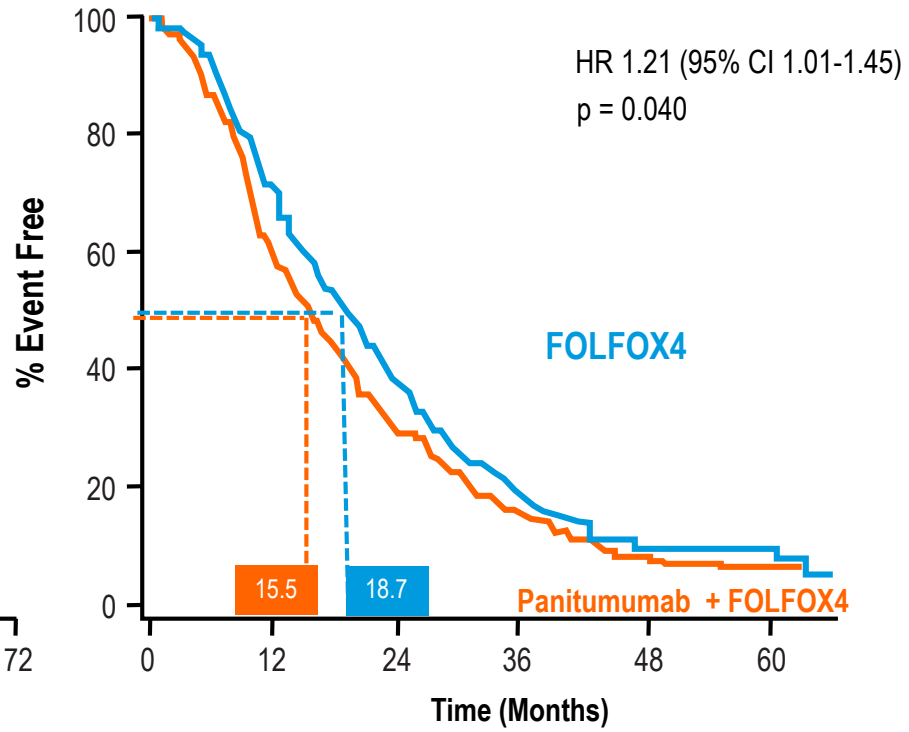
Study Schema



OS – *RAS* WT



OS – *RAS* MT*



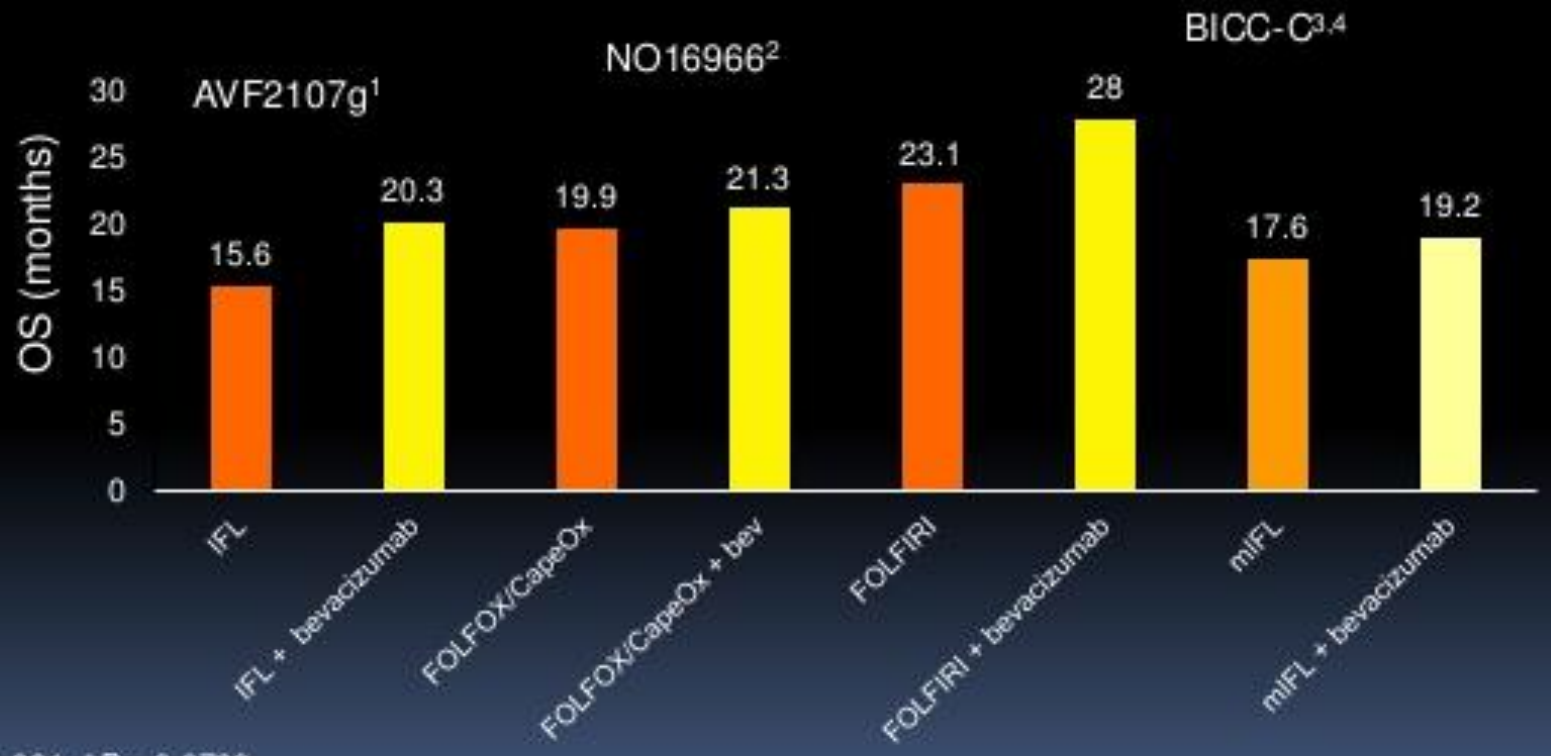
**KRAS* exon 3, 4 ; *NRAS* exon 2, 3, 4; or *BRAF* exon 15;
†Prospective-retrospective analysis; ‡Exploratory analysis

Adapted from Douillard JY, et al. *N Engl J Med* 2013;369:1023-1034.

TOPIC FOUR

WHICH BIOLOGICAL: BEV OR anti-EGFR?

First-Line Bevacizumab in mCRC: Overall Survival



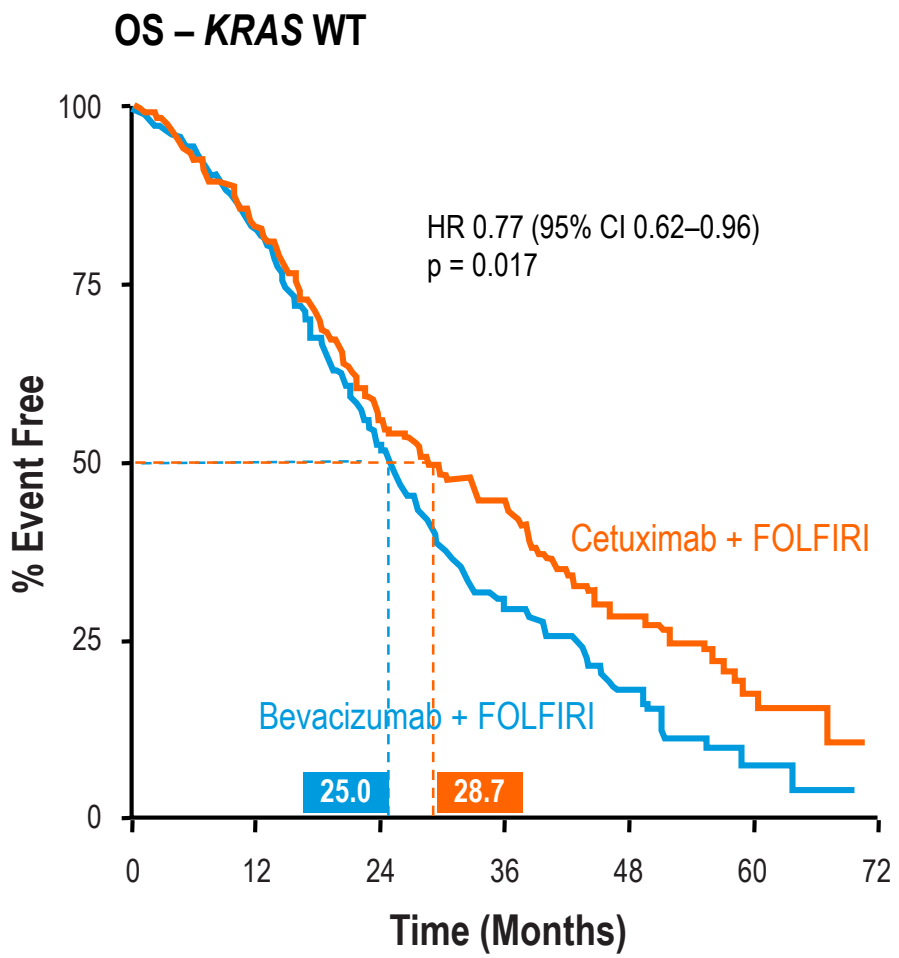
*$P<0.001$; †$P = 0.0769$.

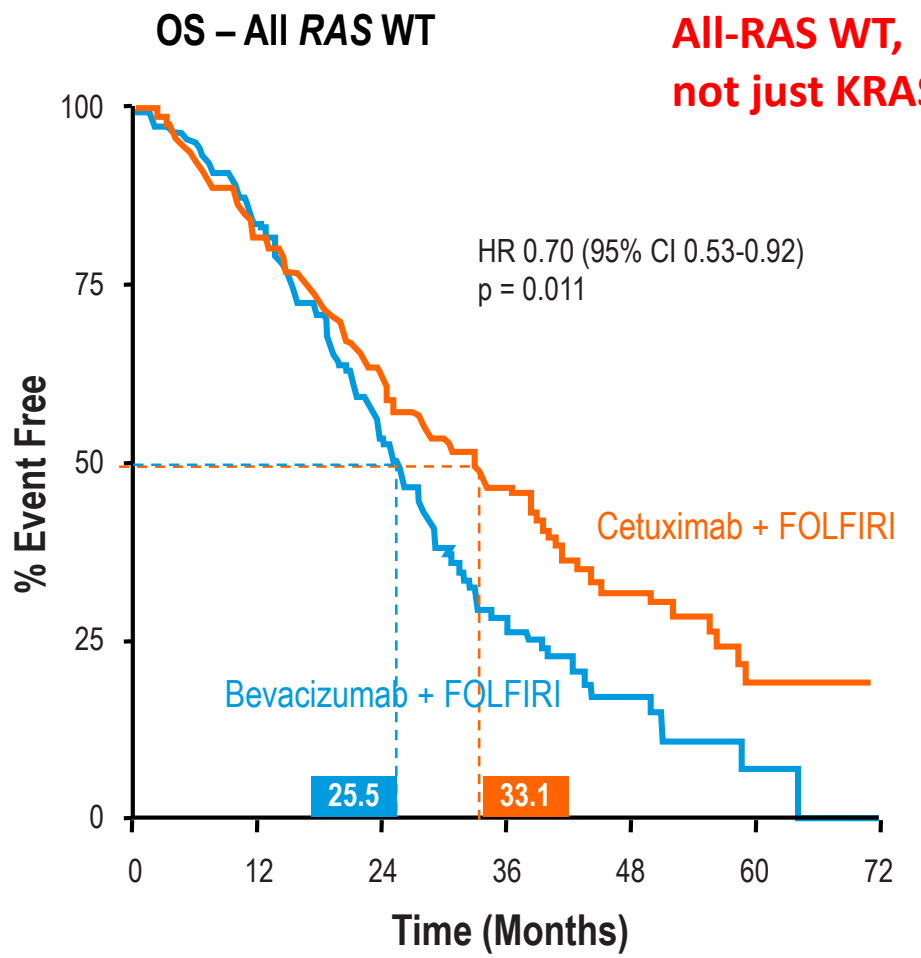
1. Hurwitz H et al. *N Engl J Med.* 2004;350:2335-2342; 2. Saltz LB et al. *J Clin Oncol.* 2008;26:2013-2019;
3. Fuchs C et al. *J Clin Oncol.* 2007;25:4779-4786; 4. Fuchs C et al. *J Clin Oncol.* 2008;26:689-690;

FIRE-3 Phase III Trial:

Cetuximab vs. Bevacizumab with FOLFIRI as First-line Treatment in *KRAS WT* Patients

EGFR MAb better than VEGF Mab, especially in All-RAS WT, not just KRAS WT





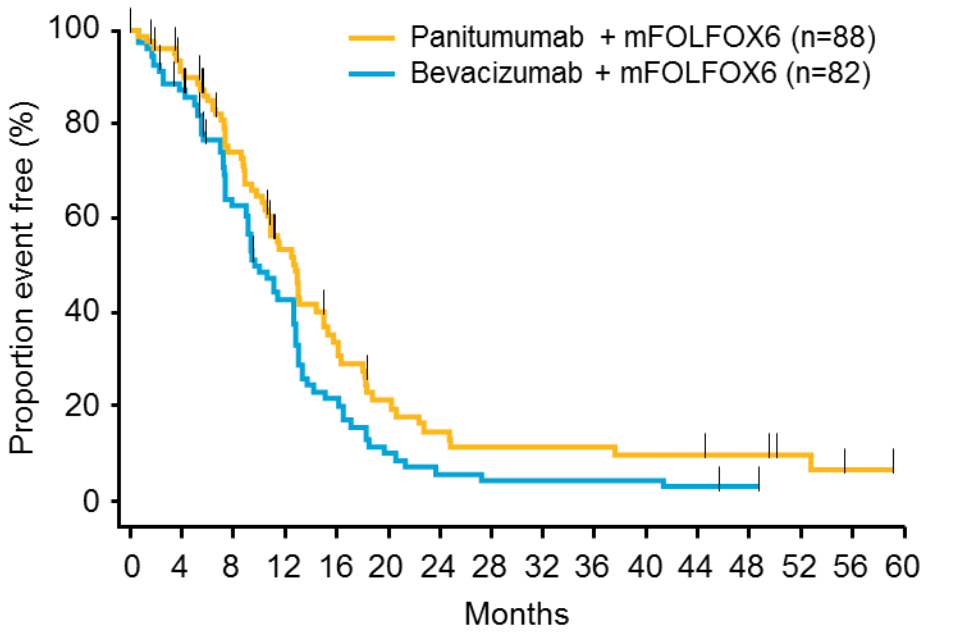
Heinemann V, et al. *Lancet Oncol* 2014;15:1065-1075.

PFS – *RAS* population

PEAK:
FOLFOX/PMAb
vs
FOLOFOX/BEV

RAS WT

	Panitumumab + mFOLFOX6 (n=88)	Bevacizumab + mFOLFOX6 (n=82)
Median PFS, (95% CI), months	12.8 (10.7, 15.1)	10.1 (9.0, 12.7)
HR (95% CI)	0.68 (0.48, 0.96)	
p-value	0.029	



Pmab*	88	72	55	36	22	13	9	7	7	7	6	6	5	3	1	0
Bmab*	82	68	45	30	14	7	4	3	3	3	3	2	1	0	0	0

Censor indicated by vertical bar

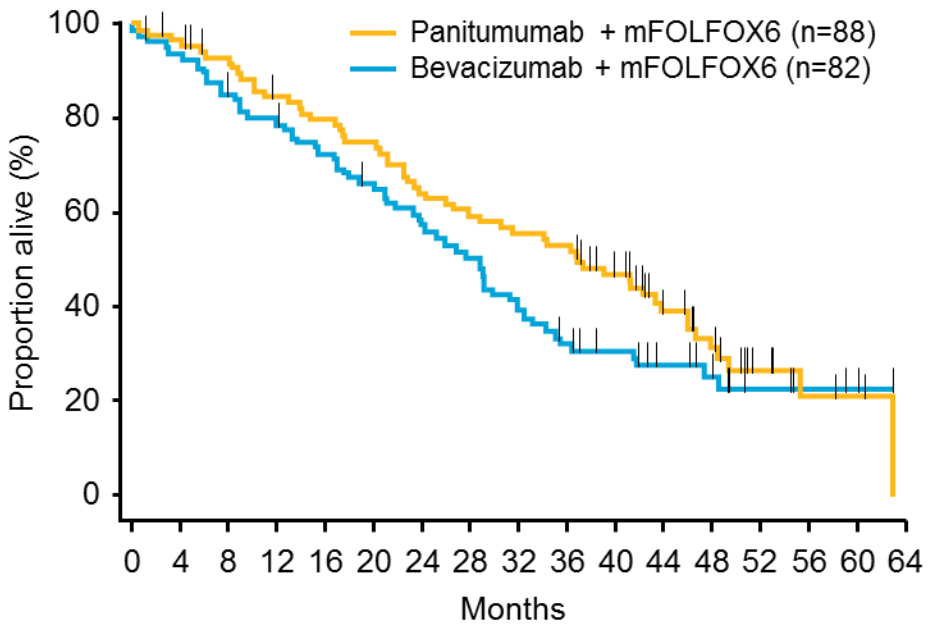
*+ mFOLFOX6

OS – *RAS* WT population

PEAK:
FOLFOX/PMAb
Vs
FOLOFOX/BEV

RAS WT

	Panitumumab + mFOLFOX6 (n=88)	Bevacizumab + mFOLFOX6 (n=82)
Median OS, (95% CI), months	36.9 (27.9, 46.1)	28.9 (23.3, 32.0)
HR (95% CI)	0.76 (0.53, 1.11)	
p-value	0.15	



Pmab*	88	84	78	70	66	62	53	49	46	44	34	22	15	7	3	2	0
Bmab*	82	76	69	63	57	51	44	39	31	23	19	14	10	5	3	2	0

Censor indicated by vertical bar

*+ mFOLFOX6

Tumour response-related efficacy – *RAS* WT population

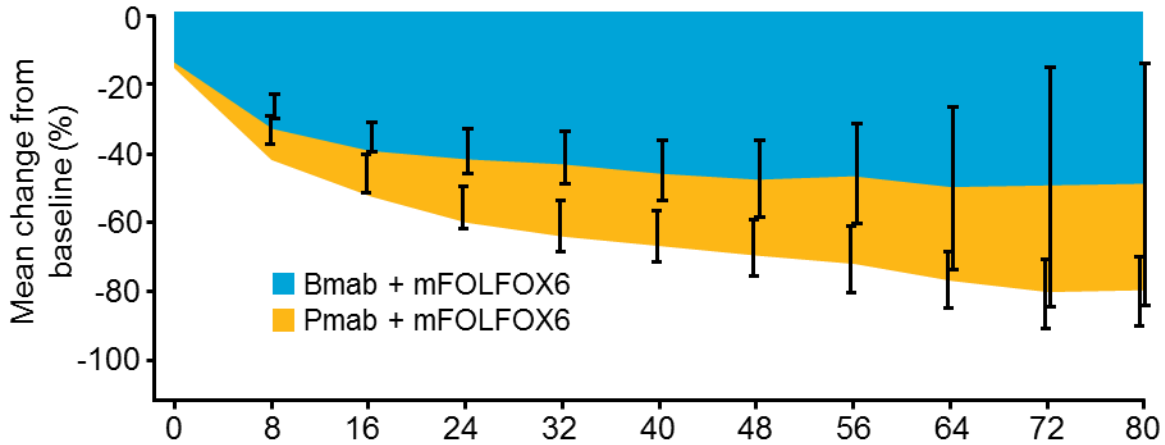
	Pmab + mFOLFOX6 (n=88)	Bmab + mFOLFOX6 (n=82)
Median DoR, months (95% CI)	11.4 (10.0, 16.3)	9.0 (7.6, 9.5)
HR (95% CI); p-value	0.59 (0.39, 0.88); 0.011	
Median TTR, months (95% CI)	2.3 (1.9, 3.7)	3.8 (2.1, 5.7)
HR (95% CI); p-value	1.19 (0.81, 1.74); 0.37	
Median DpR, months (Q1, Q3)	65.0 (45.7, 89.5)	46.3 (29.5, 63.3)
p-value	0.0018	

Longer

Quicker

Deeper

Mean (95% CI) percentage change from baseline in tumour load[a] over time



Pmab + mFOLFOX6	88	80	70	63	53	42	42	27	25	17	17
Bmab + mFOLFOX6	81	74	66	57	45	36	26	22	13	11	8

[a]Sum of all target lesions - includes those patients evaluable for objective response who had baseline tumour shrinkage data

DoR = duration of response;
DpR = depth of response;
ETS = early tumour shrinkage;
TTR = time to response

THE BENEFITS OF ACHIEVING A PARTIAL RESPONSE

Between-treatment comparisons of PFS and OS outcomes by tumour shrinkage at week 8 – *RAS* WT population

	Tumour shrinkage at week 8			
	<30		≥30	
	Panitumumab + mFOLFOX6	Bevacizumab + mFOLFOX6	Panitumumab + mFOLFOX6	Bevacizumab + mFOLFOX6
n (%)	29 (36)	41 (55)	51 (64)	33 (45)
Odds ratio[a], (95% CI) p-value	—		1.99 (0.99, 4.10) 0.052	
Median PFS, months (95% CI)	11.6 (7.5, 15.4)	9.7 (7.5, 12.9)	13.0 (10.9, 18.1)	11.1 (9.0, 16.6)
HR (95% CI) p-value	0.79 (0.45, 1.38) 0.40		0.74 (0.45, 1.23) 0.24	
Median OS, months (95% CI)	34.2 (17.5, 42.3)	23.9 (20.1, 29.0)	43.8 (36.4, 63.0)	35.1 (29.9, NE)
HR (95% CI) p-value	0.75 (0.43, 1.31) 0.31		0.77 (0.42, 1.42) 0.41	

More pts achieve 30%+ shrinkage on pmab

Pts achieving 30%+ shrinkage have better PFS

Pts achieving 30%+ shrinkage have better OS

Both PFS and OS are longer if the tumor shrinkage exceeds 30% by week 8

[a]Odds ratio is defined as the odds of having ≥30% tumour shrinkage in the panitumumab + mFOLFOX6 arm relative to the odds in the bevacizumab + mFOLFOX6 arm

REMOVING BRAF PTS MEANS EVEN MORE BENEFIT FOR P-MAb

Summary of PFS, OS and ORR results – *RAS* WT and *RAS* WT/*BRAF* WT populations

	RAS WT		*RAS* WT / *BRAF* WT	
	Pmab + mFOLFOX6 (n=88)	Bmab + mFOLFOX6 (n=82)	Pmab + mFOLFOX6 (n=77)	Bmab + mFOLFOX6 (n=79)
PFS				
Patients with event, n (%)	64 (73)	70 (85)	55 (71)	67 (85)
Median, months (95% CI)	12.8 (10.7, 15.1)	10.1 (9.0, 12.7)	13.1 (11.6, 16.2)	10.1 (9.0, 12.7)
HR (95% CI); p-value	0.68 (0.48, 0.96); 0.029		0.61 (0.42, 0.88); 0.0075	
OS				
Patients with event, n (%)	57 (65)	58 (71)	48 (62)	55 (70)
Median, months (95% CI)	36.9 (27.9, 46.1)	28.9 (23.3, 32.0)	41.3 (31.6, 46.7)	28.9 (23.9, 33.1)
HR (95% CI); p-value	0.76 (0.53, 1.11); 0.15		0.70 (0.48, 1.04); 0.08	
ORR				
Responders, n (%) [95% CI]	57 (65) [54, 75]	49 (60) [49, 71]	49 (64) [52, 74]	46 (59) [47, 70]
Odds ratio (95% CI); p-value	1.12 (0.56, 2.22); 0.86		1.17 (0.58, 2.38); 0.76	

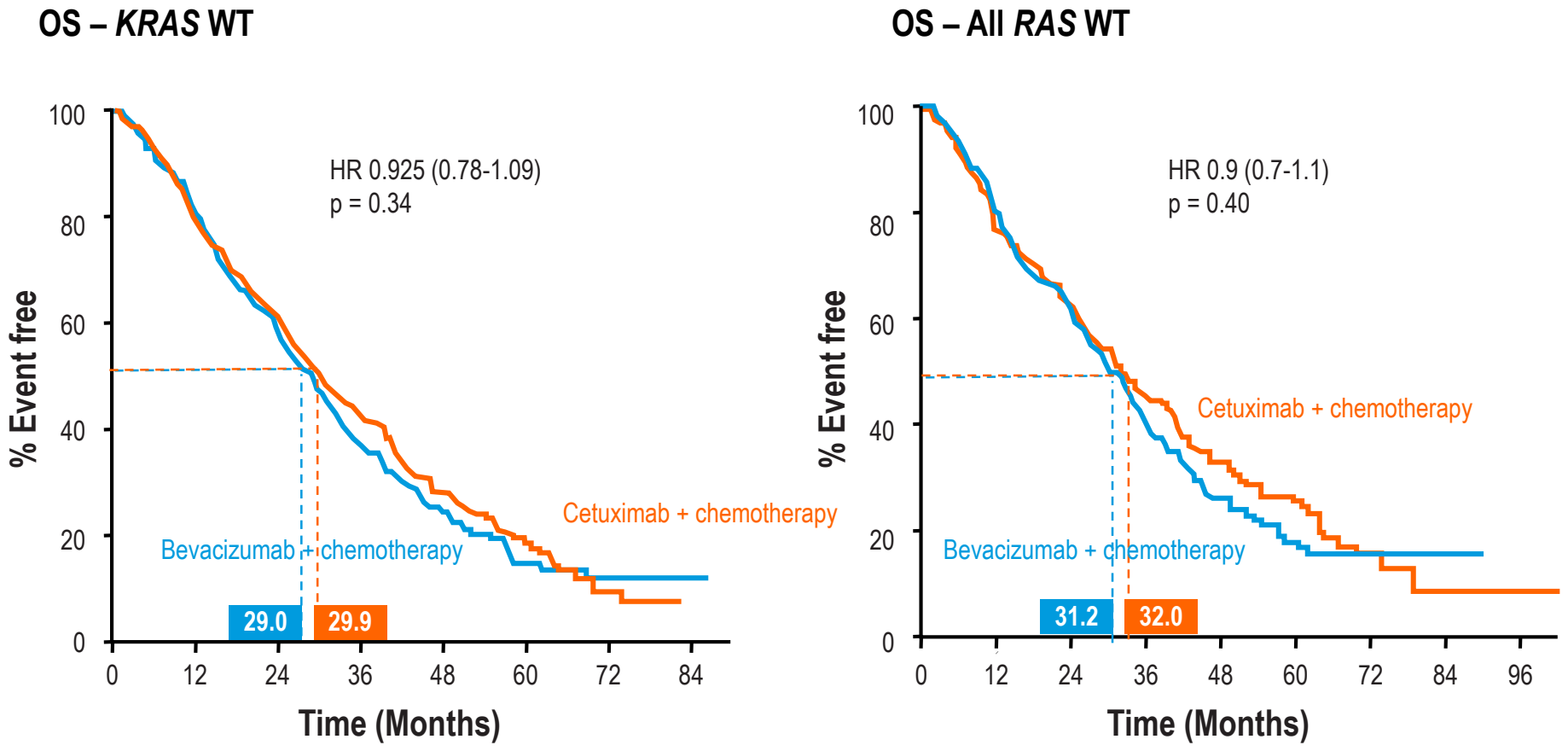
Bmab = bevacizumab; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Pmab = panitumumab; WT = wild type

Conclusions

- This final analysis of the PEAK trial found a significant improvement in PFS for patients with *RAS* WT mCRC receiving first-line treatment with panitumumab + mFOLFOX6 vs bevacizumab + mFOLFOX6 (HR: 0.68; p=0.029)
- Median OS was numerically longer in the panitumumab vs bevacizumab arm
  - 8.0 months longer in the *RAS* WT population (36.9 vs 28.9 months)
  - 12.4 months longer in the *RAS* WT/*BRAF* WT population (41.3 vs 28.9 months)
- ORR was similar between treatments, but tumour responses with panitumumab occurred earlier, lasted longer and were deeper vs bevacizumab
- Based on PEAK, panitumumab + mFOLFOX6 is an effective first-line treatment for patients with *RAS* WT mCRC

CALGB/SWOG 80405:

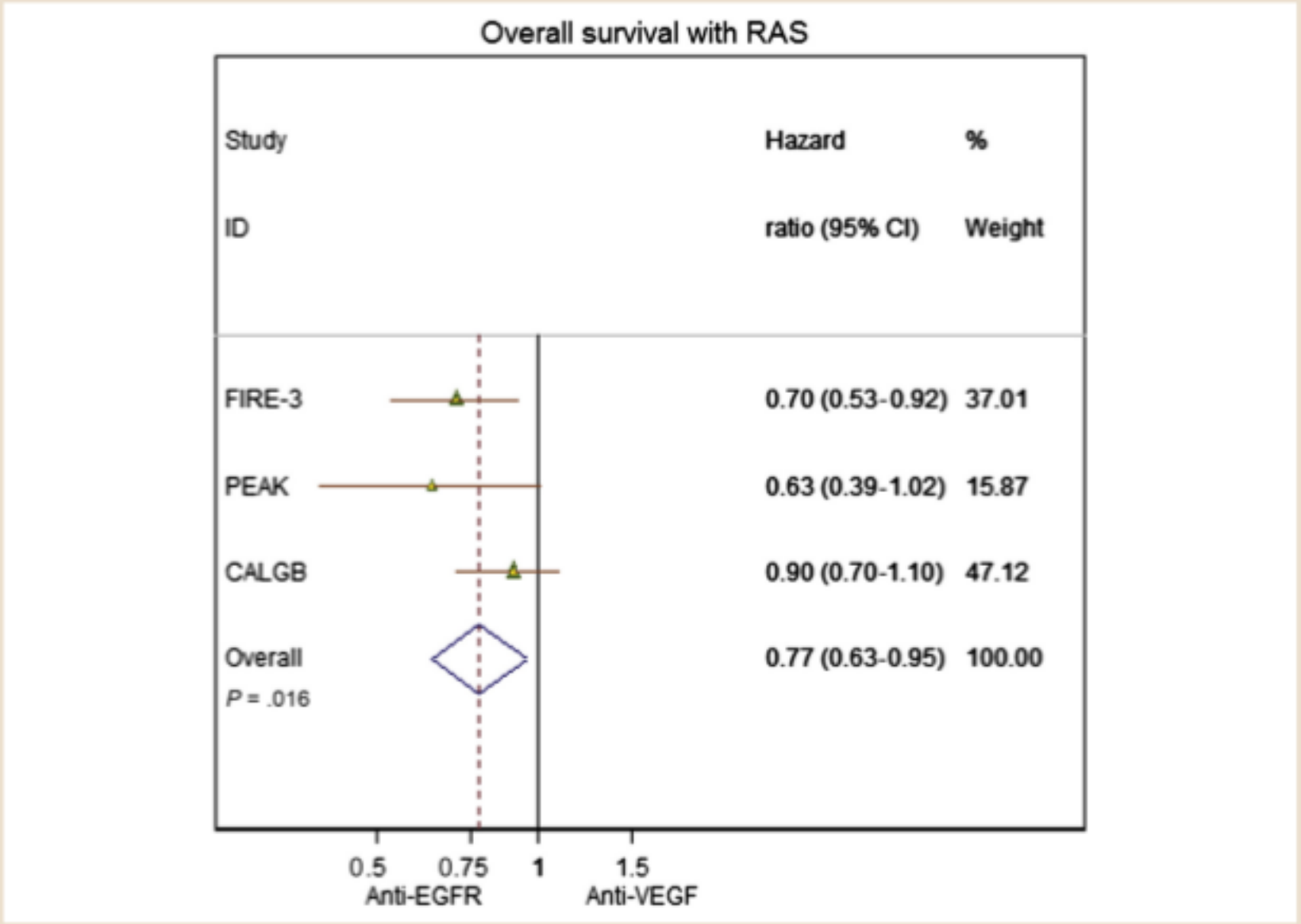
Phase III trial of FOLFIRI or FOLFOX with Bevacizumab or Cetuximab for patients with *KRAS* exon 2 WT untreated mCRC



Venook A, et al. *J Clin Oncol* 2014;32:5s(suppl). Abstr LBA3

Three major trials of CT + anti-EGFR Mab vs Bev a/c to ras

Figure 7 Forest Plot for Overall Survival (OS) for All RAS Wild Type (RAS-WT) Patients

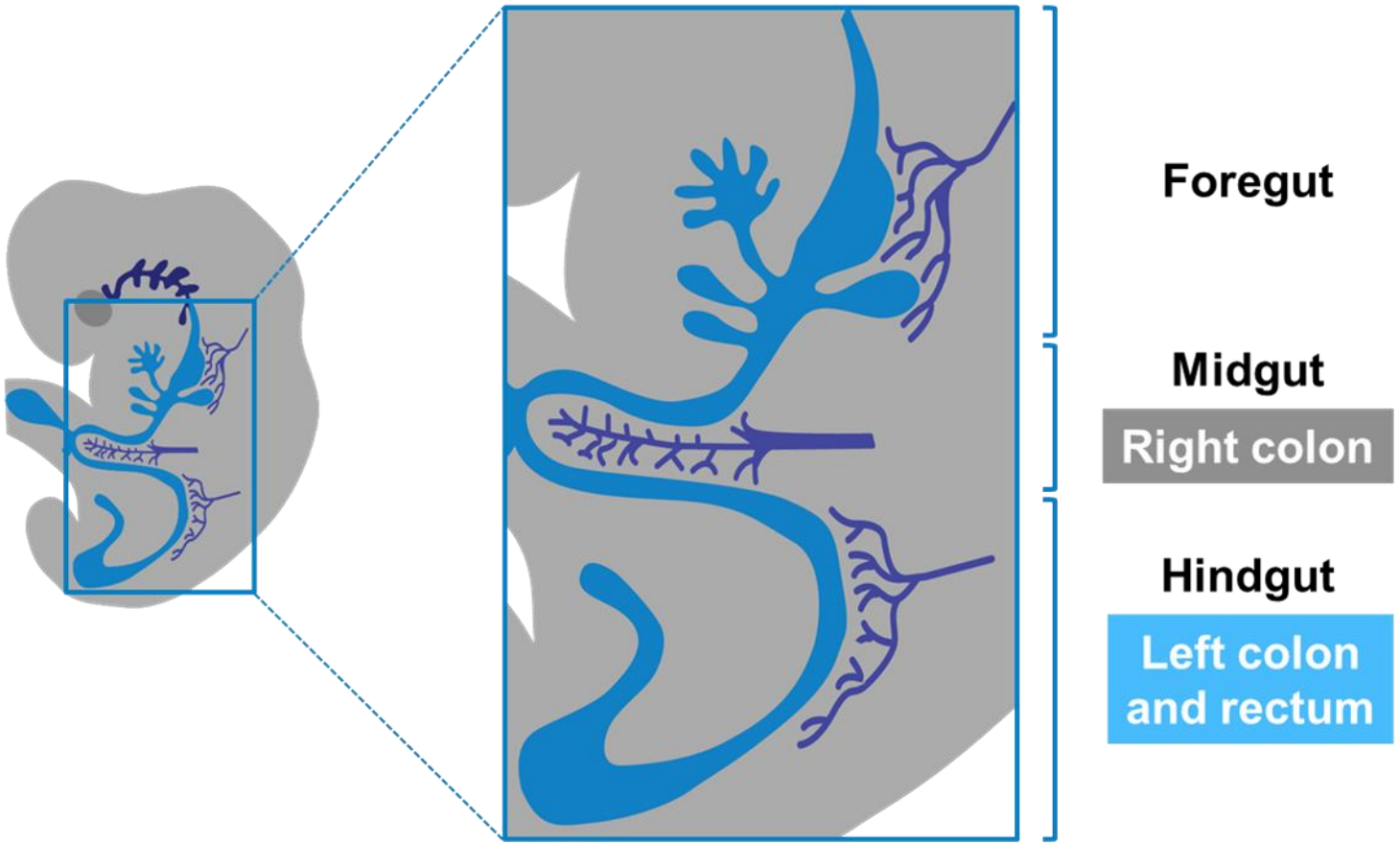


TOPIC FIVE

SIDEDNESS

Anatomy, embryology and physiology

The right colon and left colorectum have different embryonic origins and vascular supplies



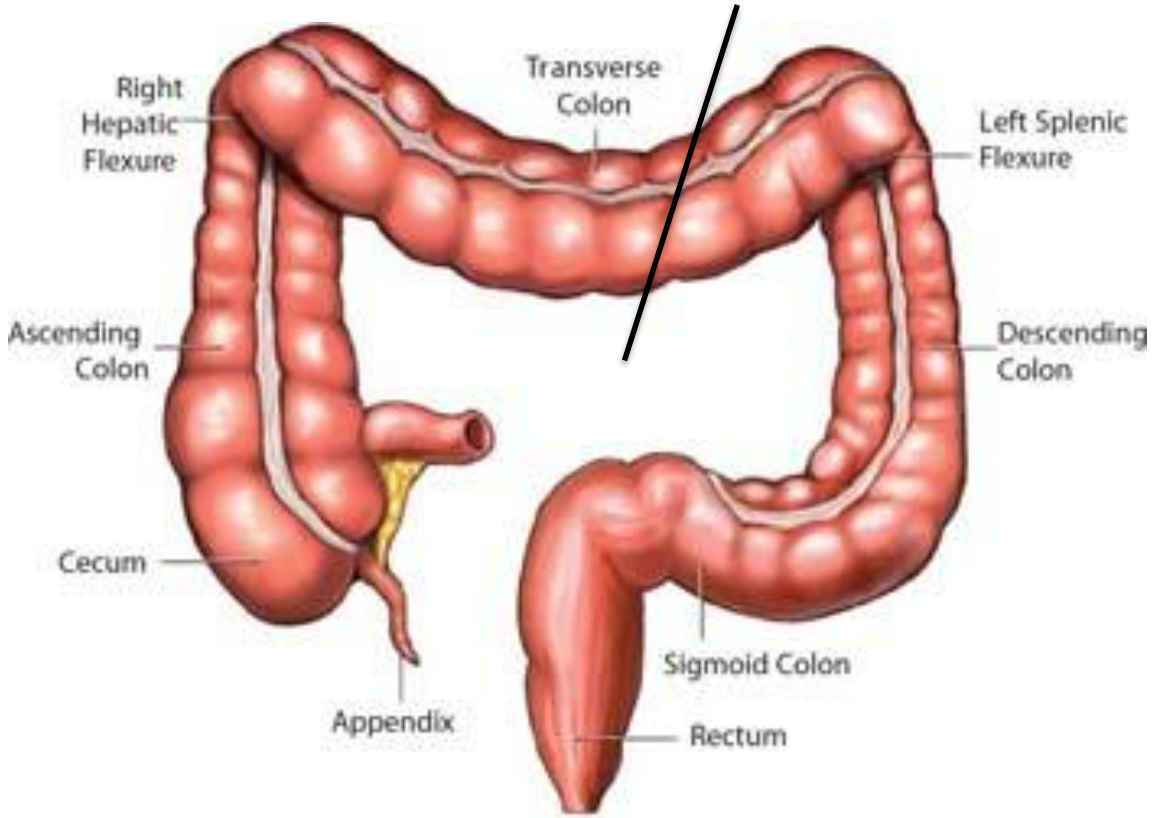
Li F, Lai M. J Zhejiang Univ Sci B 2009;10:219–29;
Kuo B, Urma D. GI Motility online 2006. doi:10.1038/gimo6 (accessed 25-08-16).

The right colon is supplied by branches of the superior mesenteric artery; the left colorectum is supplied by tributaries from the inferior mesenteric artery.

Right and Left Colon: Different Cancers, Different Biology, Different Outcomes.

Right Cancers:

- Female
- Older
- More BRAF mutations
- MSI high
- More co-morbidities
- Less acute presentation
- WORSE prognosis



Anatomy of Large Intestine

Left Cancers:

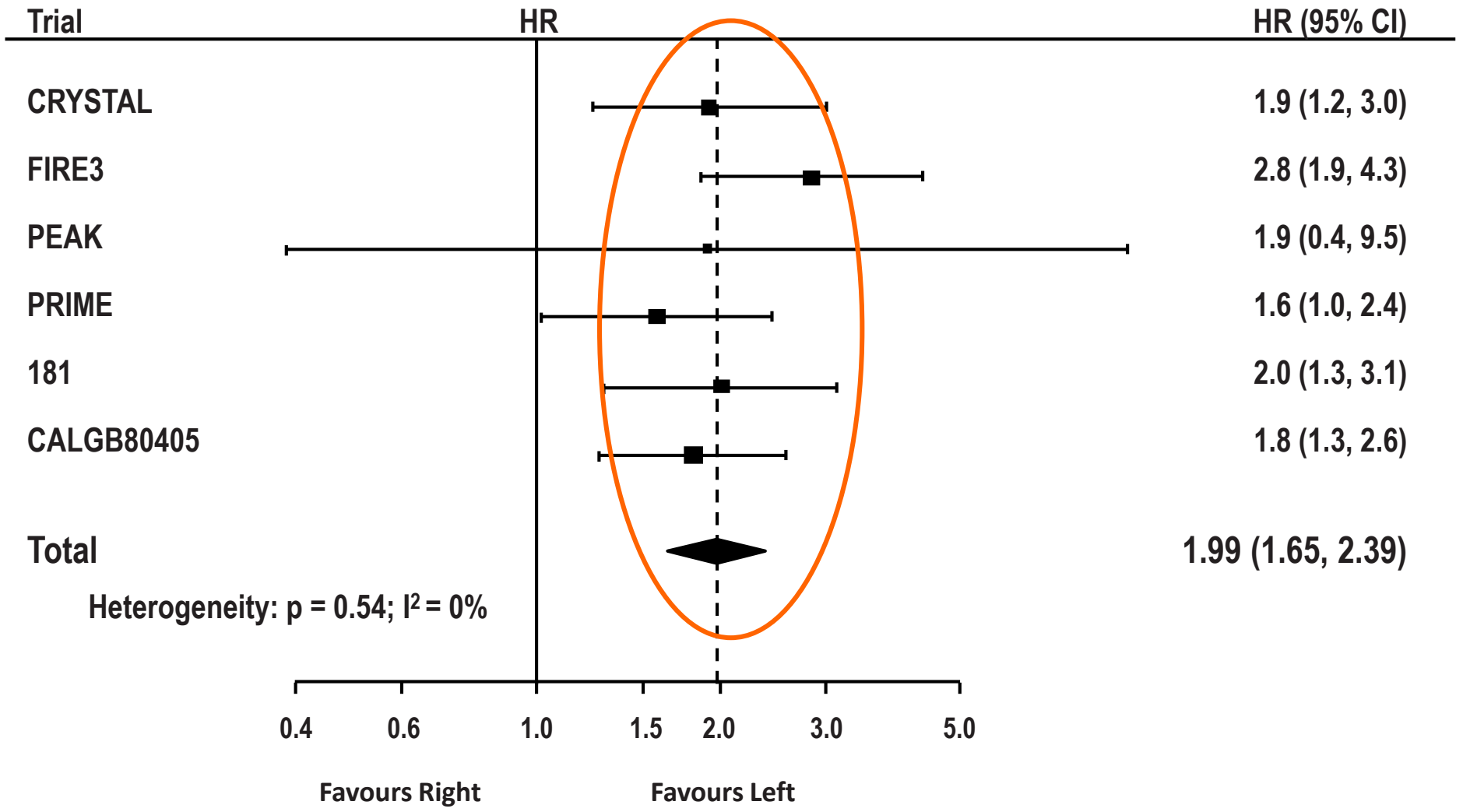
- Male
- Younger
- Earlier Diagnosis
- More acute presentation
- Better Prognosis

Is right and left too simplistic? Is this instead a continuum?

Hansen IO and Jess P, Dan Med J 2012;59:A4444; Loupakis F, et al. JNCI 2015;107.

Prognostic Analysis: OS

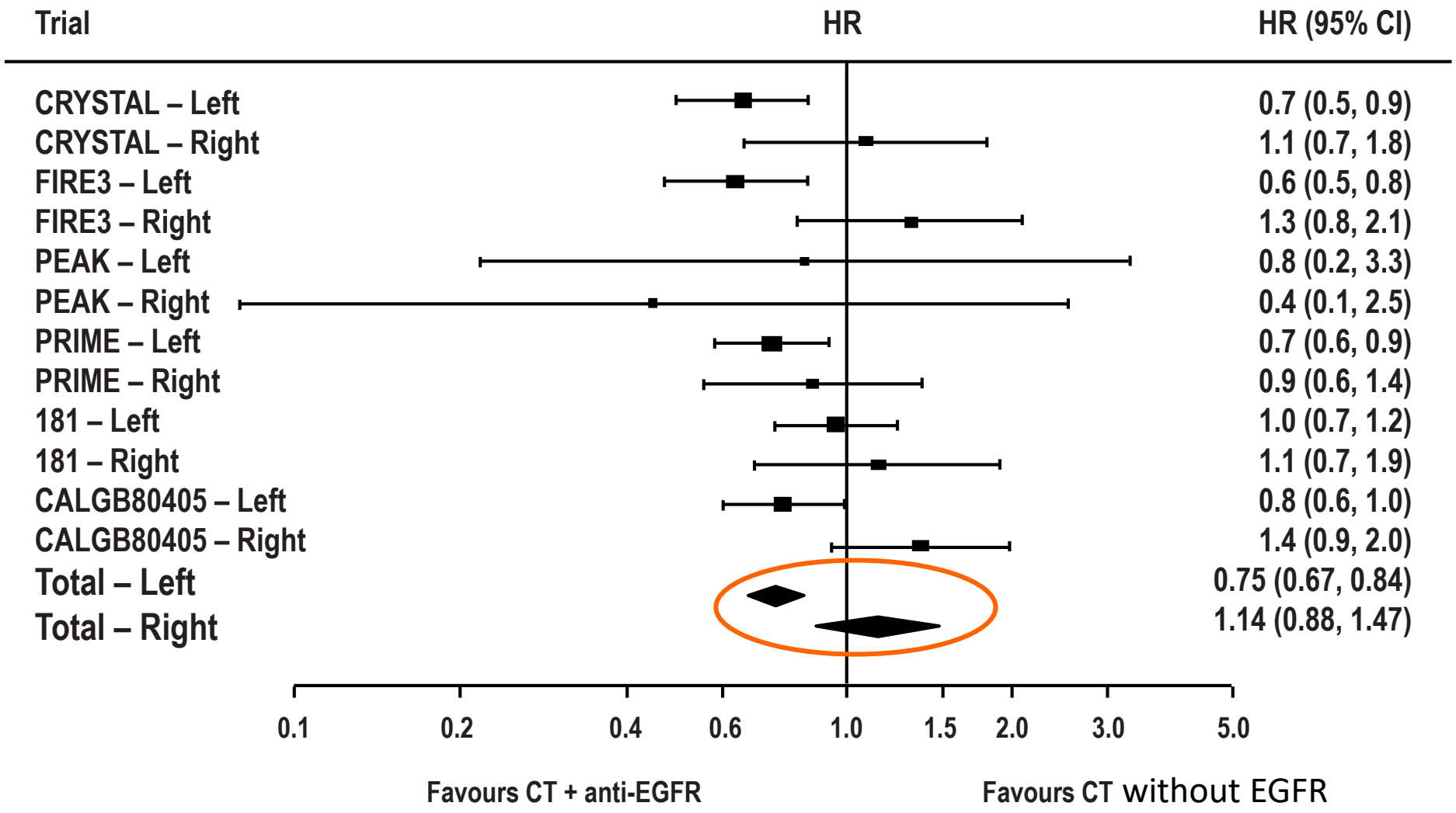
In all trials, OS favours left- over right-sided cancer



Dirk A (presentations), ESMO Congress 2016.

Predictive Analysis: OS

LEFT-SIDED TUMORS(RAS WT) DO BETTER ON EGFR Rx

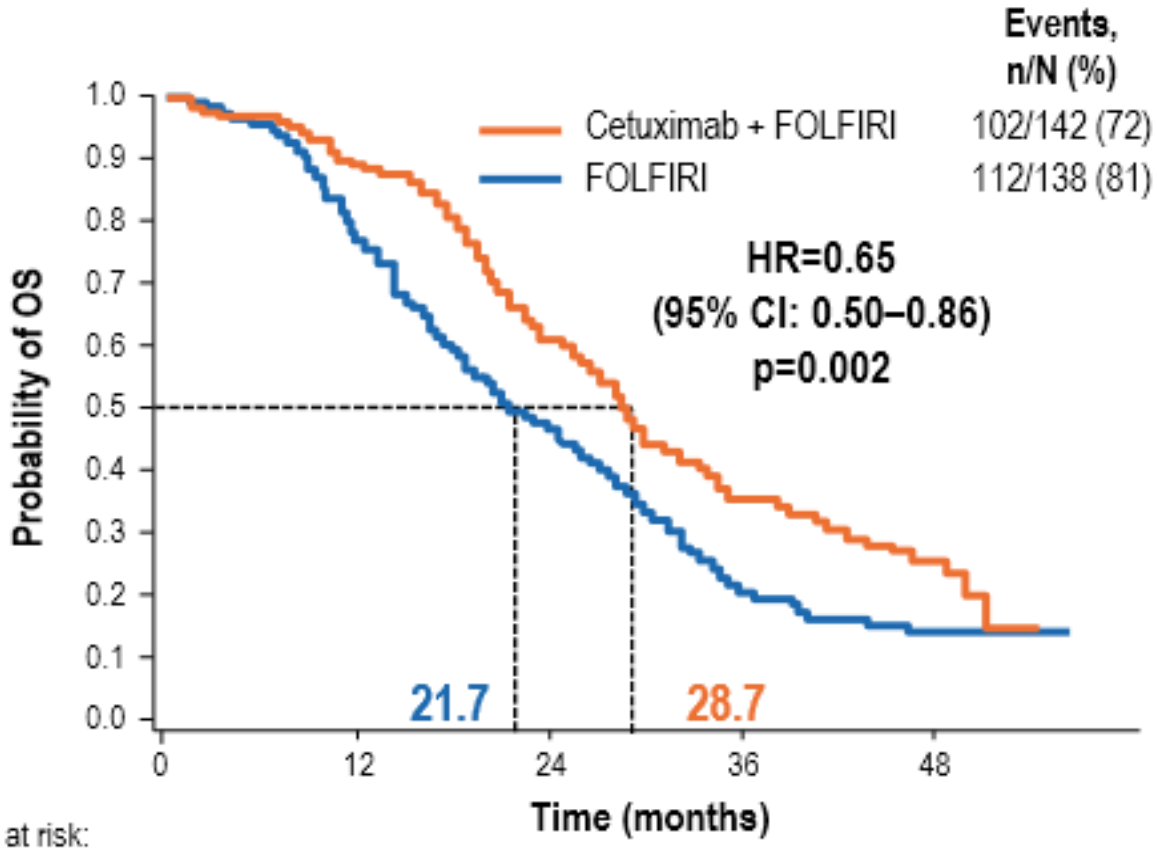


Dirk A (presentations), ESMO Congress 2016.

CRYSTAL

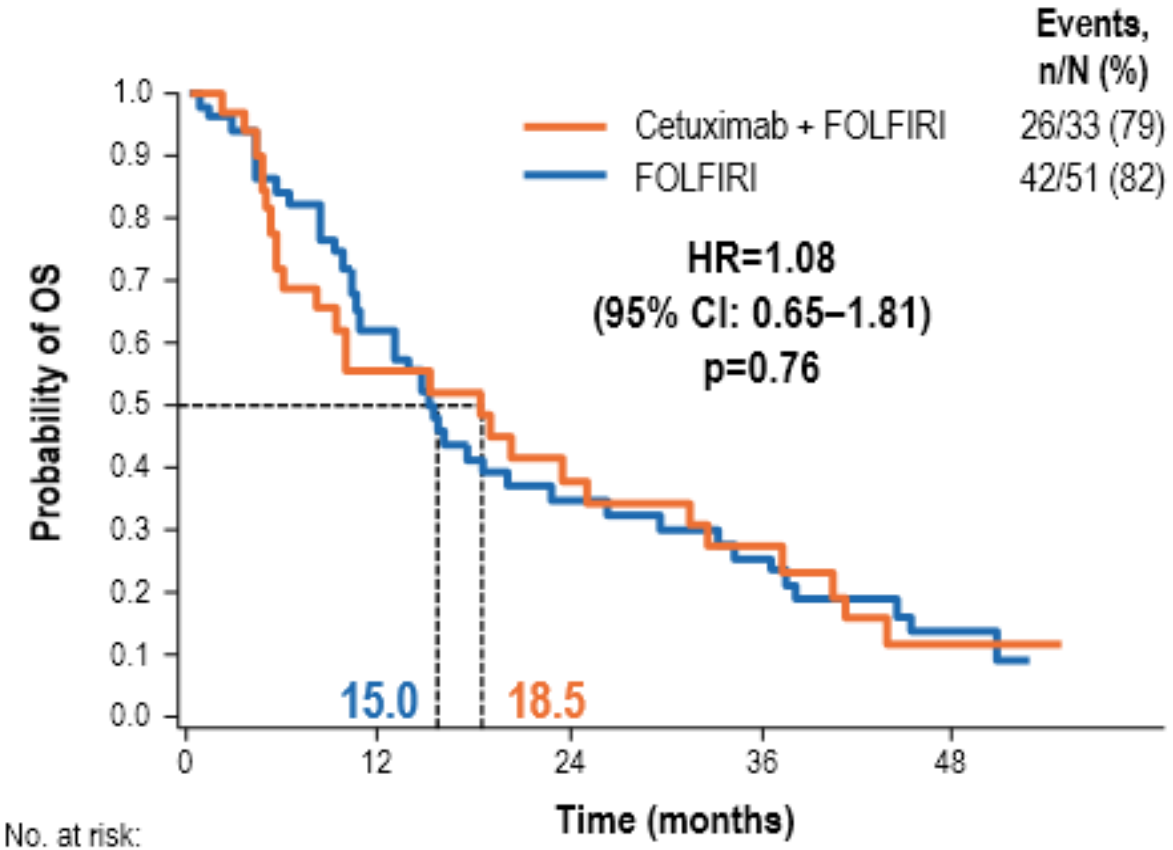
Relevant predictive value of primary tumor location: OS (*RAS*-wt)

Left-sided tumors



No. at risk:					
Cet + FOLFIRI	142	123	83	47	14
FOLFIRI	138	104	63	27	7

Right-sided tumors



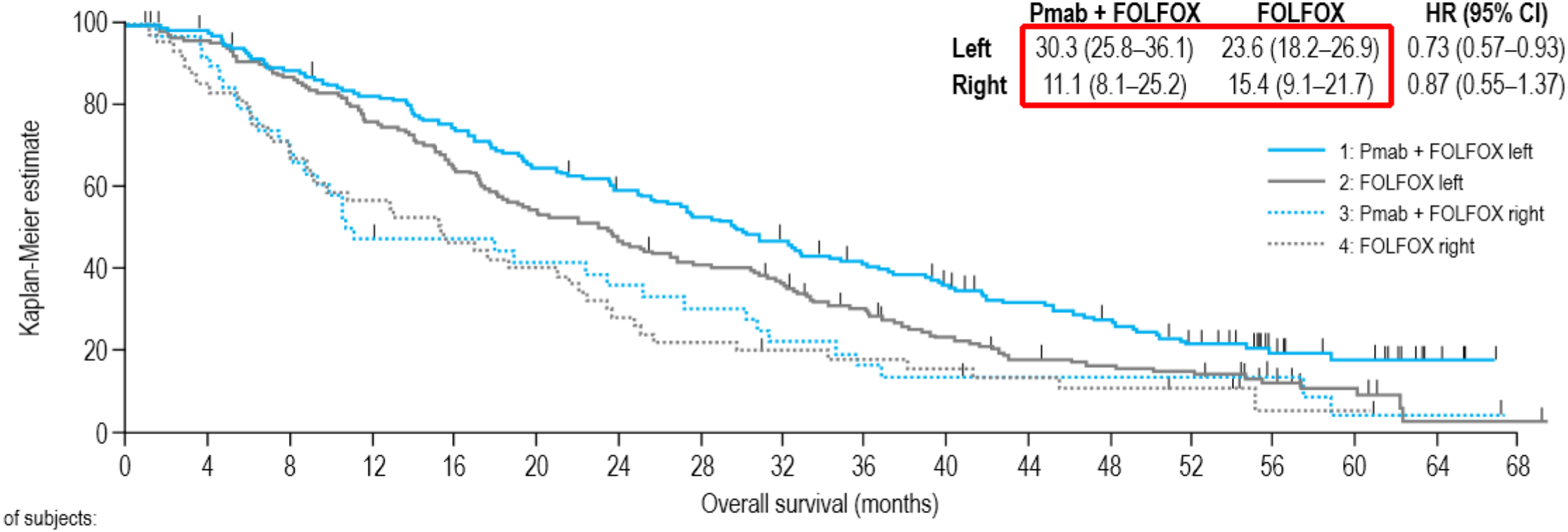
No. at risk:					
Cet + FOLFIRI	33	16	11	7	1
FOLFIRI	51	31	16	11	3

COPENHAGEN 2016 ESMO congress

Interaction p-value: 0.17

PRIME – OS – 1st line

	Median OS (95% CI), months		
	Pmab + FOLFOX	FOLFOX	HR (95% CI)
Left	30.3 (25.8–36.1)	23.6 (18.2–26.9)	0.73 (0.57–0.93)
Right	11.1 (8.1–25.2)	15.4 (9.1–21.7)	0.87 (0.55–1.37)



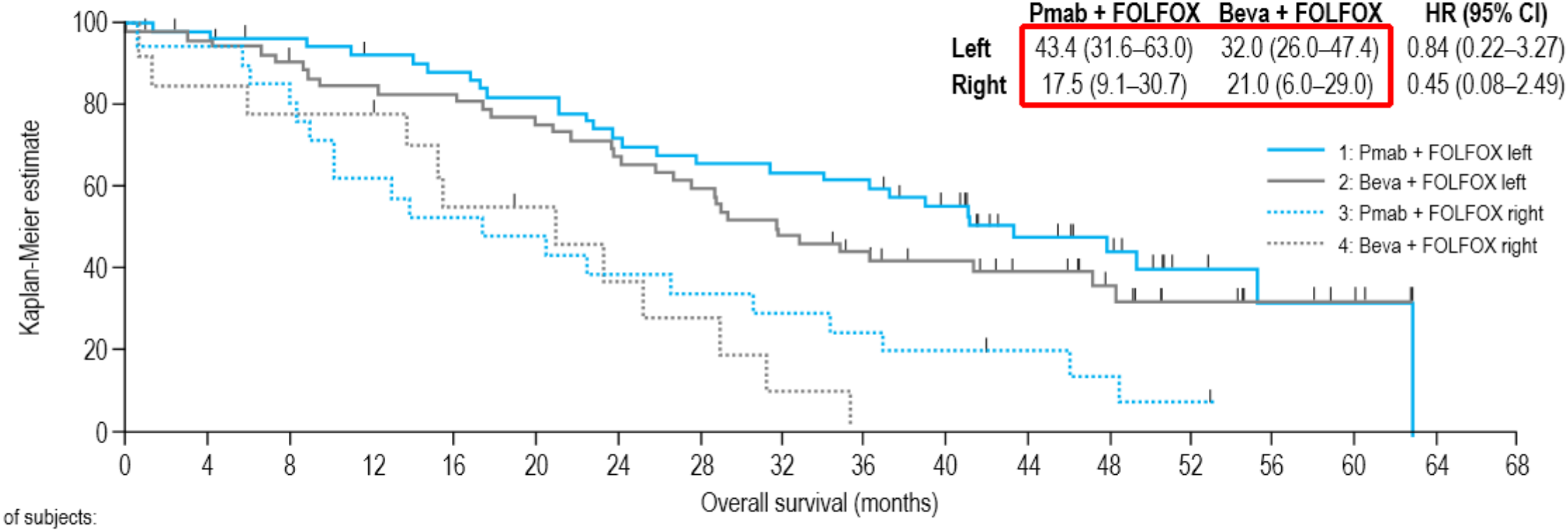
No. of subjects:

1:	169	164	147	136	124	107	97	86	77	66	56	46	39	30	16	11	3	0
2:	159	151	137	120	103	86	76	64	56	44	32	24	21	19	11	6	1	1
3:	39	36	26	18	17	15	13	11	8	6	5	4	4	4	3	1	1	0
4:	49	42	34	28	23	20	14	11	9	8	7	6	5	4	1	1	0	

Censor indicated by vertical bar

PEAK – OS – 1st line

	Median OS (95% CI), months		
	Pmab + FOLFOX	Beva + FOLFOX	HR (95% CI)
Left	43.4 (31.6–63.0)	32.0 (26.0–47.4)	0.84 (0.22–3.27)
Right	17.5 (9.1–30.7)	21.0 (6.0–29.0)	0.45 (0.08–2.49)



No. of subjects:

1:	53	51	49	46	44	41	36	33	32	31	25	17	13	6	3	2	0
2:	54	51	48	44	43	40	35	31	26	21	17	13	10	5	3	2	0
3:	22	21	18	13	11	10	8	7	6	5	4	3	2	1	0		
4:	14	12	11	11	7	6	4	3	1	0							

Censor indicated by vertical bar

Panitumumab efficacy by tumour location analysis

Prognostic effect of primary tumour location

WT *RAS*	PRIME		PEAK	
Panitumumab arm	Panitumumab + FOLFOX4		Panitumumab + mFOLFOX6	
	Left	Right	Left	Right
Median OS, months	30.3	11.1	43.4	17.5
Adjusted HR,† right vs left (95% CI)	1.58 (1.02–2.45)		2.68 (1.31–5.46)	
Comparator arm	FOLFOX4		Bevacizumab + mFOLFOX6	
	Left	Right	Left	Right
Median OS, months	23.6	15.4	32.0	21.0
Adjusted HR,† right vs left (95% CI)	1.27 (0.88–1.84)		2.86 (1.40–5.84)	

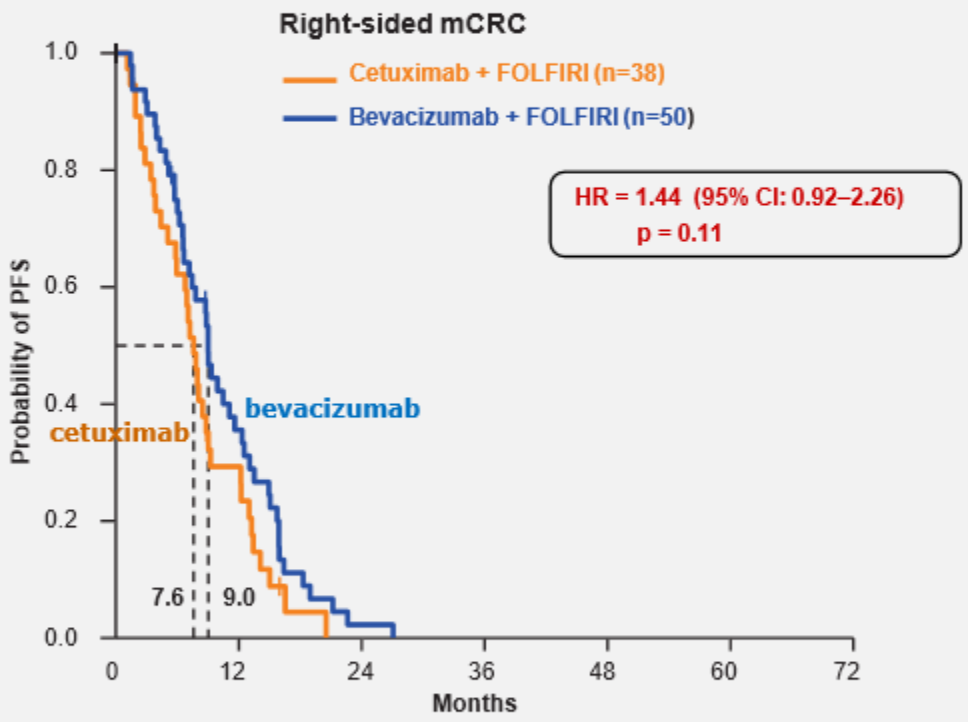
- Right-sided primary tumours were associated with worse prognosis compared with left-sided tumours, regardless of treatment received

Boeckx N, et al. Ann Oncol 2017 (and Supplementary Table 1); Epub ahead of print.

†Adjusted for *BRAF* status, prior adjuvant therapy and baseline ECOG PS score. HR > 1 means worse prognosis in right-sided tumours.

FIRE-3: Right-sided tumors

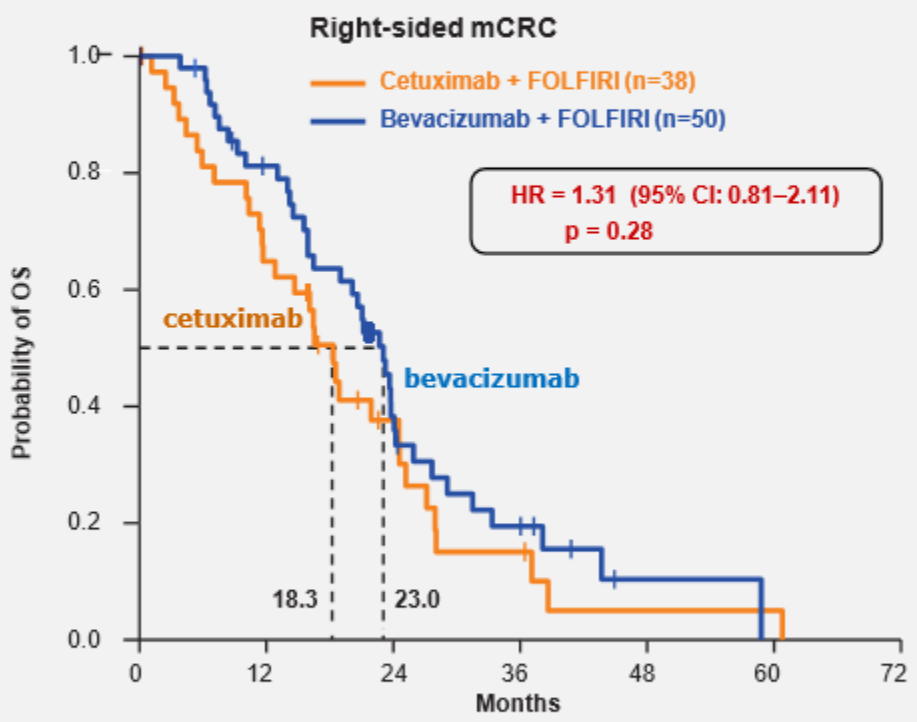
Progression-free survival



Numbers at Risk

Cetuximab + FOLFIRI	38	10	0	0	0	0	0
Bevacizumab + FOLFIRI	50	16	1	0	0	0	0

Overall survival

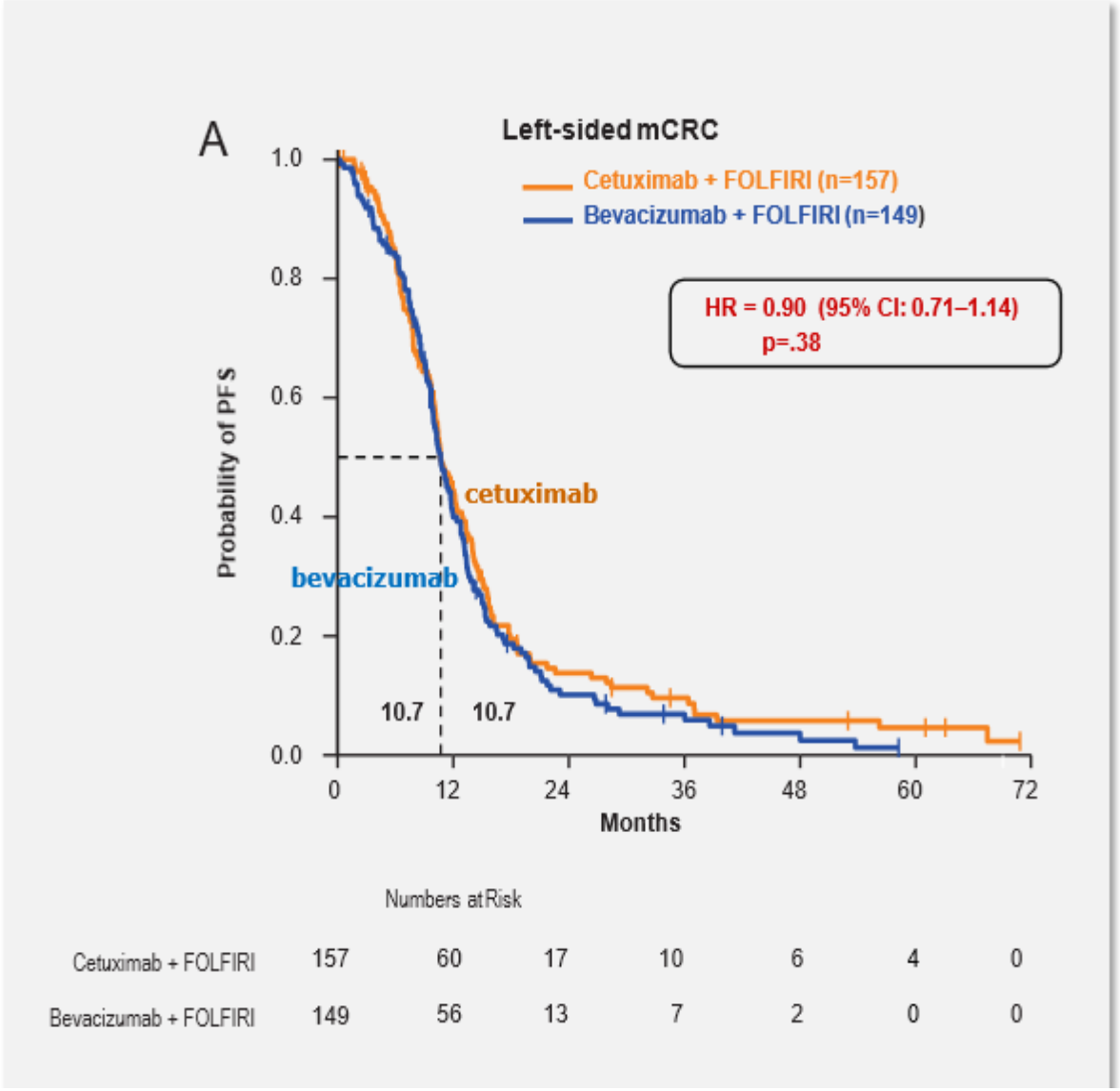


Numbers at Risk

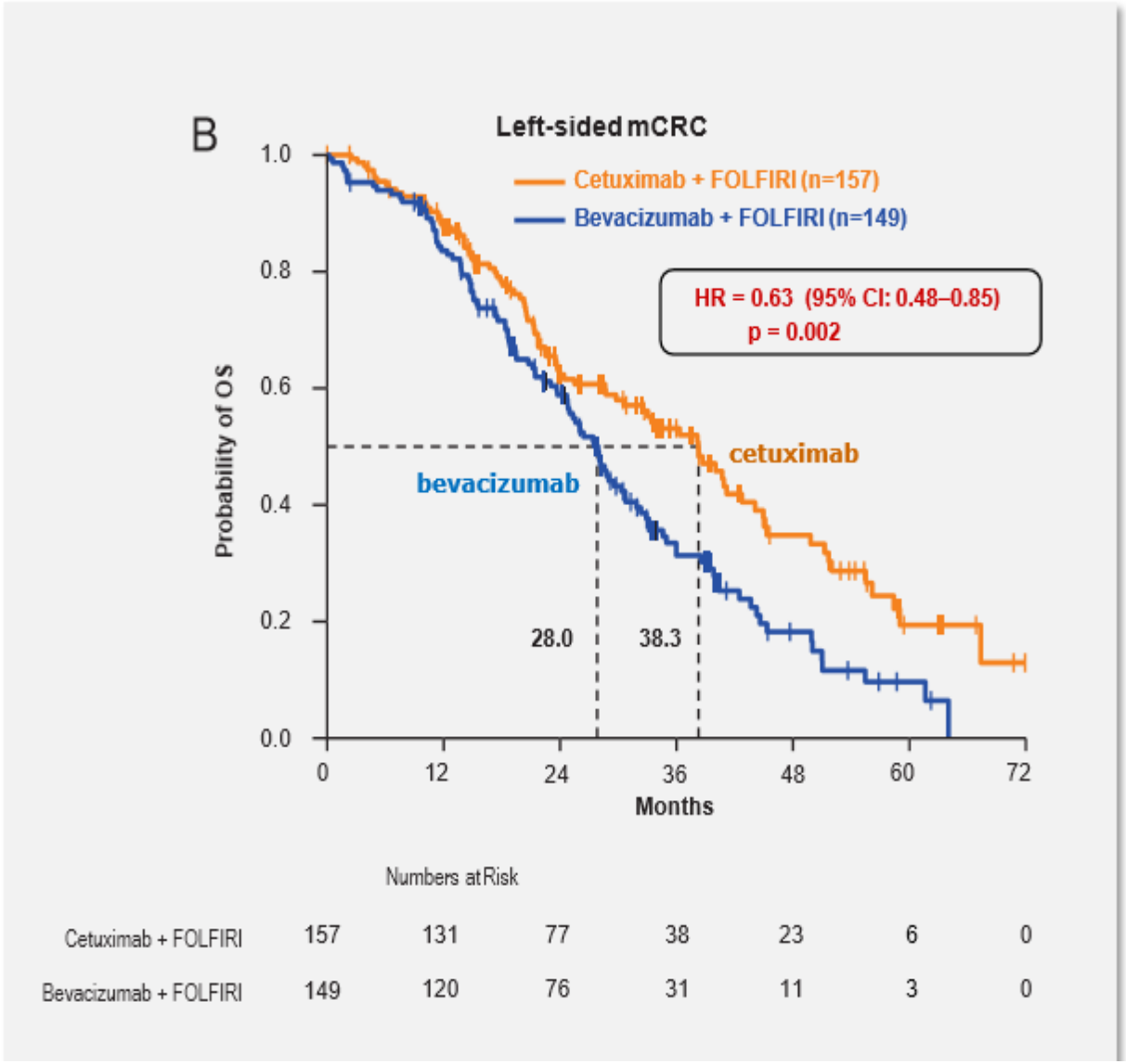
Cetuximab + FOLFIRI	38	24	10	4	1	1	0
Bevacizumab + FOLFIRI	50	37	16	7	1	0	0

FIRE-3: Left-sided tumors

Progression-free survival

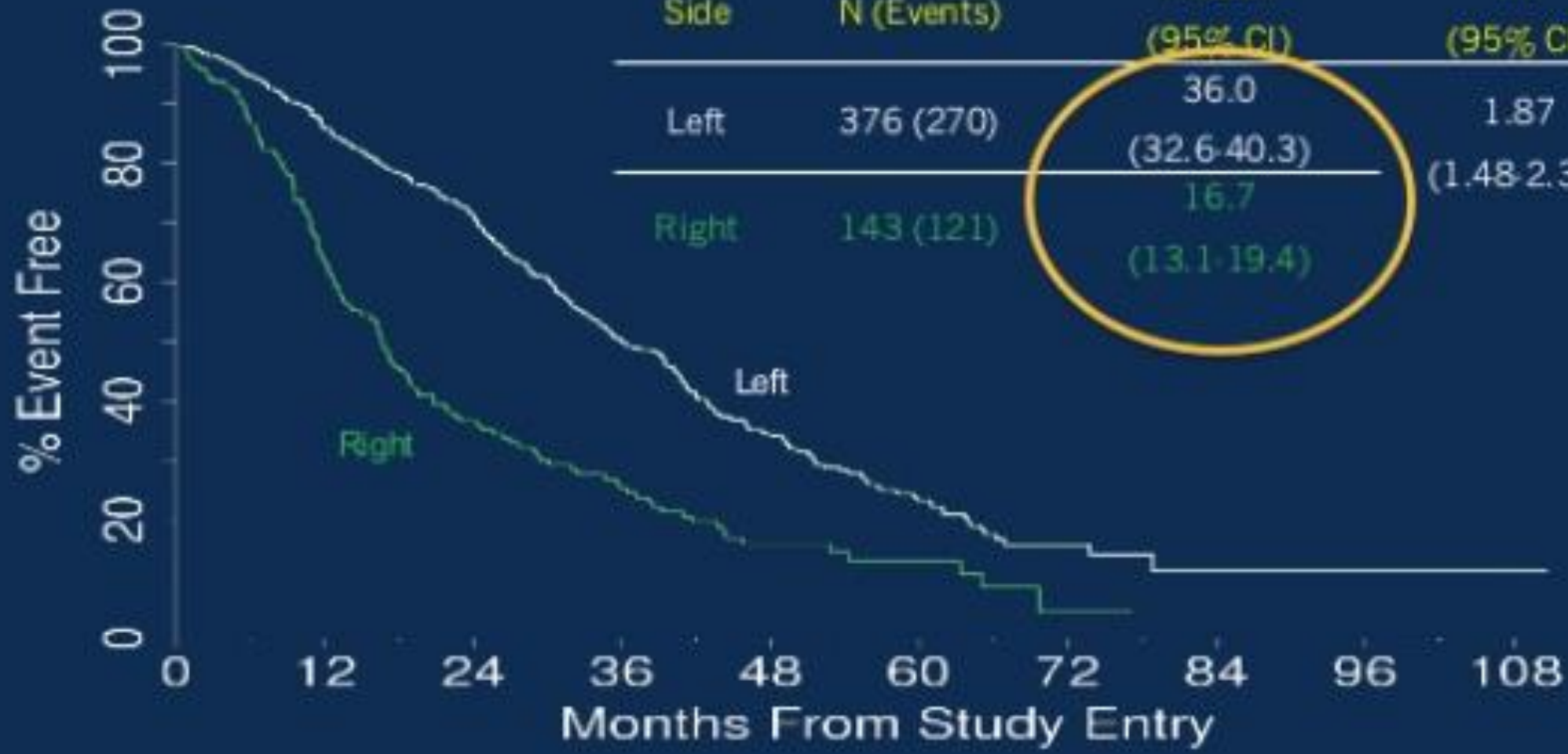


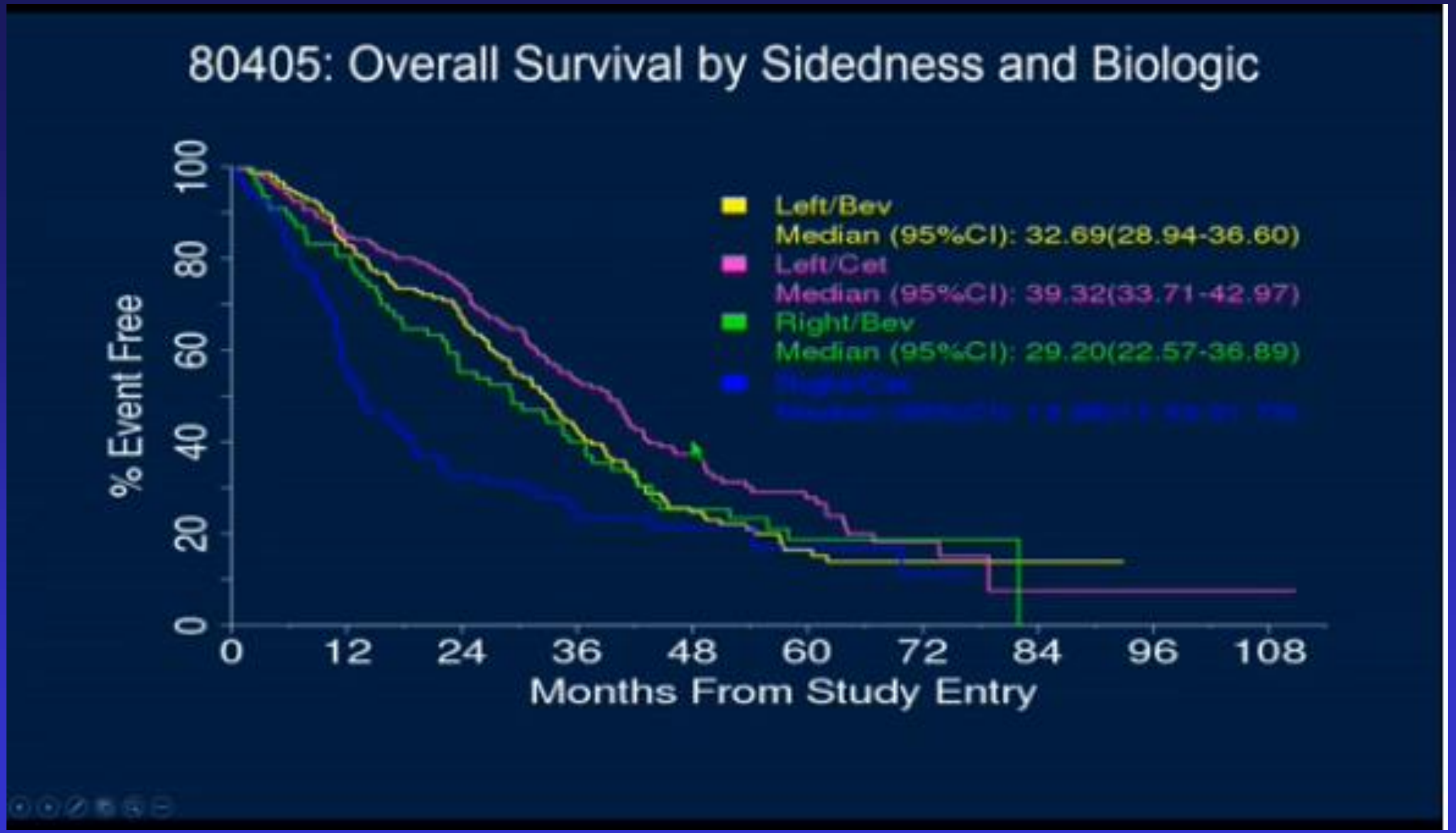
Overall survival



80405: OS by Sidedness (Cetuximab)

Side	N (Events)	Median (95% CI)	HR (95% CI)	p
Left	376 (270)	36.0 (32.6-40.3)	1.87 (1.48-2.32)	<0.0001
Right	143 (121)	16.7 (13.1-19.4)		



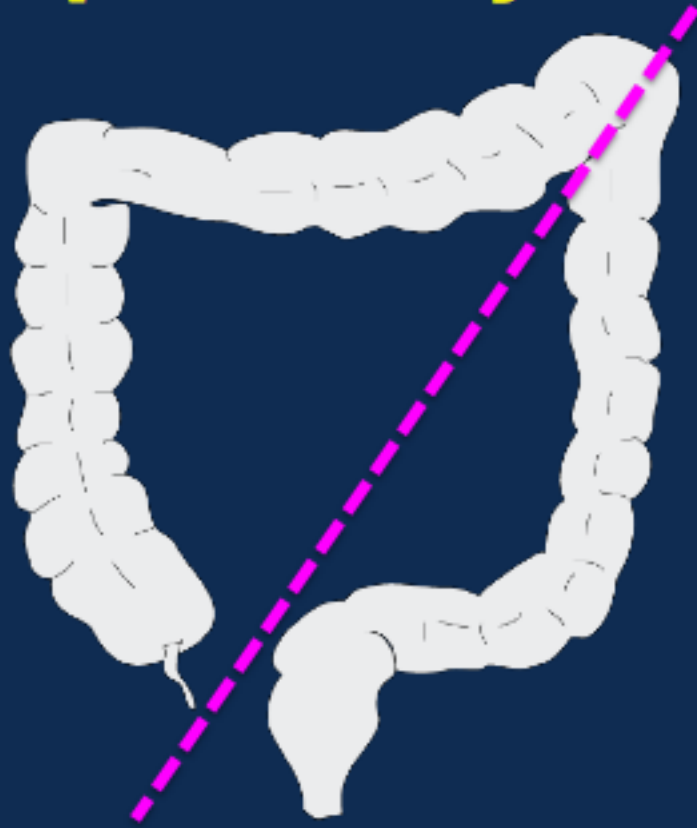

80405: Overall Survival by Sidedness and Biologic
% Event Free
0
20
40
60
80
100
0
12
24
36
48
60
72
84
96
108
Months From Study Entry
Left/Bev
Median (95%CI): 32.69(28.94-36.60)
Left/Cet
Median (95%CI): 39.32(33.71-42.97)
Right/Bev
Median (95%CI): 29.20(22.57-36.89)

Potential explanatory factors

Clinical

Embryologic / Physiologic

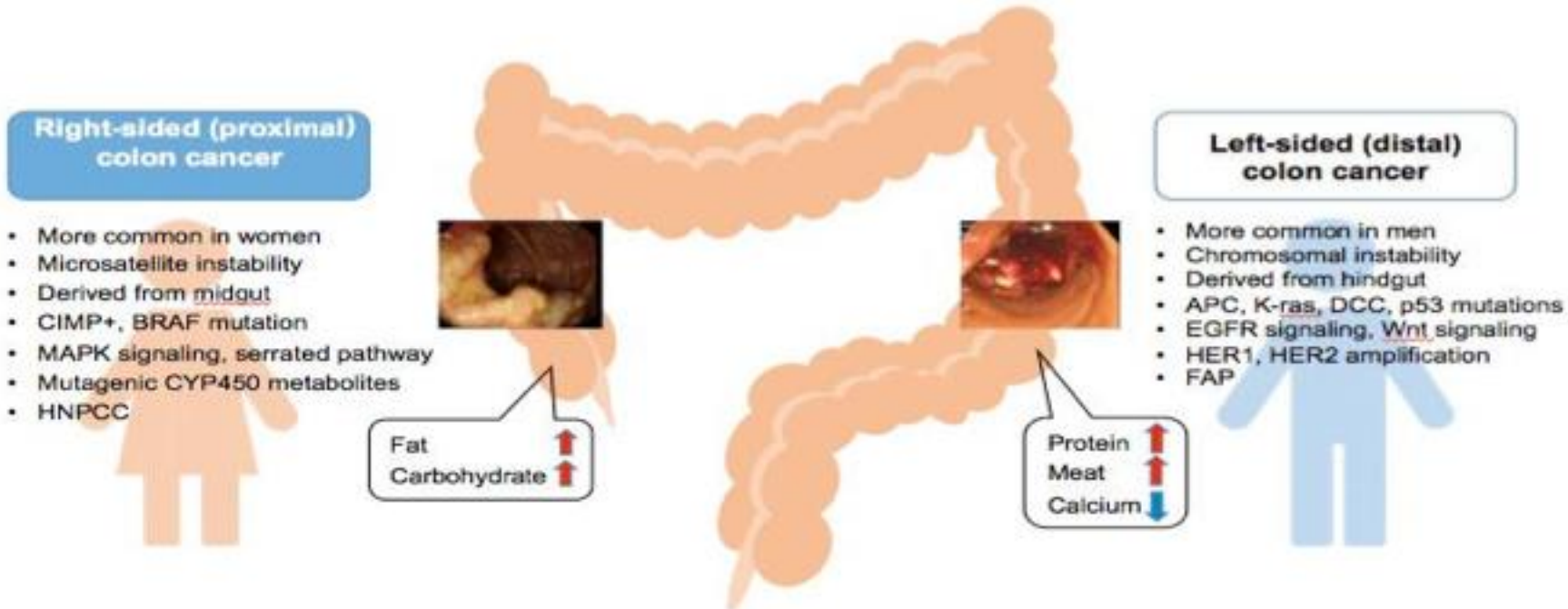
Epidemiologic



Environmental

Molecular / Genetic

Midgut vs Hindgut



Summary of common clinical and molecular characteristics of right- and left-sided colon tumors and associations with dietary factors. CIMP = CpG island methylator phenotype; HNPCC = hereditary non-polyposis colorectal cancer; APC = adenomatous polyposis coli; K-ras = Kirsten-ras; DCC = deleted in colorectal cancer; FAP = familial adenomatous polyposis.

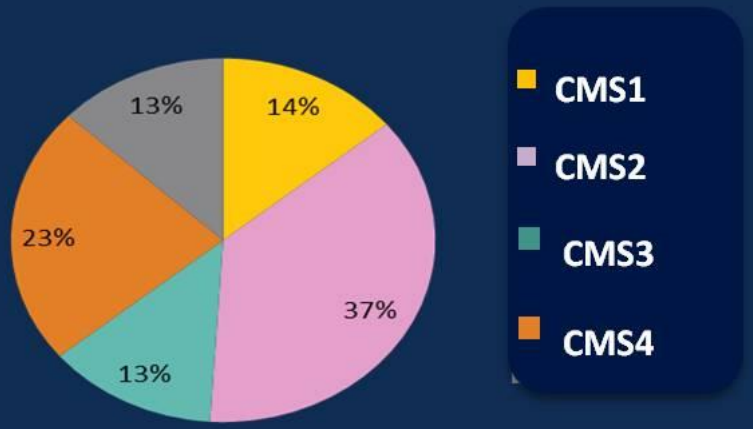
World J Gastroenterol. May 7, 2015; 21(17): 5167-5175

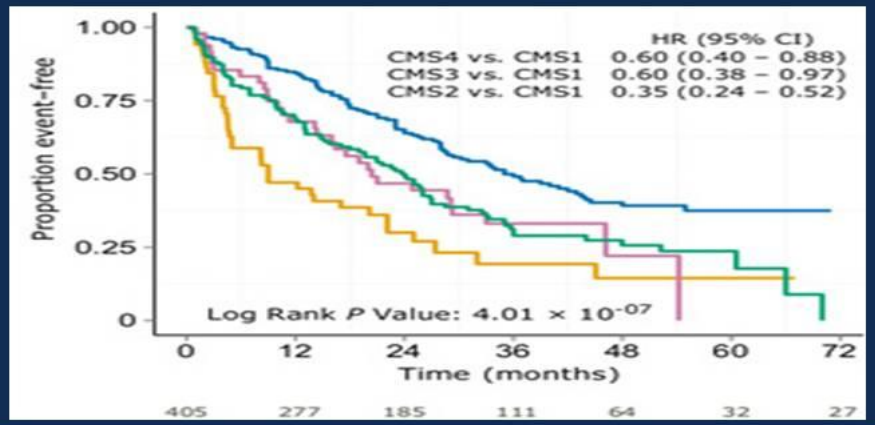
Discussion: Relating Phenotype to Genotype

Consensus Molecular Subtypes in Colorectal Cancer

Guinney et al. *Nature Medicine* Nov 2015

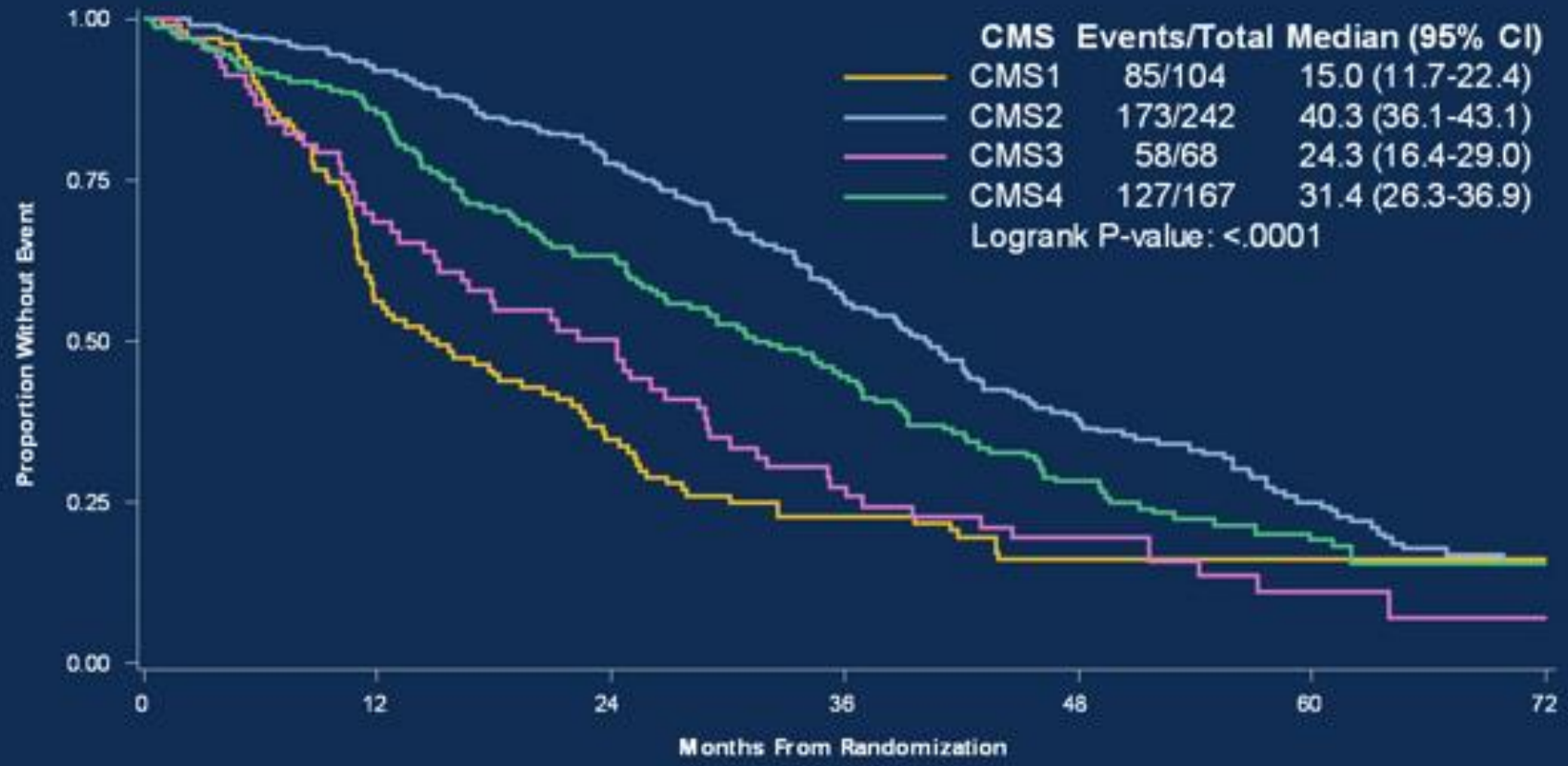
4 Consensus Molecular Subtypes





CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	**37%**	**13%**	**23%**
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGFB activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

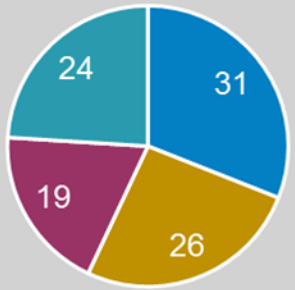
OS – All Patients by CMS Subtype

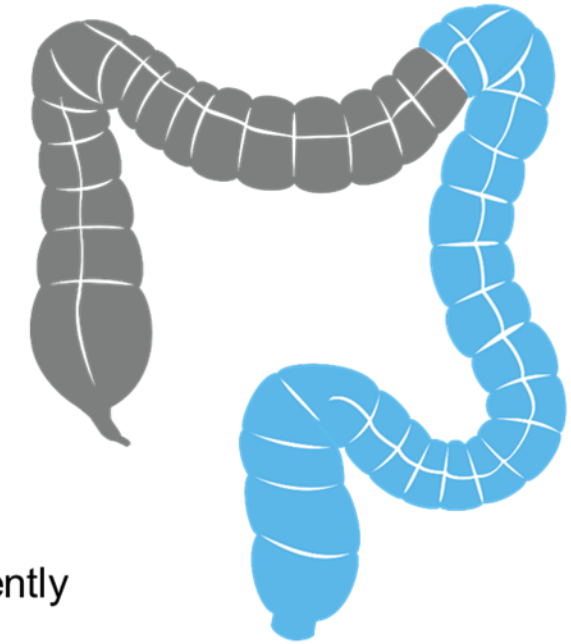


Molecular pathways/tumour classification models

Distribution of CMS groups varies by colorectal tumour location

Right colon (%)



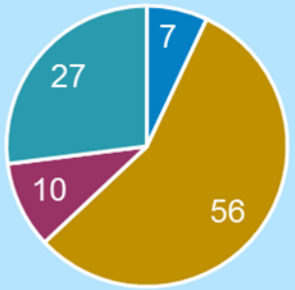


- CMS1 tumours were frequently diagnosed in females with right-sided lesions
- CMS2 tumours were mainly left-sided

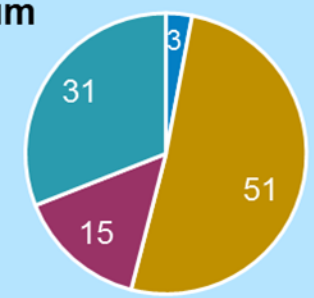
CMS1
CMS2
CMS3
CMS4

Left colorectum (%)

Colon



Rectum



Guinney J, et al. Nat Med 2015;21:1350–6 (and Supplementary Figure 10).

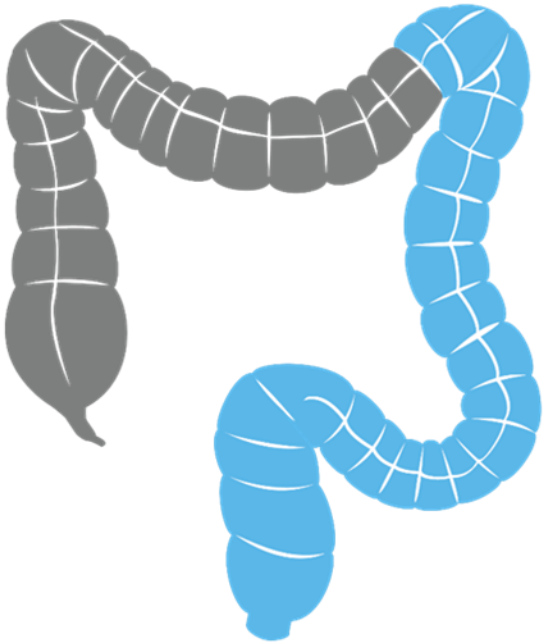
Right colon = caecum to transverse colon;
left colon = splenic flexure to sigmoid colon (n = 2651).

Molecular pathways/tumour classification models

CIMP-high, MSI-high and CMS distribution varies between colorectal locations

Right colon

- +++ MSI-high[1,2]
- +++ CIMP-high[1,2]
- +++ CMS1[3]
- +++ Serrated pathway[2†]



Left colorectum

Colon

- +++ CIN+[2†]
- +++ CMS2[3]

Rectum

- +++ CMS2[3]

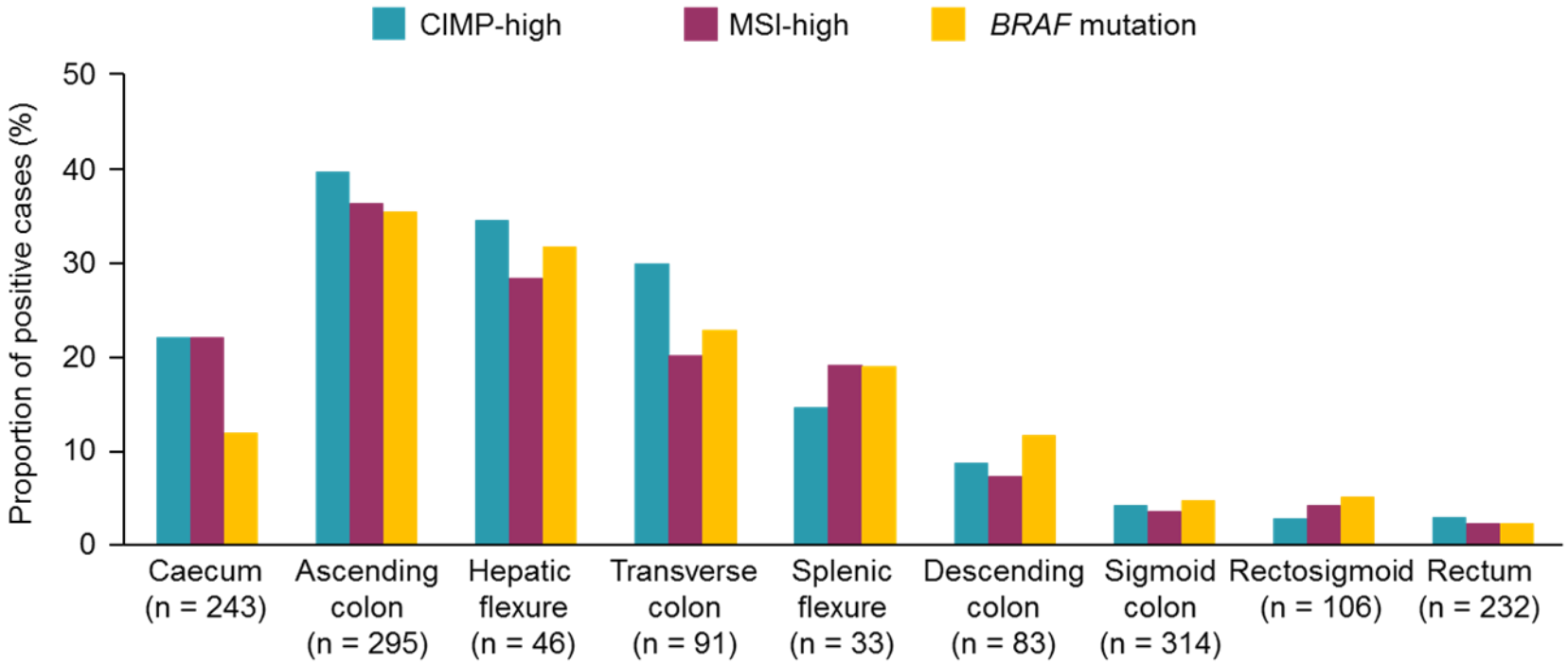
- Molecular heterogeneity may be captured by the anatomical location of the tumour

1. Yamauchi M, et al. Gut 2012;61:847–54;
2. Missiaglia E, et al. Ann Oncol 2014;25:1995–2001;
3. Guinney J, et al. Nat Med 2015;21:1350–6 (and Supplementary Figure 10).

+++ denotes that a molecular or morphological subtype is more prevalent compared with other colorectal segments.
†CIN expression and serrated pathway data are not available for rectal tumours.
CIMP, CpG island methylator phenotype; CIN, chromosomal instability; CMS, Consensus Molecular Subtypes; MSI, microsatellite instability.

Is classification by side an over-simplification?

Distribution of molecular characteristics varies across colorectal cancer subsites

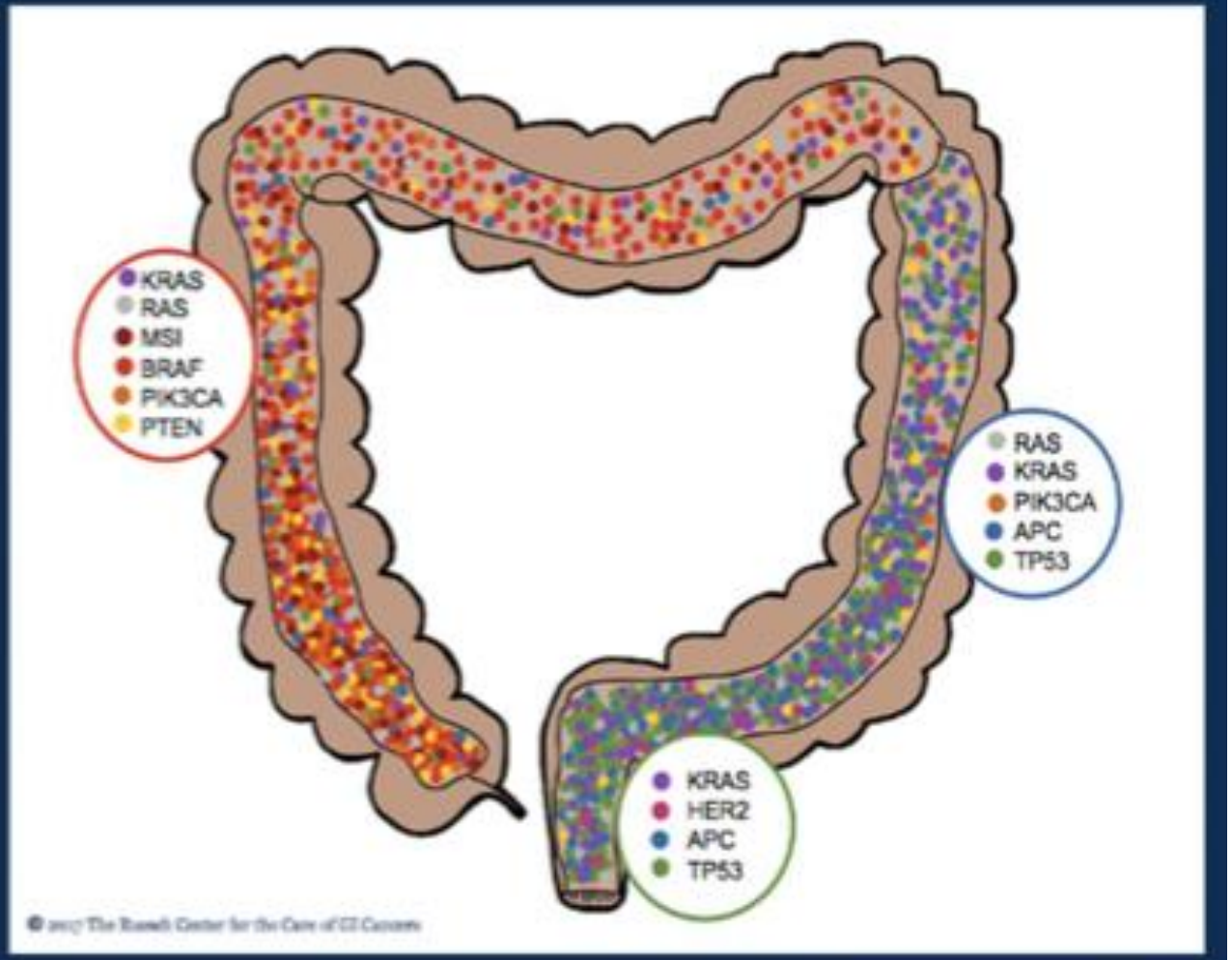


Variation in molecular characteristics across bowel subsites challenges the concept of discrete right colon and left colorectal tumour characteristics

Yamauchi M, et al. Gut 2012;61:847–54.

Conclusions

- CRCs carry a continuum of molecular alterations from right to left, rather than having a sharp, clear-cut distinction



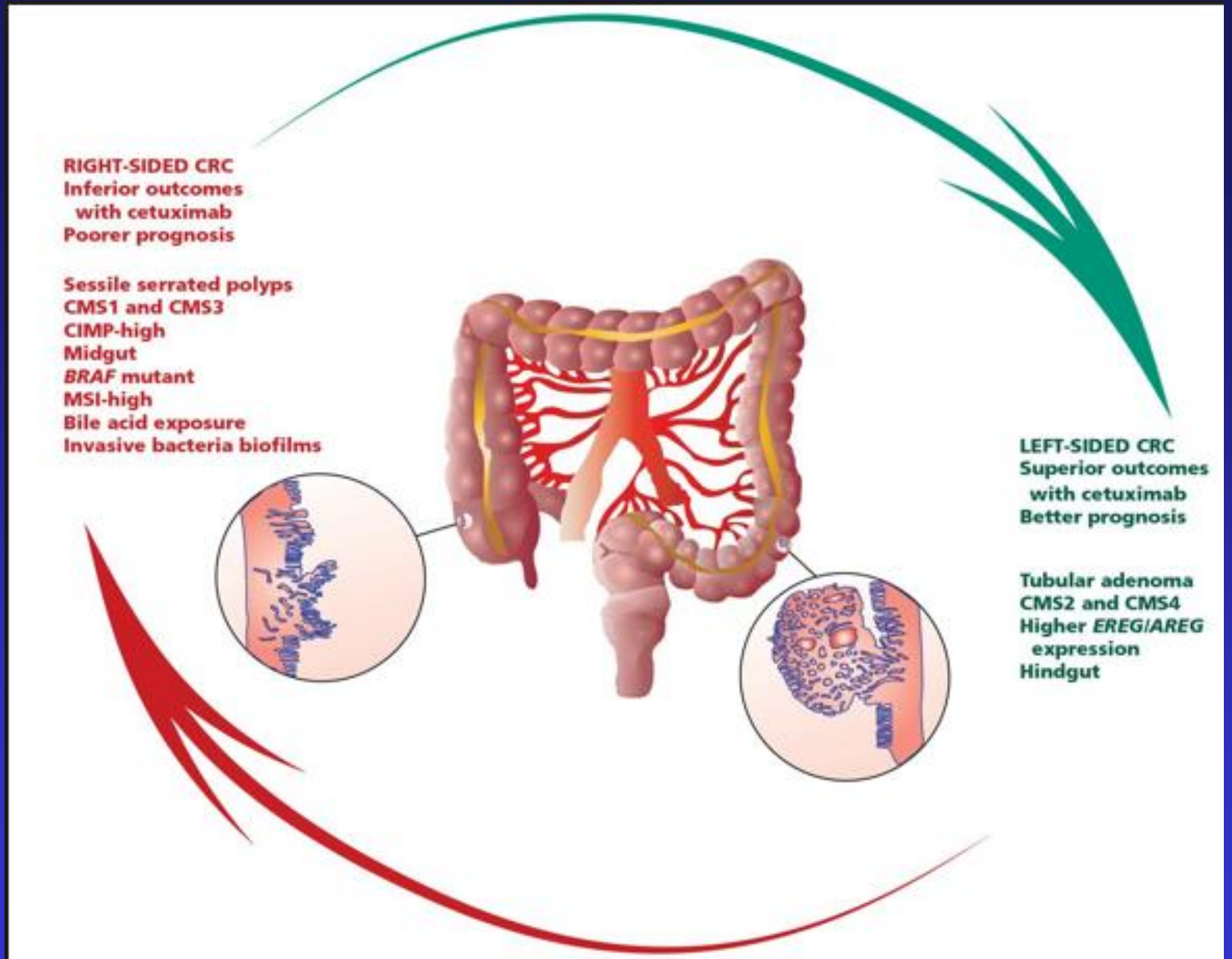


Figure 2. Summary of key biologic differences between right- and left-sided CRCs.
Abbreviations: AREG, amphiregulin; CIMP, CpG island methylator phenotype; CMS, consensus molecular subtype; CRCs, colorectal cancers; EREG, epiregulin; MSI, microsatellite instability.

TOPIC SIX

MSI

Two different pathways of carcinogenesis

85%

Chromosomal instability (CIN):
Proficient DNA Mismatch Repair (pMMR)
and Microsatellite stable (MSS)

15%

Microsatellite instability (MSI):
Deficient Mismatch Repair (dMMR)

2/3

$BRAF^{V600E}$ mutation ≈50%

Sporadic cases
Epigenetic *MLH1* inactivation
(*MLH1* promoter methylation)

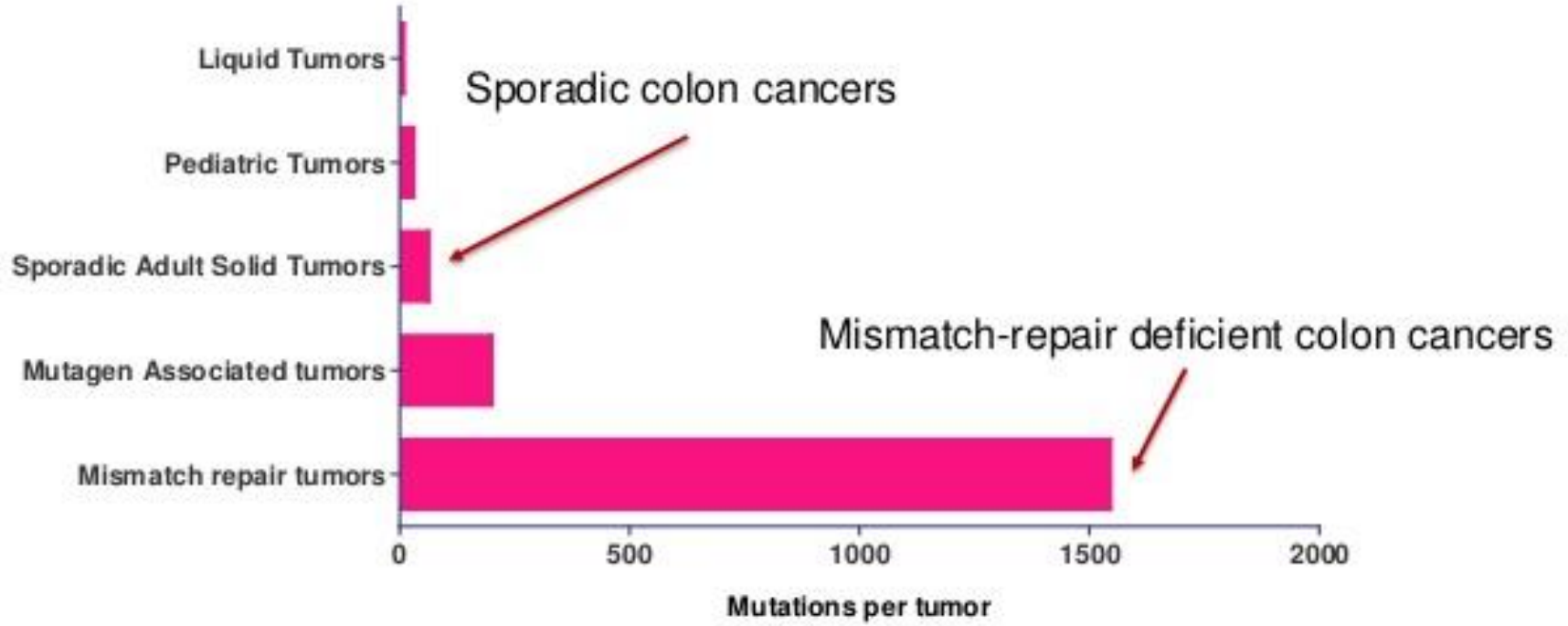
1/3

No $BRAF^{V600E}$ mutation

Familial cases
Lynch syndrome
germline mutation:
(*MLH1*, *MSH2*, *MSH6*, *PMS2*)

Sinicrope FA, Nat. Rev. Clin. Oncol 7:174-177, 2010

Mutations per tumor



The James

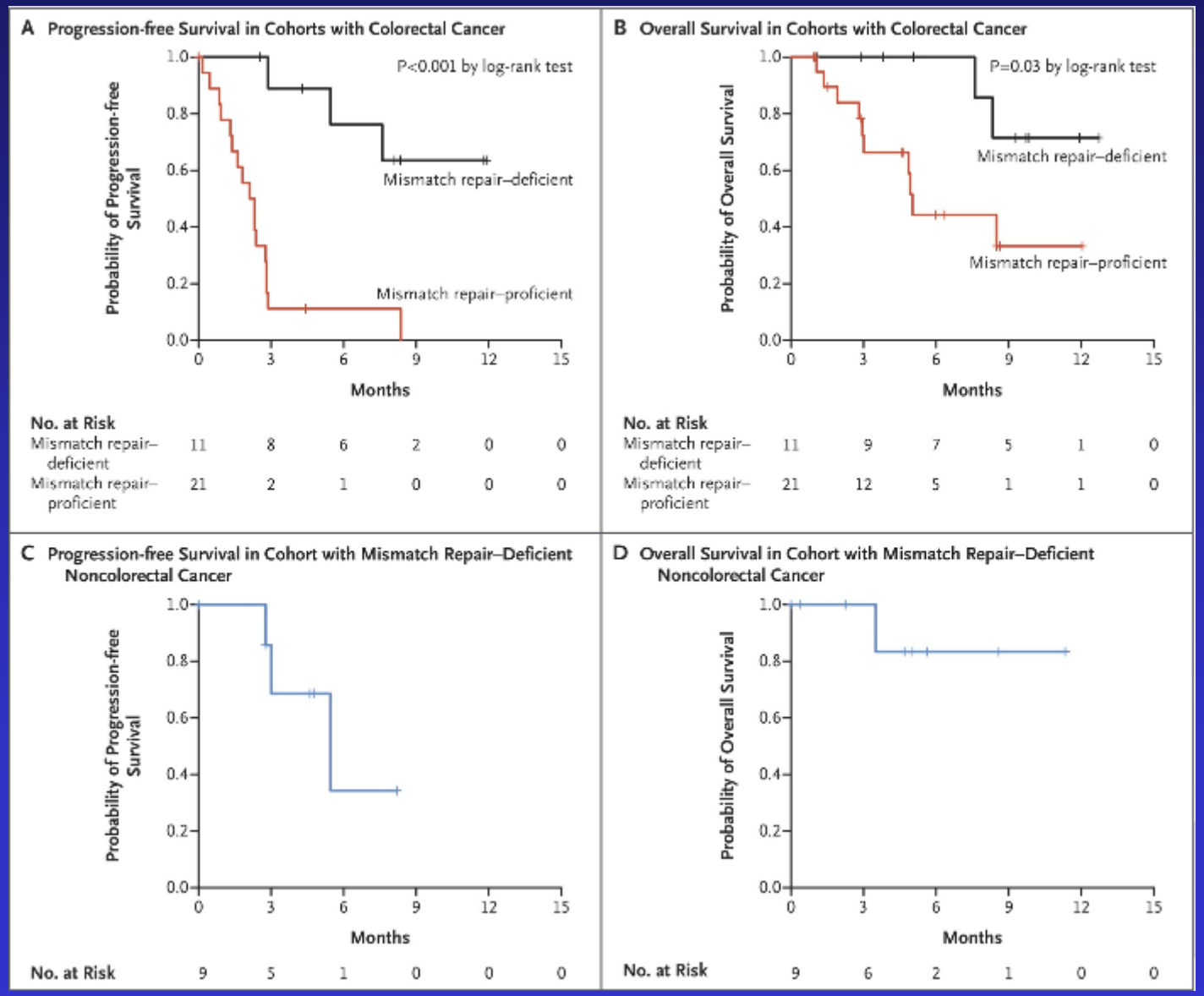
The Ohio State University

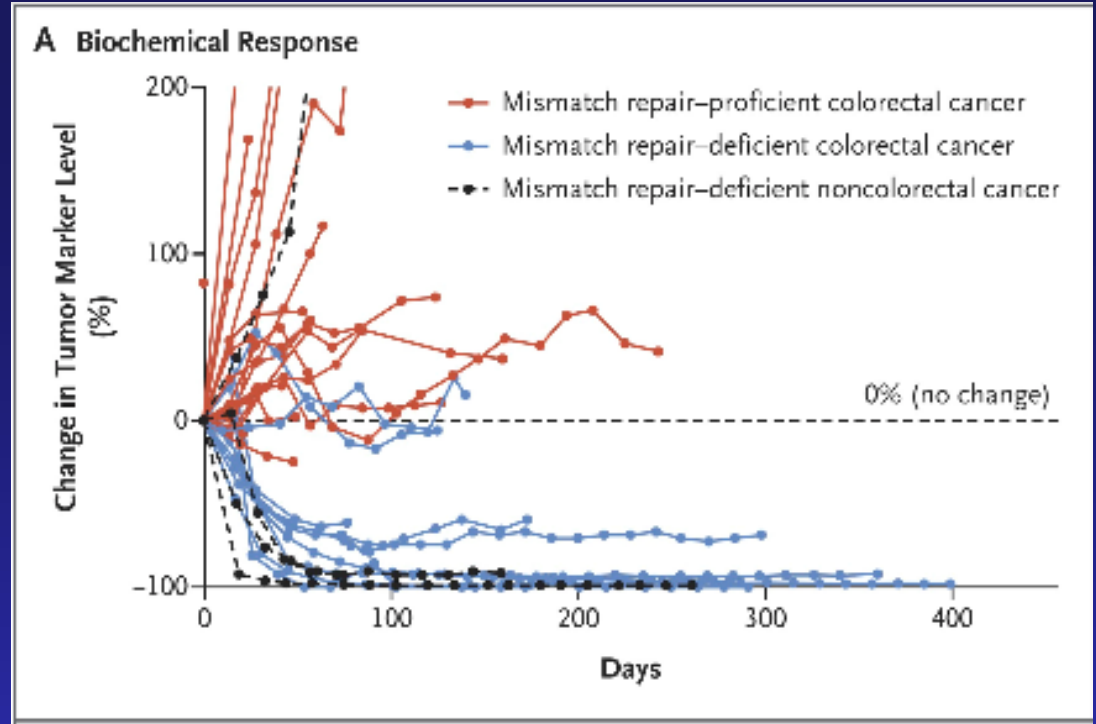
Mismatch repair deficiency

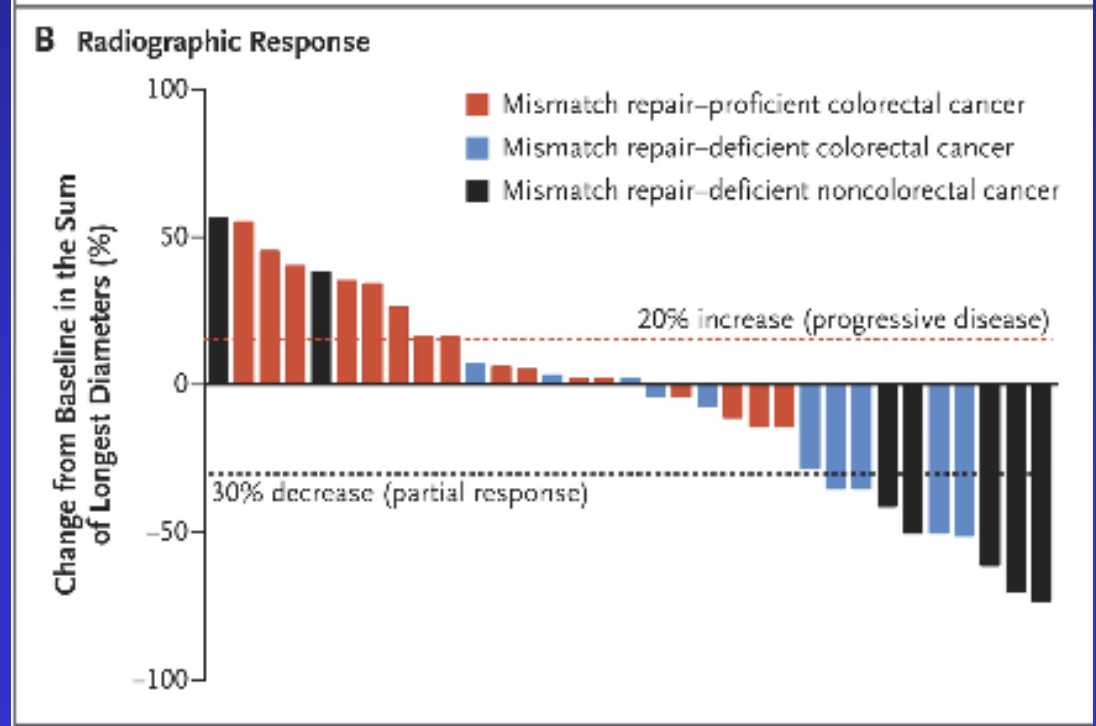
- Proficient mismatch repair (pMMR) = microsatellite stable (MSS)
- Deficient mismatch repair (dMMR) = microsatellite instable (MSI)
- Detected by:
  - IHC- missing mismatch repair proteins
  - PCR- microsatellite instable
- Present clinical use:
  - Lynch syndrome
  - Determine whether to offer adjuvant chemotherapy for Stage II colon cancer patients

The NEW ENGLAND JOURNAL of MEDICINE

Le DT et al NEJM 2015

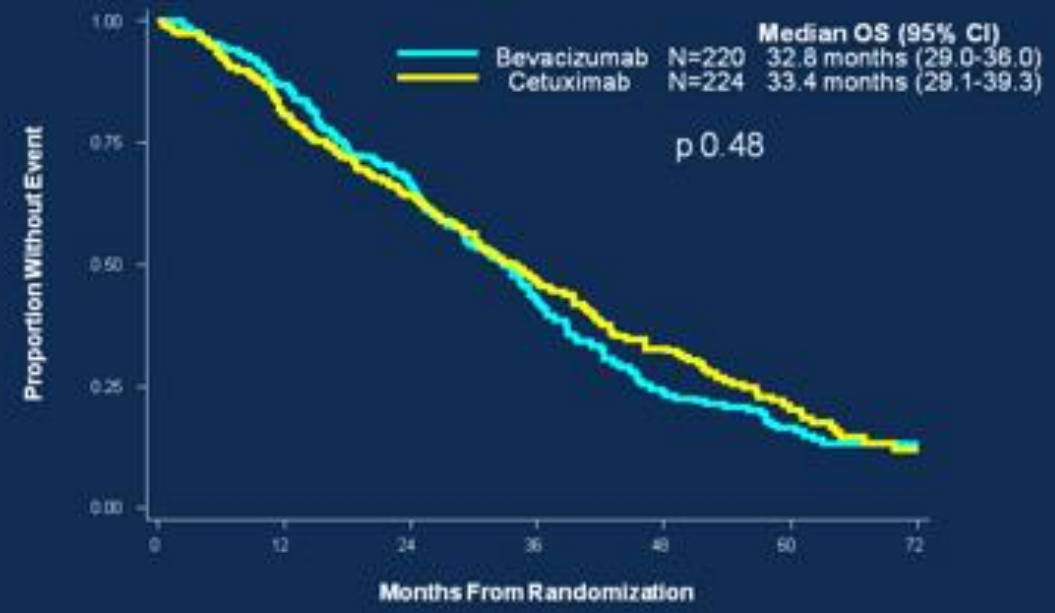






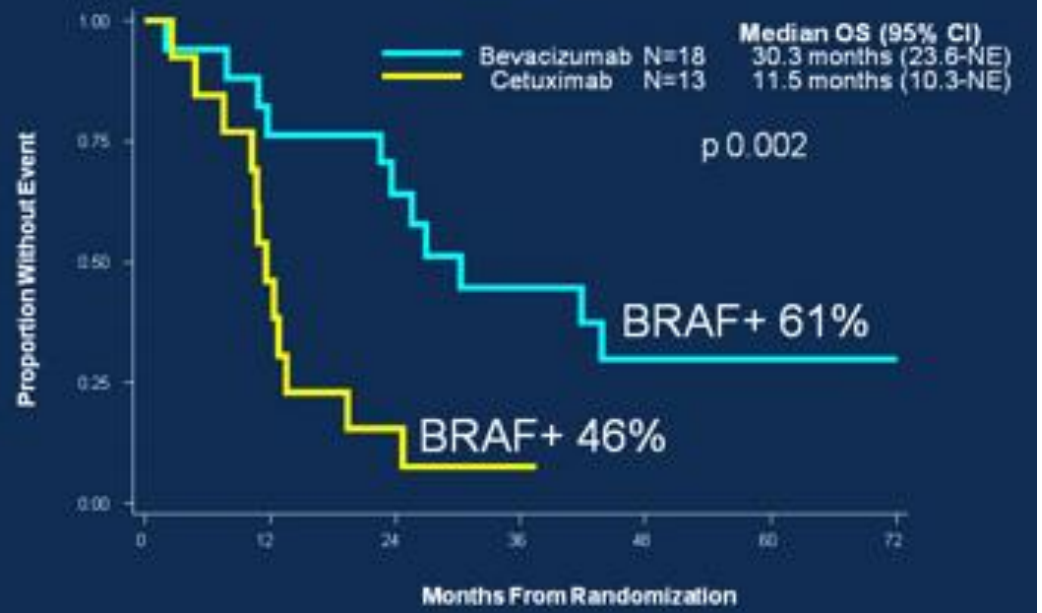
Interaction of MSI status with biologics

MSS



HR_{adj} 1.03 (95% CI 0.82-1.30)

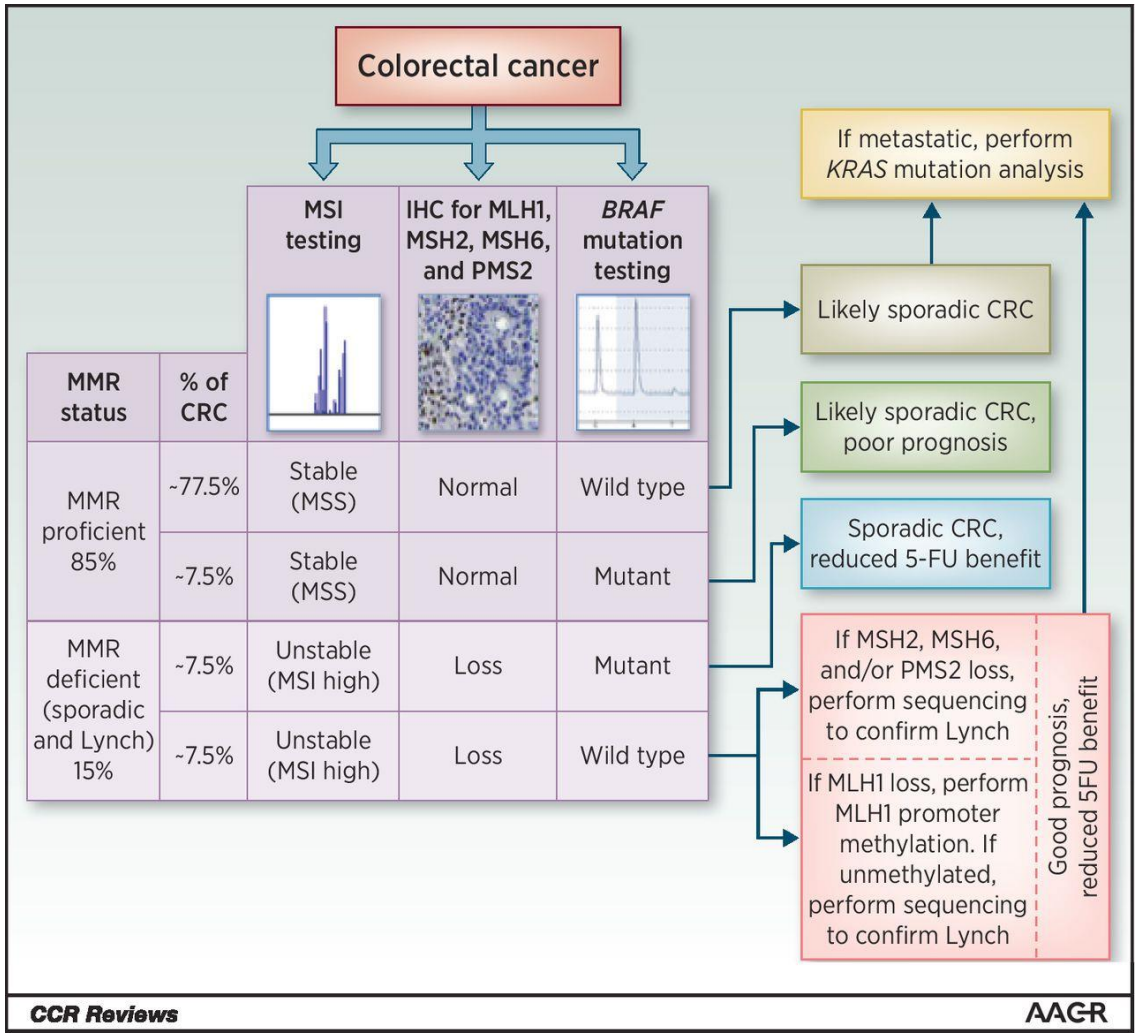
MSI-H



HR_{adj} 0.17 (95% CI 0.07-0.41)

Interaction p 0.0002

MSI testing algorithm proposed in 2012 by the Association for Molecular Pathology.



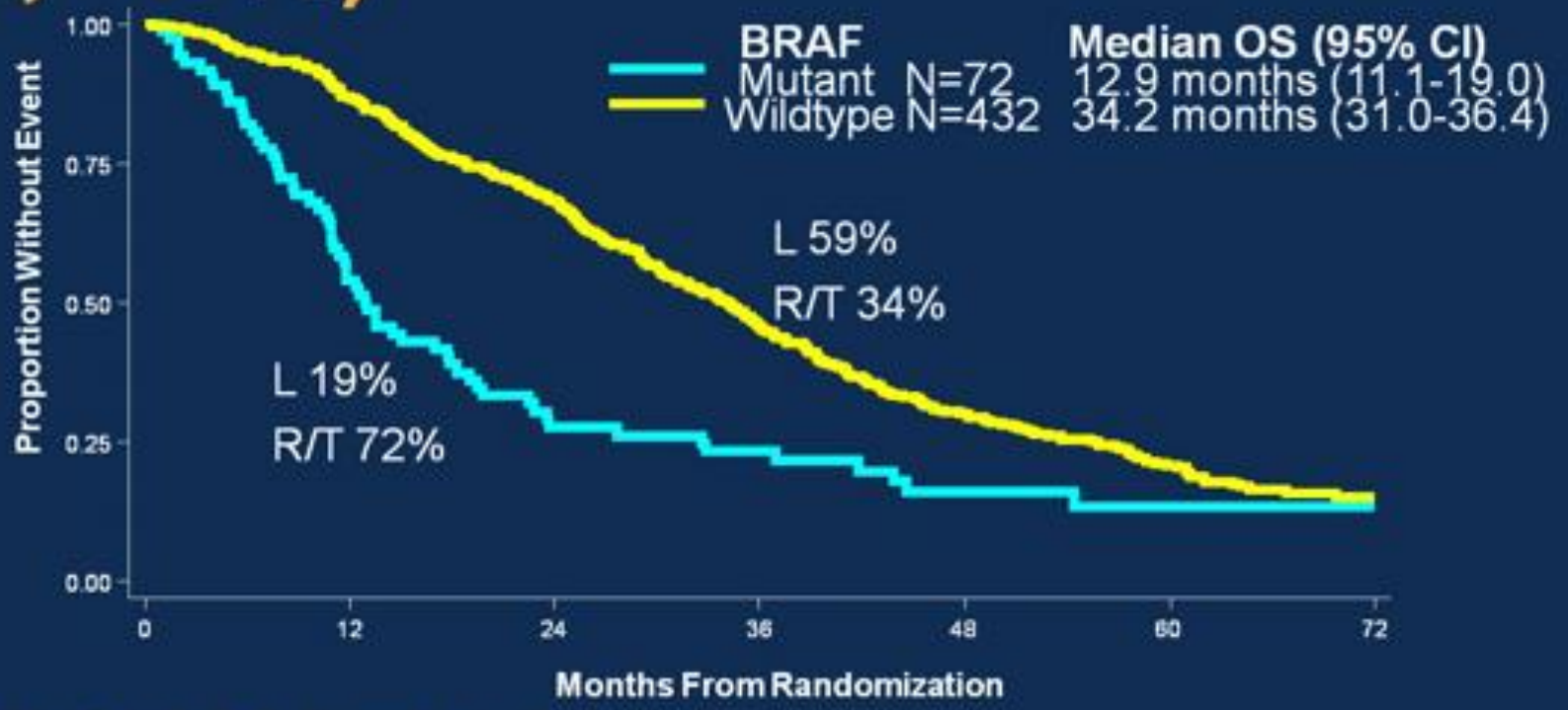
Jonathan C. Dudley et al. Clin Cancer Res 2016;22:813-820

Clinical Cancer Research
AACR American Association for Cancer Research

TOPIC SEVEN

BRAF M+

OS is affected by BRAF mutations (72/504, 14%)

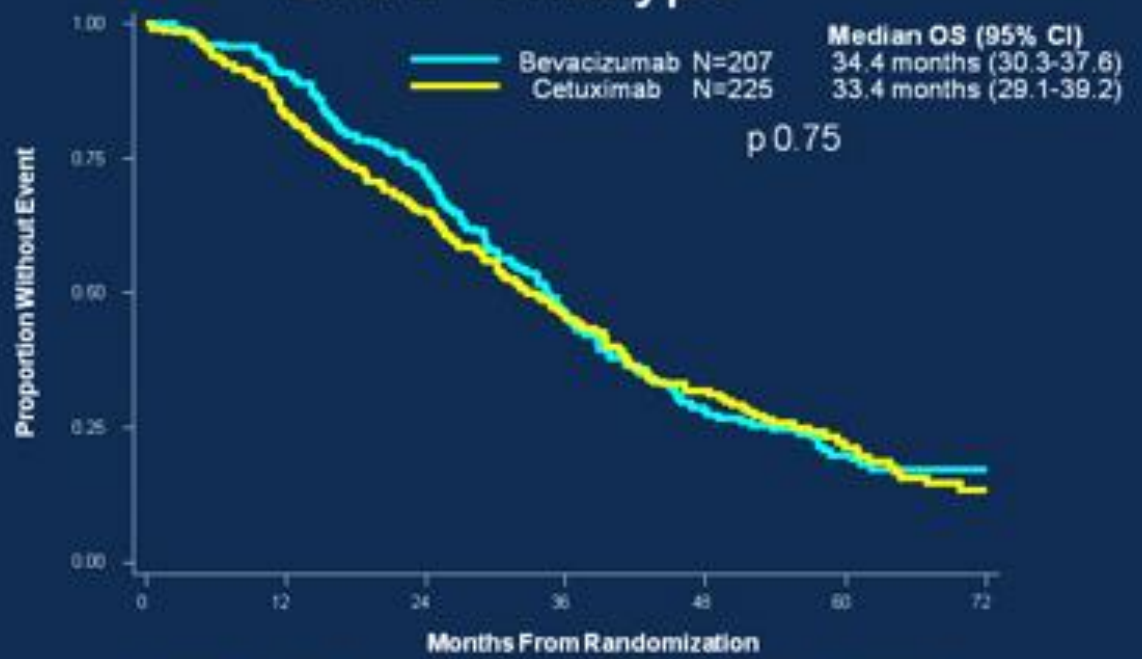


HR_{adj} 1.67 (95% CI 1.20-2.33) p 0.0035

Without sidedness: HR_{adj} 1.82 (95% CI 1.37-2.44) p 0.0001

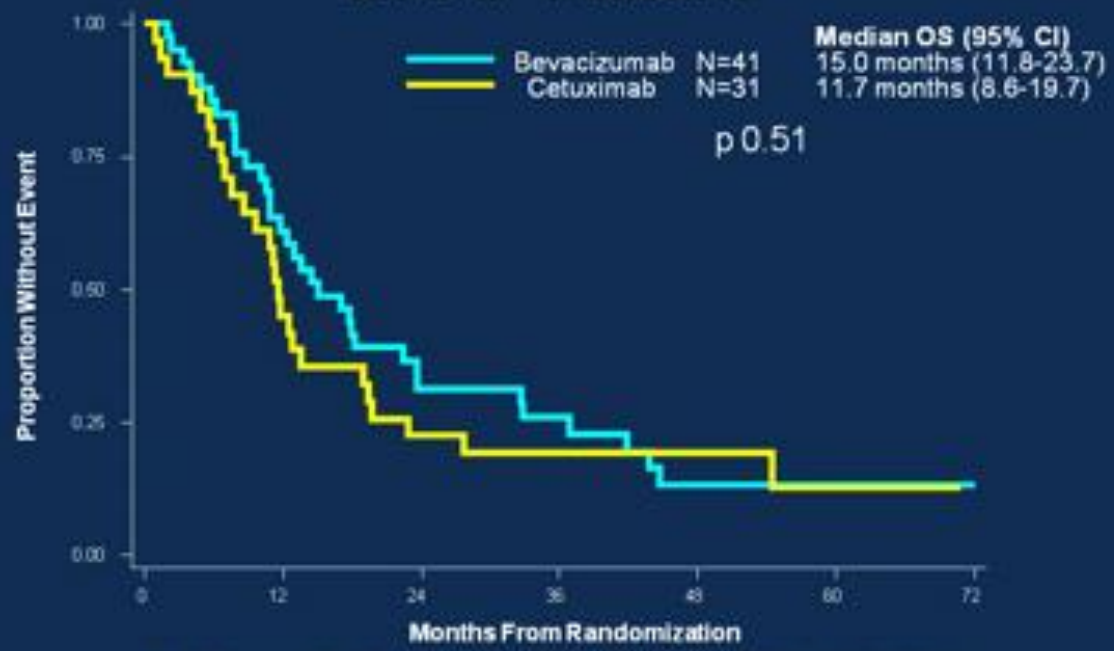
Interaction of BRAF status with biologics

BRAF Wildtype



HR_{adj} 0.97 (95% CI 0.77-1.23)

BRAF Mutant



HR_{adj} 0.61 (95% CI 0.35-1.06)

Interaction p 0.13

Efficacy Results According to *RAS* and *BRAF* Mutation Status in the Primary-Analysis Population.

Table 3. Efficacy Results According to *RAS* and *BRAF* Mutation Status in the Primary-Analysis Population.*

Variable	Panitumumab–FOLFOX4	FOLFOX4 Alone	Hazard Ratio (95% CI)	P Value
No *RAS* or *BRAF* mutations				
No. of patients	228	218		
Months of progression-free survival — median (95% CI)	10.8 (9.4–12.4)	9.2 (7.4–9.6)	0.68 (0.54–0.87)	0.002
Months of overall survival — median (95% CI)	28.3 (23.7–NE)	20.9 (18.4–23.8)	0.74 (0.57–0.96)	0.02
No *RAS* mutation, *BRAF* mutation				
No. of patients	24	29		
Months of progression-free survival — median (95% CI)	6.1 (3.7–10.7)	5.4 (3.3–6.2)	0.58 (0.29–1.15)	0.12
Months of overall survival — median (95% CI)	10.5 (6.4–18.9)	9.2 (8.0–15.7)	0.90 (0.46–1.76)	0.76
***RAS* or *BRAF* mutation**				
No. of patients	296	305		
Months of progression-free survival — median (95% CI)	7.3 (6.3–7.7)	8.0 (7.5–9.0)	1.24 (1.02–1.49)	0.03
Months of overall survival — median (95% CI)	15.3 (12.7–17.6)	18.0 (15.9–20.8)	1.21 (0.99–1.47)	0.06
No *KRAS* mutation in exon 2, other *RAS* or *BRAF* mutation				
No. of patients	75	86		
Months of progression-free survival — median (95% CI)	6.7 (5.3–8.2)	7.3 (5.7–8.0)	1.05 (0.73–1.52)	0.80
Months of overall survival — median (95% CI)	14.5 (10.4–18.5)	15.8 (11.9–18.8)	1.14 (0.78–1.66)	0.51

* NE denotes not evaluated.

PRIME

RAS WT/RAF WT do better, and do benefit from P-mab

RAF M+ pts do poorly but still marginally benefit from P-mab

Douillard J-Y et al. N Engl J Med 2013;369:1023-1034

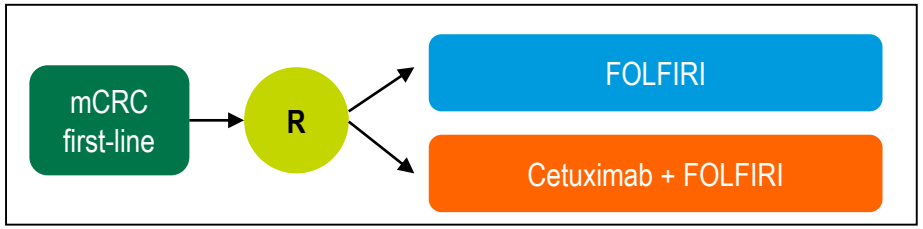
The NEW ENGLAND JOURNAL of MEDICINE

CRYSTAL Phase III Study

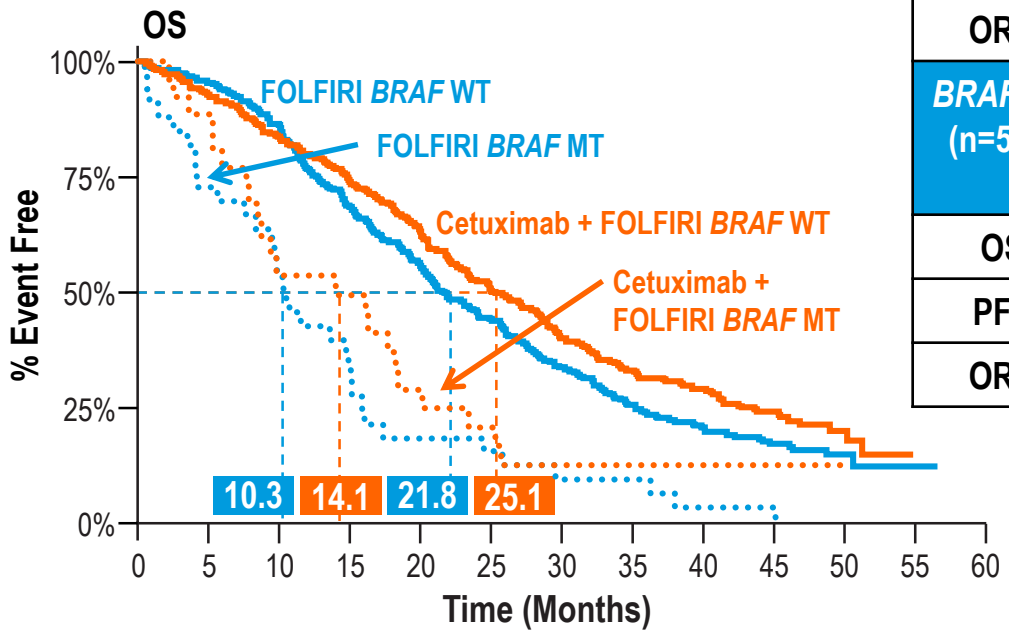
BRAF Status and Response with Cetuximab

RAF M+ pts have an overall poor outcome, but still can benefit from EGFR inhibitors (in this case, C-mab)

Study Schema



Results



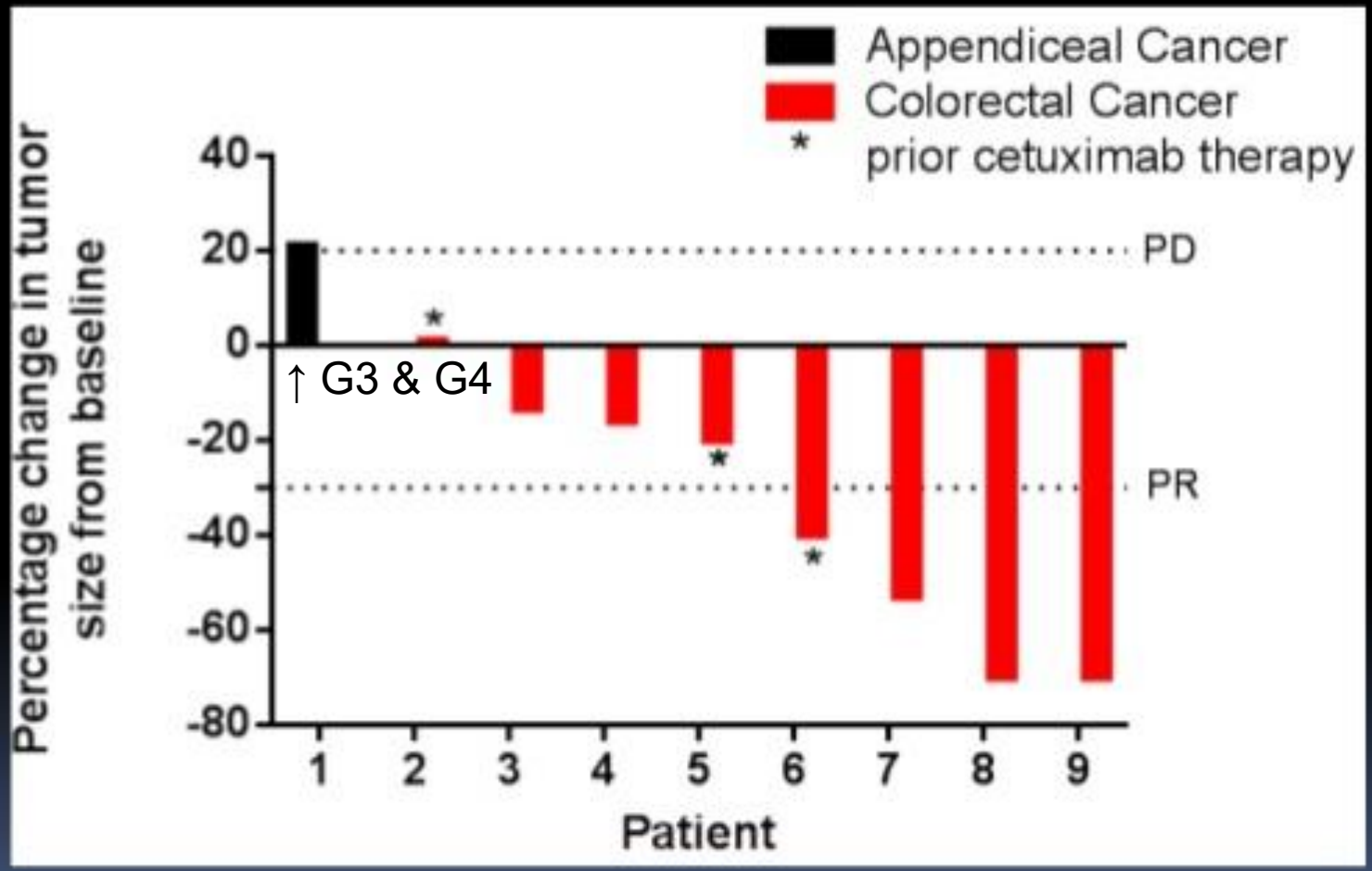
BRAF MT (n = 59)	Cmab + FOLFIRI (n = 26)	FOLFIRI (n = 33)	HR	p
OS	14.1	10.3	0.908	0.74
PFS	8.0	5.6	0.934	0.87
ORR	19.2	15.2	NR	0.91
***BRAF* WT (n=566)**	**Cmab + FOLFIRI (n = 277)**	**FOLFIRI (n = 289)**	**HR**	**p**
OS	25.1	21.6	0.830	0.0547
PFS	10.9	8.8	0.673	0.0013
ORR	61.0	42.6	NR	< 0.001

CRYSTAL = Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer;
NR = not reported; ORR = Overall response rate

Adapted from Van Cutsem E, et al. *J Clin Oncol* 2011;29:2011-2019.

VEMURAFENIB, IRINOTECAN AND C-Mab in BRAF M+ pts

Responses by RECIST 1.1 in all restaged patients



Hong et al: ASCO 2014

TRIBE Phase III Study Design

Patients

- Unresectable mCRC
- No prior mCRC treatment
- Adjuvant oxali-containing chemotherapy allowed if >12 mo between tx and relapse

FOLFIRI + Bev (up to 12 cycles)
5-FU/LV + Bev (Maintenance)

1:1 Randomization

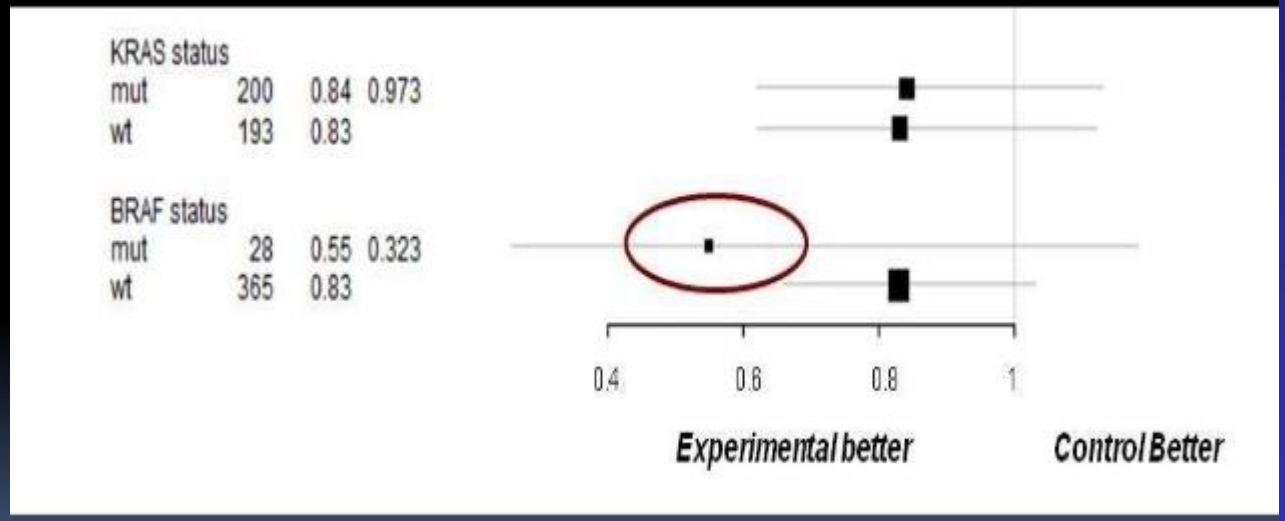
FOLFOXIRI + Bev (up to 12 cycles)
5-FU/LV + Bev (Maintenance)

Treat to progression

Falcone A. ASCO 2013. Abstract 3505.

TRIBE: PFS Subgroup Analyses

MOLECULAR CHARACTERISTICS



Falcone A. ASCO 2013. Abstract 3505.

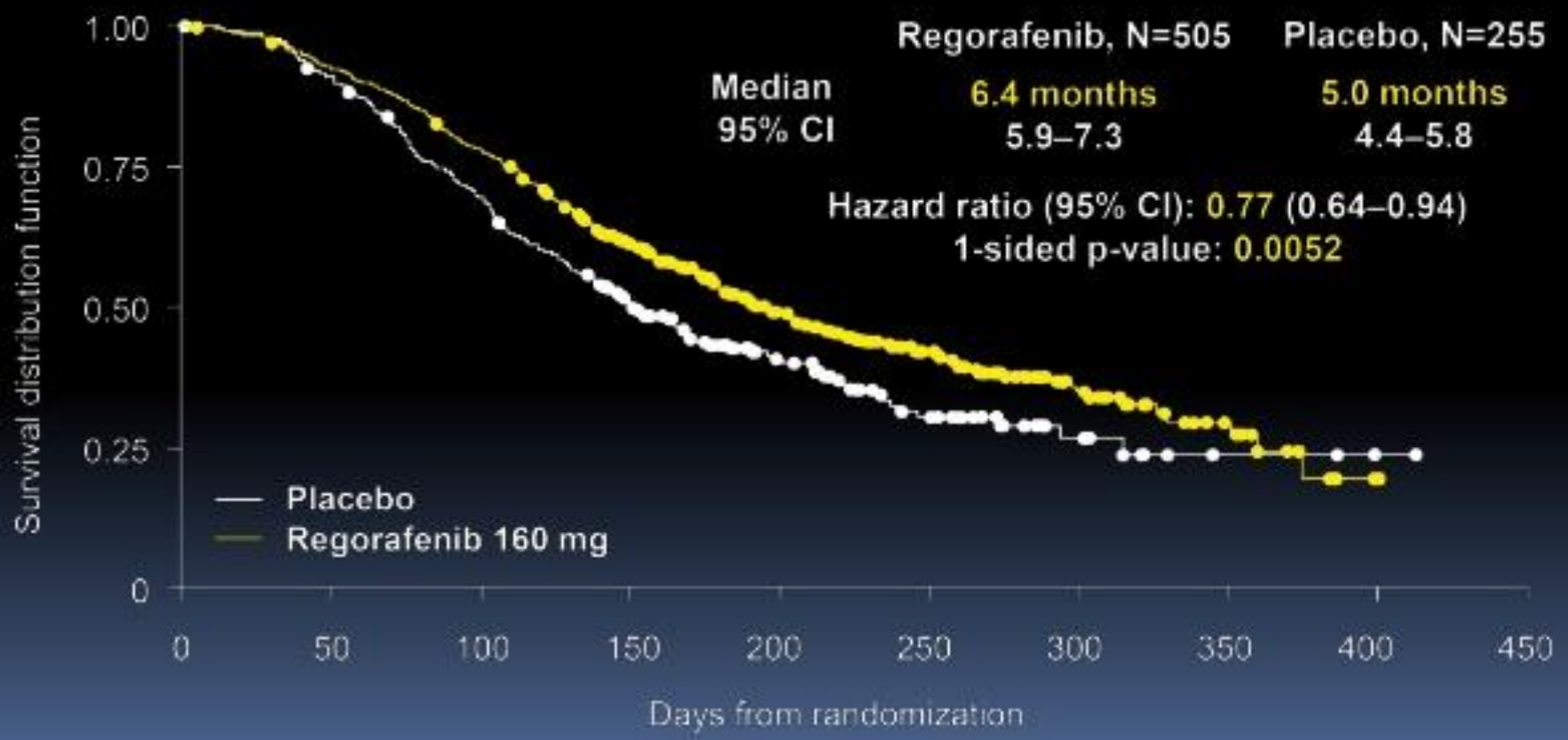
TOPIC EIGHT

OTHER NEW DRUGS

REGORAFENIB IN REFRACTORY CRCa

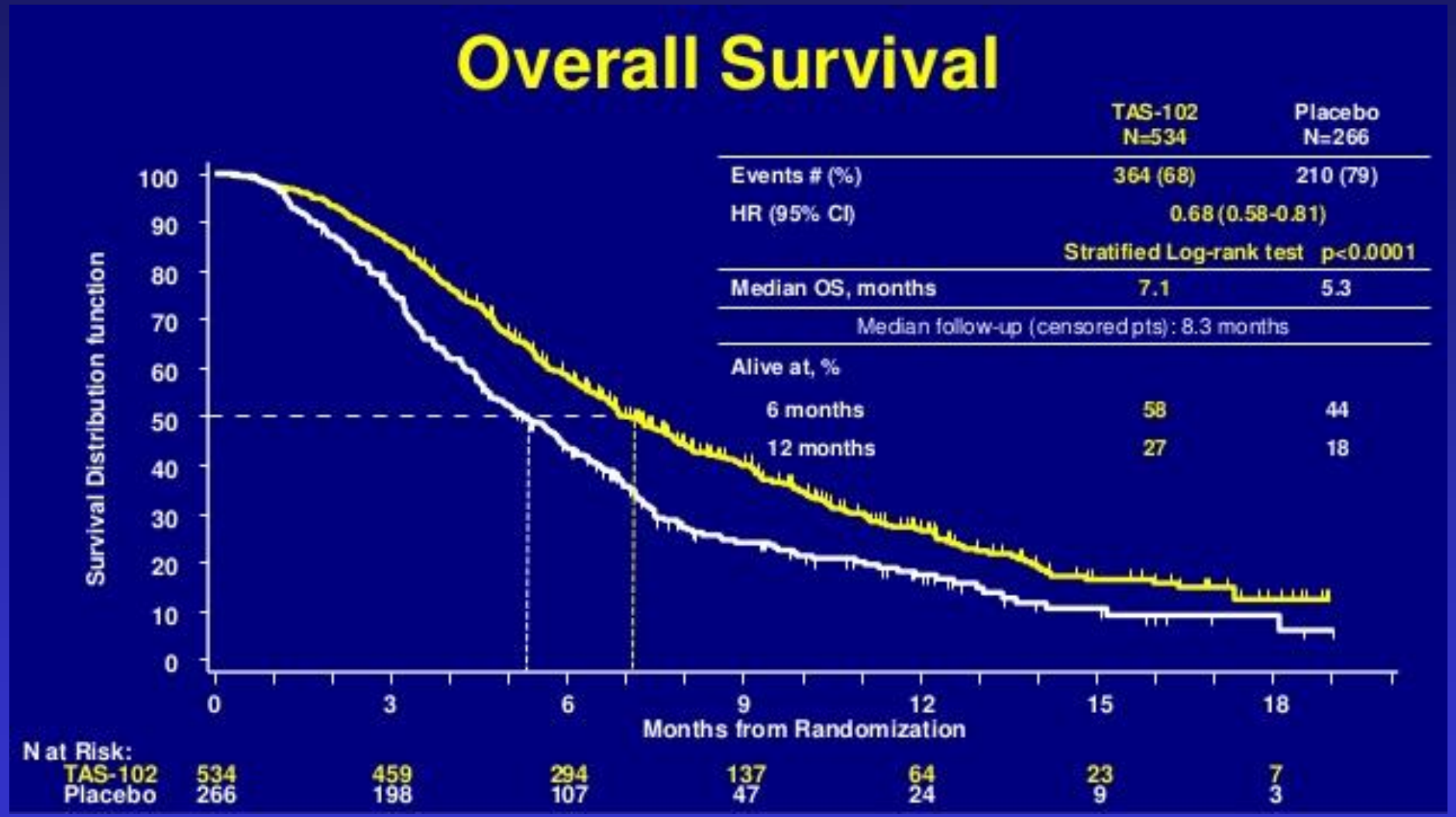
CORRECT: OS (primary endpoint)

Primary endpoint met prespecified stopping criteria at interim analysis
(1-sided p<0.009279 at approximately 74% of events required for final analysis)



Grothey et al: Lancet. 2013 Jan 26;381(9863):303-12

RECOURSE: TAS-102 IN REFRACTORY CRCa



Canadian Colorectal Cancer Consensus Statement

CURRENT ONCOLOGY
A Canadian Cancer Research Journal

PRACTICE GUIDELINE

The predictive effect of primary tumour location in the treatment of metastatic colorectal cancer: a Canadian consensus statement

A.B.K. Abrahao MD,[‡a] S. Karim MD,[†a] B. Colwell MD,[§] S. Berry MD MHSc,[‡] and J. Biagi MD*

TABLE VI Analysis of primary tumour location in first-line trials comparing EGFR monoclonal antibodies with bevacizumab

Variable	CALGB/SWOG 80405[12] (FOLFOX or FOLFIRI with cetuximab vs. FOLFOX or FOLFIRI with bevacizumab)				FIRE-3[33] (FOLFIRI with cetuximab vs. FOLFIRI with bevacizumab)				PEAK[34] (FOLFOX with panitumumab vs. FOLFOX with bevacizumab)			
	Left-sided		Right-sided		Left-sided		Right-sided		Left-sided		Right-sided	
	Cmab (*n*=173)	Bev (*n*=152)	Cmab (*n*=71)	Bev (*n*=78)	Cmab (*n*=157)	Bev (*n*=149)	Cmab (*n*=38)	Bev (*n*=50)	Pmab (*n*=53)	Bev (*n*=54)	Pmab (*n*=22)	Bev (*n*=14)
ORR (%)	69.4	57.9	42.3	39.7	69.0	62.0	52.6	50.0	64.2	57.4	63.6	50.0
OR	1.65		1.11		1.37		1.11		1.33		1.75	
95% CI	1.16 to 2.34		0.61 to 2.01		0.85 to 2.19		0.48 to 2.59		0.57 to 3.11		0.36 to 8.39	
p Value	0.005		0.73		0.23		0.83					
PFS (months)	12.7	11.2	7.5	10.5	10.7	10.7	7.6	9.0	14.6	11.5	8.7	12.6
HR	0.84		1.64		0.90		1.44		0.68		1.04	
95% CI	0.66 to 1.06		1.15 to 2.36		0.71 to 1.14		0.92 to 2.26		045 to 1.04		0.50 to 2.18	
p Value	0.15		0.006		0.38		0.11		0.07		0.90	
OS (months)	39.3	32.6	13.9	29.2	38.3	28.0	18.3	23.0	43.4	32.0	17.5	21.0
HR	0.77		1.36		0.63		1.31		0.77		0.67	
95% CI	0.59 to 0.99		0.93 to 1.99		0.48 to 0.75		0.81 to 2.11		0.46 to 1.28		0.30 to 1.50	
p Value	0.04		0.10		0.002		0.28		0.31		0.32	

FOLFOX = folinic acid–5-fluorouracil–oxaliplatin; FOLFIRI = folinic acid–5-fluorouracil–irinotecan; Cmab = cetuximab; Bev = bevacizumab; Pmab = panitumumab; ORR = overall response rate; OR = odds ratio; CI = confidence interval; PFS = progression-free survival; HR = hazard ratio; OS = overall survival.

TABLE VIII Recommendations in *RAS* wild-type metastatic colorectal cancer (mCRC)

Scenario	Recommendation
First line	■ For patients with left-sided disease, standard chemotherapy (FOLFOX or FOLFIRI) in combination with an EGFR mAb (cetuximab or panitumumab) is recommended in the first-line setting. ■ For patients with right-sided disease, first-line EGFR monoclonal antibodies are not recommended. The combination of bevacizumab with standard chemotherapy remains the standard of care for these patients. ■ Extended *RAS* testing should be available in a timely manner to allow for the appropriate selection of a biologic for first-line treatment decisions.
Second line	■ There is no evidence to recommend the selective use of EGFR monoclonal antibodies in the second-line setting based on the location of the primary tumour. ■ Patients who have not been treated with bevacizumab in the first line should be offered bevacizumab in combination with standard chemotherapy.
Third line	■ All *RAS* wild-type patients who have not previously been treated with an EGFR monoclonal antibody should be offered one.
Tumour response	■ At this time, there is insufficient evidence for the selective use of EGFR monoclonal antibodies based on primary tumour location if tumour response is the primary goal of therapy.
Future research	■ Primary tumour location should be factored into the design of future clinical trials in the treatment of *RAS* wild-type mCRC. ■ Given that primary tumour location is a surrogate for more complex biologic mechanisms, ongoing research should try to understand the patient- and tumour-related factors that underlie the differential benefit of biologics that have been observed based on primary tumour location.

FOLFOX = folinic acid–5-fluorouracil–oxaliplatin; FOLFIRI = folinic acid–5-fluorouracil–irinotecan.

Canadian Consensus Statement endorsed by GI Disease Site Committee of Cancer Care Ontario

GUIDELINES & ADVICE

The Role of Primary Tumour Location in the Selection of Biologics for the Treatment of Unresectable Metastatic Colorectal Cancer: An Endorsement of a Canadian Consensus Statement

Type of Content: Guidelines & Advice, Clinical

Document Status: Current

ID: GL END 2-31 Jul 2018

Authors: R. Goodwin, C. Agbassi, E. Kennedy, J. Biagi, R. Wong, S. Welch, S. Berry, and the Gastrointestinal Disease Site Group

RECOMMENDATIONS

The Gastrointestinal Disease Site Group of Cancer Care Ontario endorses the following recommendations from *The Predictive Effect of Primary Tumour Location in the Treatment of Metastatic Colorectal Cancer: a Canadian Consensus Statement* [1]. Rectal cancer was included in the analysis of left-sided colon cancer. See Abrahao et al [1] for more details on the development of the recommendations and the evidence that supports them.

1. **First-Line**
   a. In patients with *RAS* wild-type left-sided colon cancer, standard chemotherapy (FOLFOX or FOLFIRI) in combination with an EGFR mAb (cetuximab or panitumumab) is recommended in the first-line setting.

      Qualifying statement

      Standard chemotherapy in combination with an EGFR mAb is the preferred option over the current standard of standard chemotherapy and bevacizumab.

   b. In patients with *RAS* wild-type right-sided colon cancer, the use of an EGFR mAb first-line is not recommended. The combination of bevacizumab plus standard chemotherapy remains the standard of care for these patients.

c. Extended *RAS* testing should be available in a timely manner to allow for the appropriate selection of biologic for first-line treatment decisions.

2. **Second-Line**
   a. At this time, there is no evidence to recommend the selective use of EGFR mAbs in the second-line setting based on PTL.
   b. In the second-line setting, patients who were treated with an EGFR mAb instead of bevacizumab in the first line of therapy can be considered to receive bevacizumab in combination with standard chemotherapy.

3. **Third-Line**
   All patients with *RAS* wild-type disease who have not previously been treated with an EGFR mAb should be offered one.

4. **Tumour Response**
   At this time, in cases where tumour response is the primary goal of therapy, the evidence is insufficient for the selective use of EGFR mAbs based on PTL.

Does not mention sidedness (yet)
Disallows use of bevacizumab in 2nd line after 1st line EGFR mabs

Cancer Care Ontario

1. **New Drug Funding Program and Ministry Funding Announcement**

The following drug funding policy will be added under Cancer Care Ontario's (CCO's) ***New Drug Funding Program*** effective September 1, 2017, according to specific criteria:

Disease Site	Drug	Indication	New/ Revised
Gastrointestinal	Panitumumab	First-line metastatic colorectal, small bowel, or appendiceal cancer for patients who have contraindications or intolerance to bevacizumab	New

- Examples of contraindications or intolerance to bevacizumab include:
  - High risk of bleeding or wound healing issues due to temporal proximity to surgery – recently received or planned for resectable/potentially resectable liver metastases.
  - A history of cardiovascular disease, or established class-specific side effects to bevacizumab such as hypertension, thromboembolic events, atrial fibrillation, as well as, proteinuria, risk of or presence of fistulae, risk of or current GI perforation, primary tumour in place, active bleeding, non-healing wound, ulcer, recent trauma, etc.
- Treatments administered prior to RAS testing will not be reimbursed.
- Patients who use panitumumab in the first line setting will not be eligible for bevacizumab, cetuximab, or panitumumab in later lines of therapy.
- Switches between bevacizumab and panitumumab will only be considered within the first 3 months of starting therapy with either agent, provided there is no disease progression on treatment. Patients will only be approved for one switch (i.e., from bevacizumab to panitumumab or vice versa). A clinic note indicating the reason(s) for switching and contraindication(s) to bevacizumab is required.
- Panitumumab must be used in addition to combination chemotherapy. Single agent treatments will not be reimbursed.

BASE CASE
UNRESECTABLE, NO RECENT ADJUVANT, 5FU TOLERANT, FIT, YOUNG, NO C/I TO BEV

RAS M+	RAF M+	RAS WT (R)	RAS WT (L)	MSI-H	
FOLFOX/Bev or FOLFIRI/Bev	FOLFOXIRI/Bev	FOLFOX/Bev or FOLFIRI/Bev	FOLFOX/P-mab or FOLFIRI/P-mab	Pembrolizumab	1st L
FOLFIRI or FOLFOX	Pembrolizumab if associated with MSI-H	FOLFIRI or FOLFOX	FOLFIRI/Bev or FOLFOX/Bev	FOLFOX/Bev or FOLFIRI/Bev	2nd L
TAS-102 or Regorafenib	Regorafenib or P-mab	P-mab or C-mab/irinotecan	TAS -102 or Regorafenib	FOLFIRI or FOLFOX	3rd L
SoL	SoL	TAS -102 or Regorafenib	SoL	Regorafenib or TAS-102	4th L

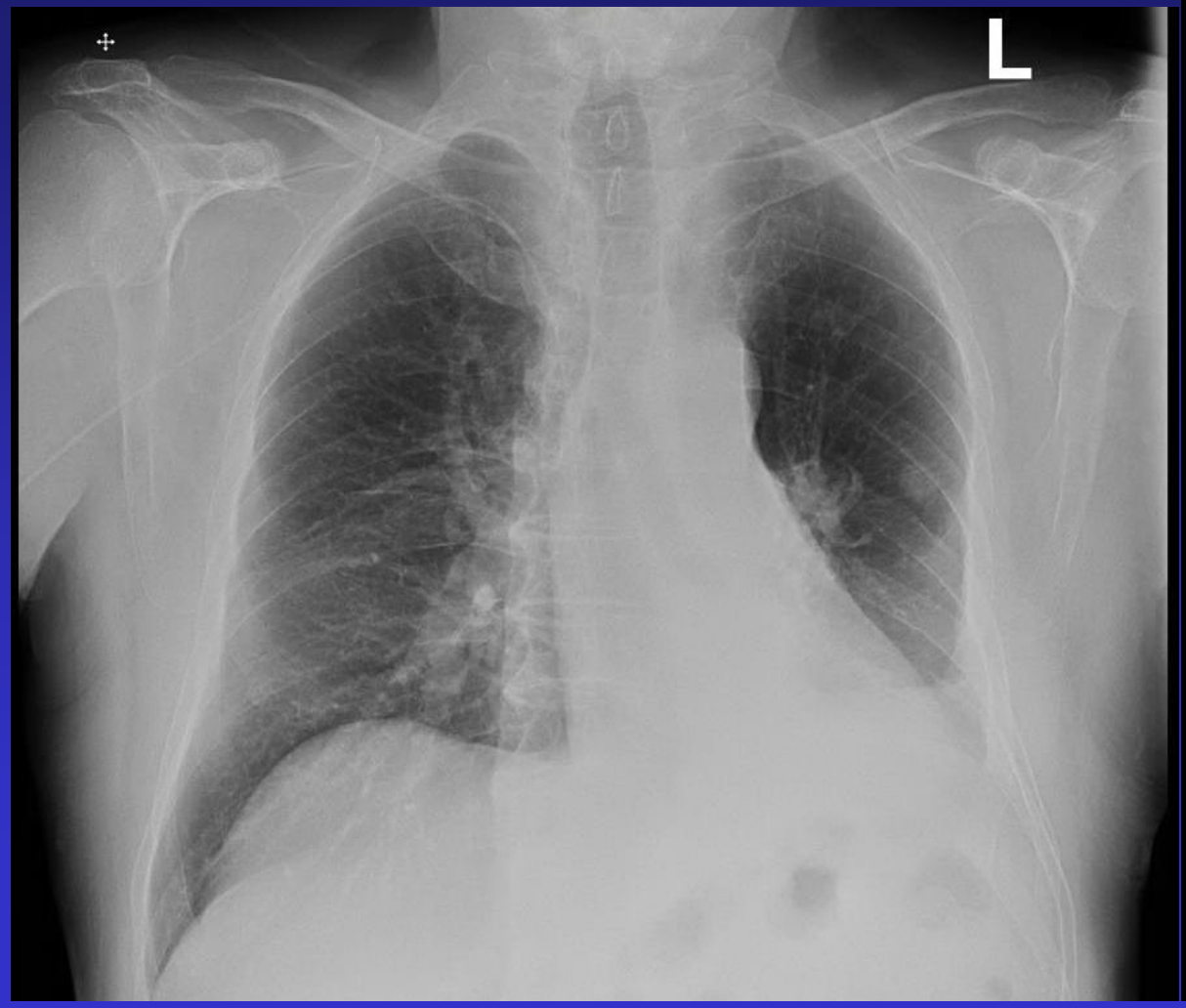
Monitoring and Management of EGFR-related Hypomagnesemia

- Magnesium levels should be monitored closely (*e.g.*, every two weeks)
- Infusions of magnesium sulfate, as well as oral supplementation, may be required
  - Administer 2 g/hr in a solution
  - Can administer up to 10 g over 5 hours
  - Supplements may not always be effective

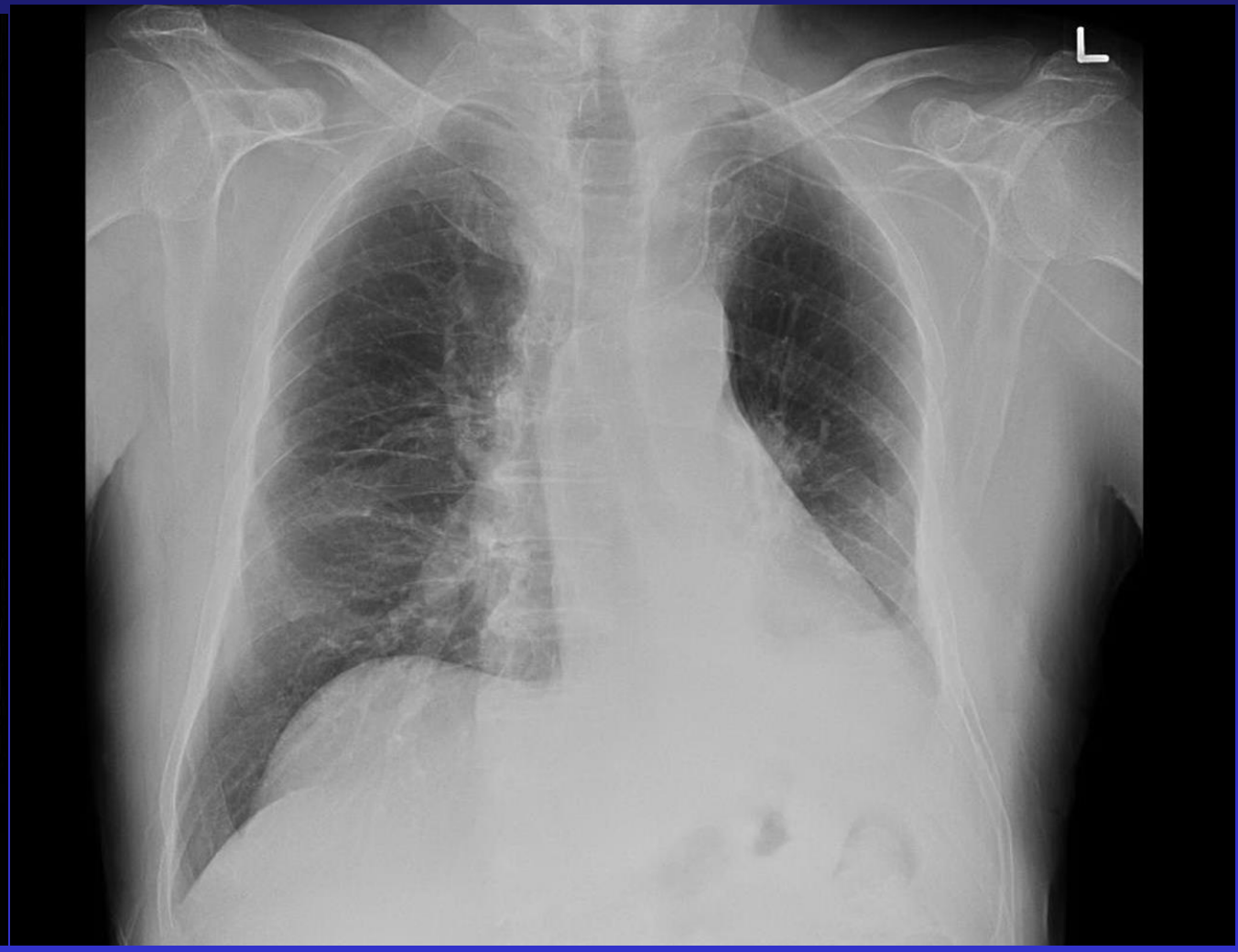
Adapted from British Columbia Cancer Agency Protocols, accessed on-line at www.bccancer.bc.ca.

AFTER ONC CYCLE OF CHEMO…

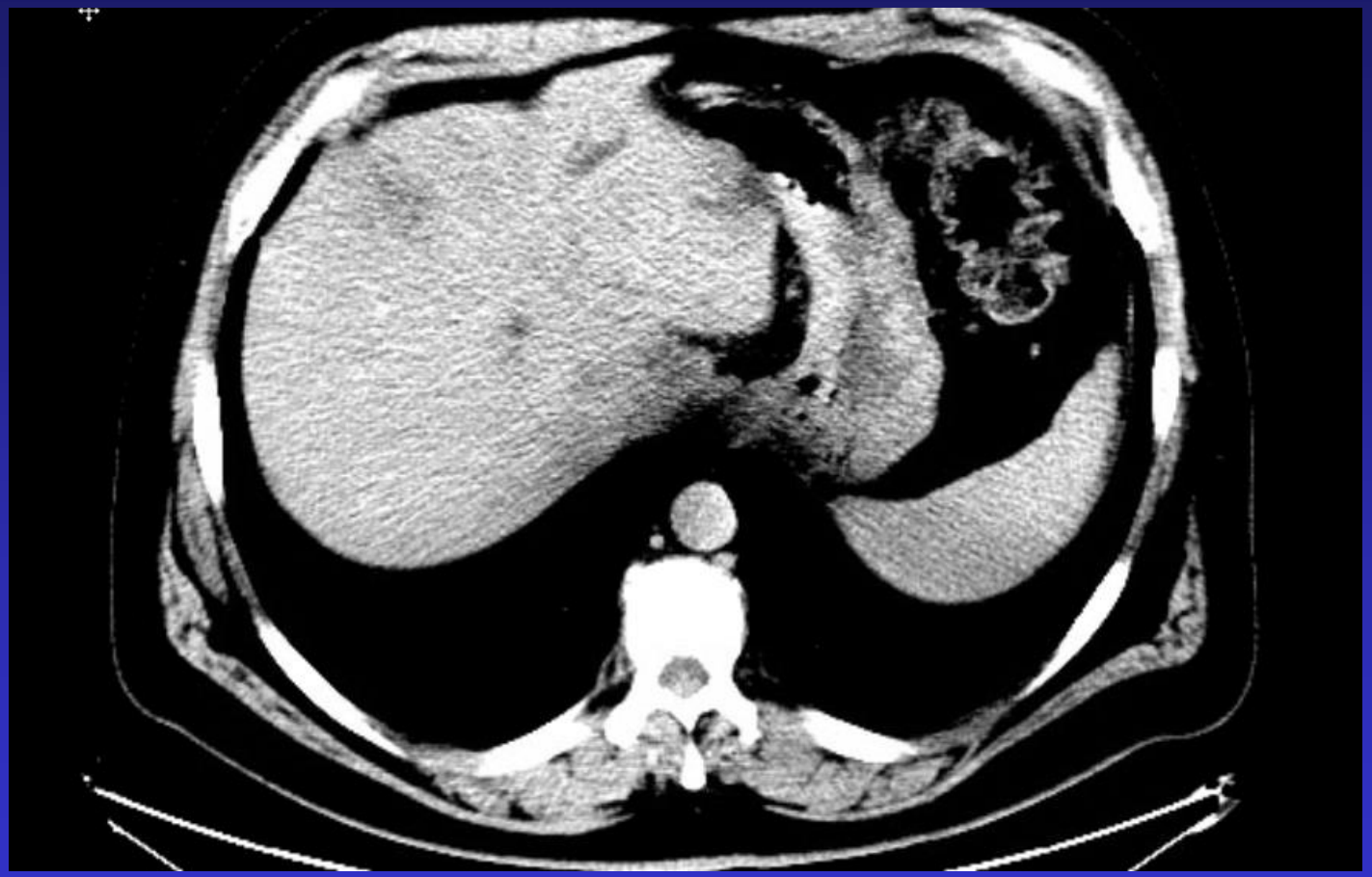
CXR 30/I/2018



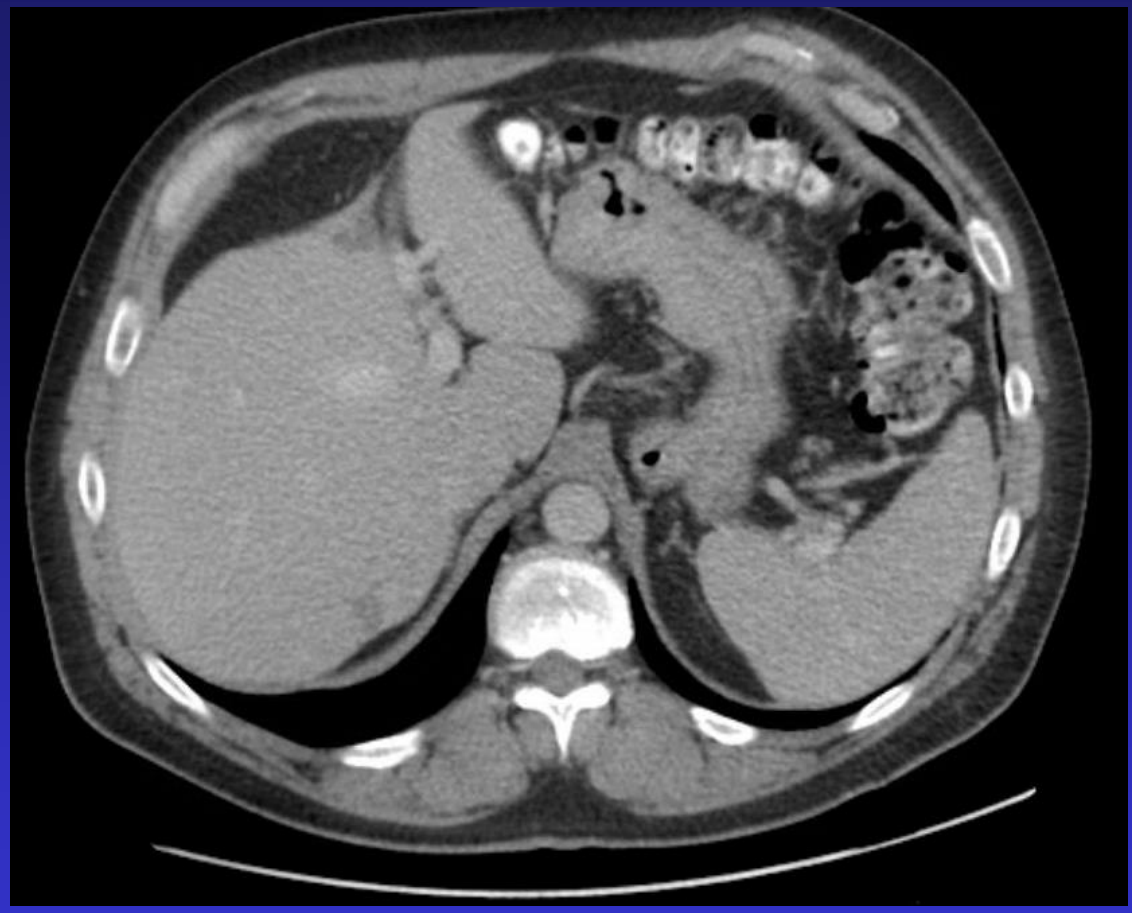
CXR 7/III/2018



1 June 2017



6 Feb 2018



THE END