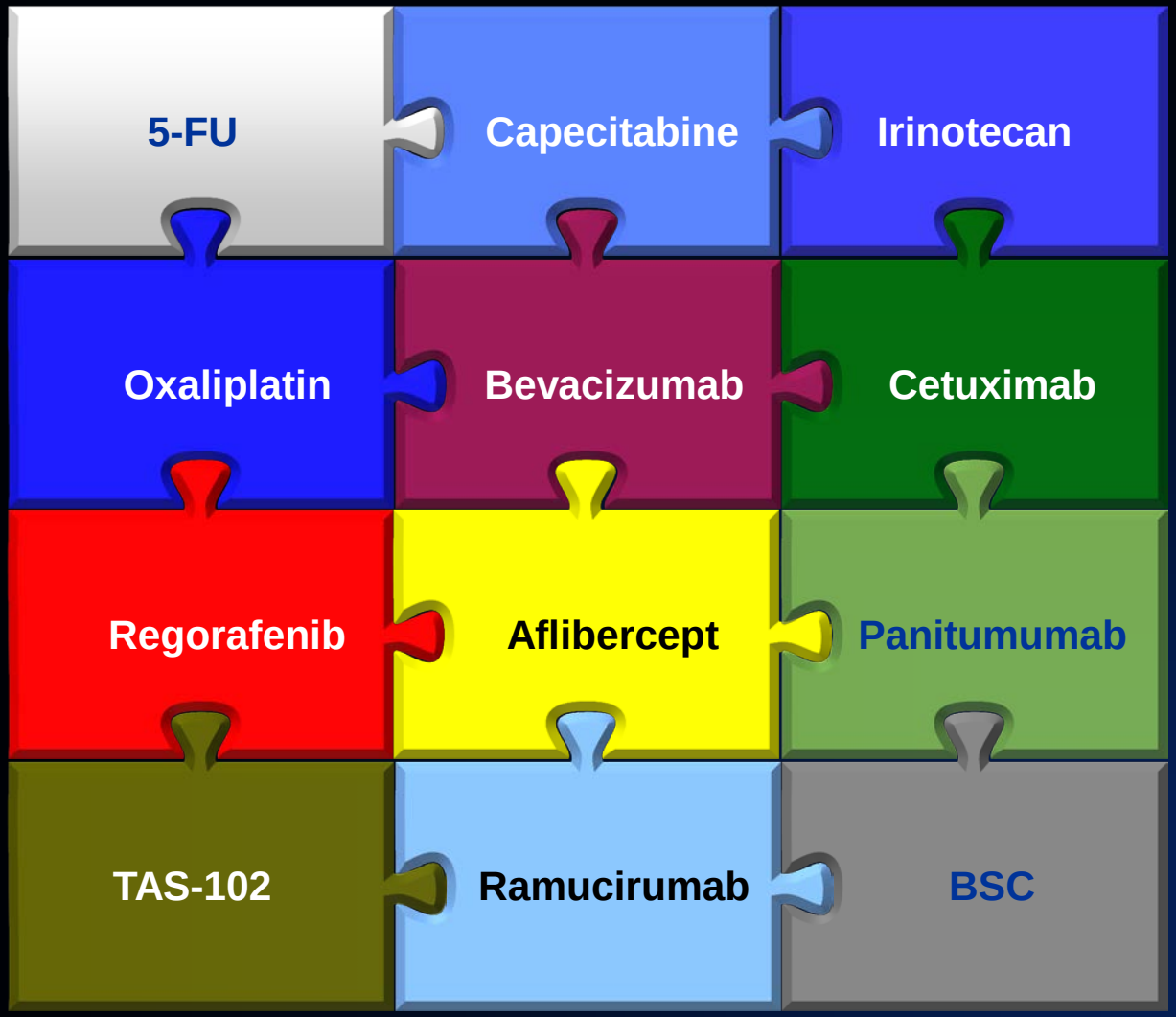
Optimizing treatment outcomes in WT RAS mCRC

A/Prof Niall Tebbutt

Director Medical Oncology

Olivia Newton-John Cancer Research and Wellness Centre

A High Number of Agents Is Currently Available for the Treatment of mCRC

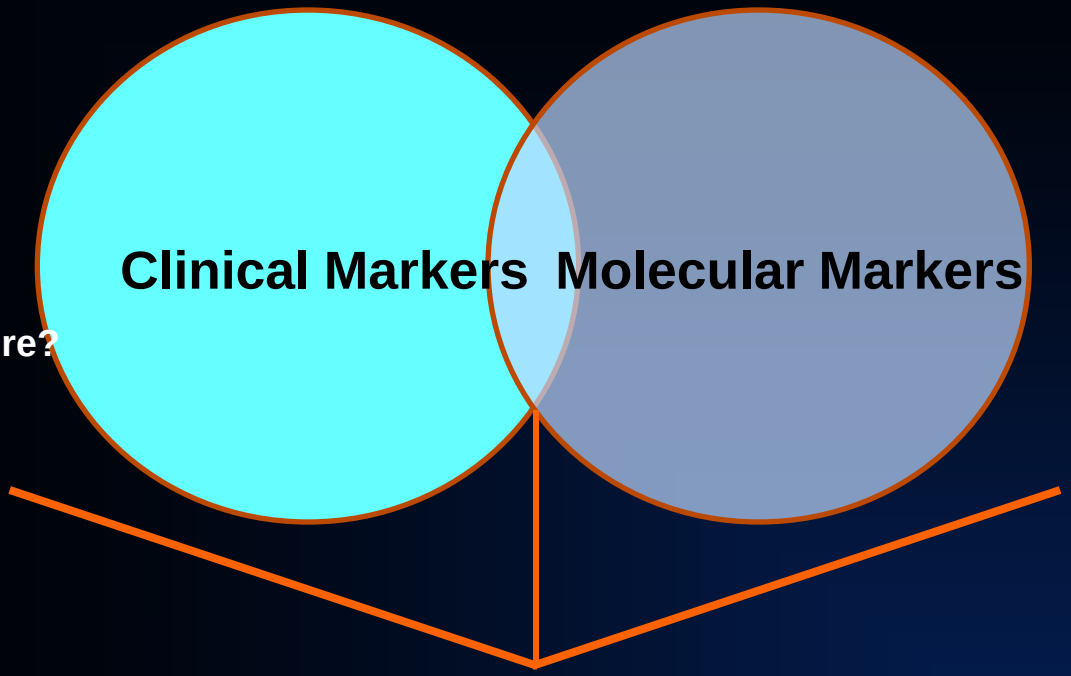


The Goals of Systemic Therapy

- Extending OS
- Maintaining quality of life as long as possible
- Tumour response; especially if symptomatic or potentially resectable
  - Consider intensity of therapy/toxicities
  - Consider patient wishes
  - Which situation needs more aggressive and which a more gentle therapy?

Tools for Treatment Selection

- Age
- PS
- Comorbidities
- Tumor burden
  - Potential for cure?
  - Symptoms?
- Tumor location



- Histologic grade
- CEA
- *KRAS*
- *NRAS*
- *BRAF*
- *MSI/MMR*

Patient characteristics

+

Tumor characteristics

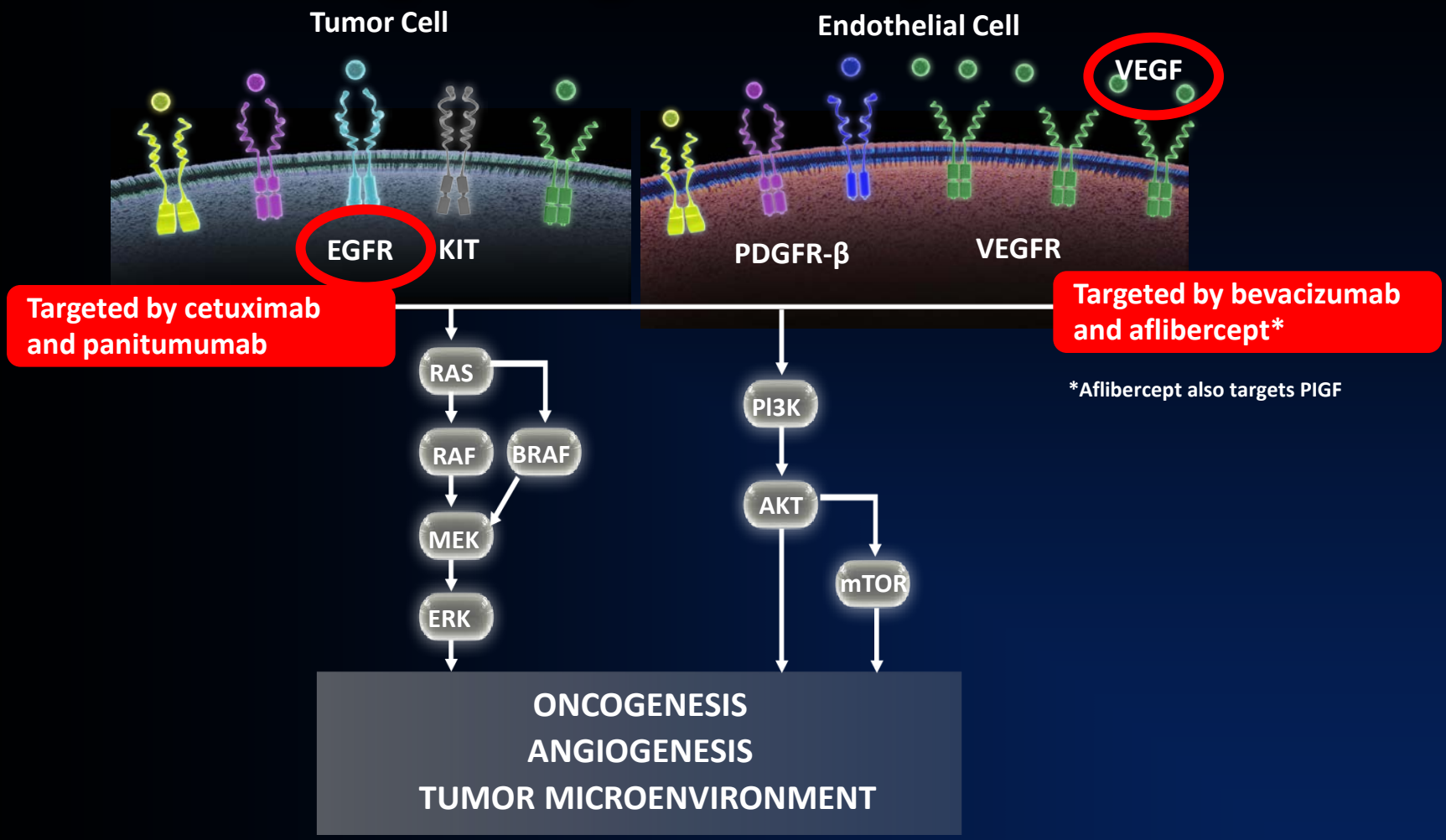
Why personalized medicine?

> **Personalized management is considered the future of cancer care: medicine aiming at giving patients the best treatment according to their personal medical history, their physiological status, and the molecular characteristics of their tumours**

European Society for Medical Oncology (ESMO)

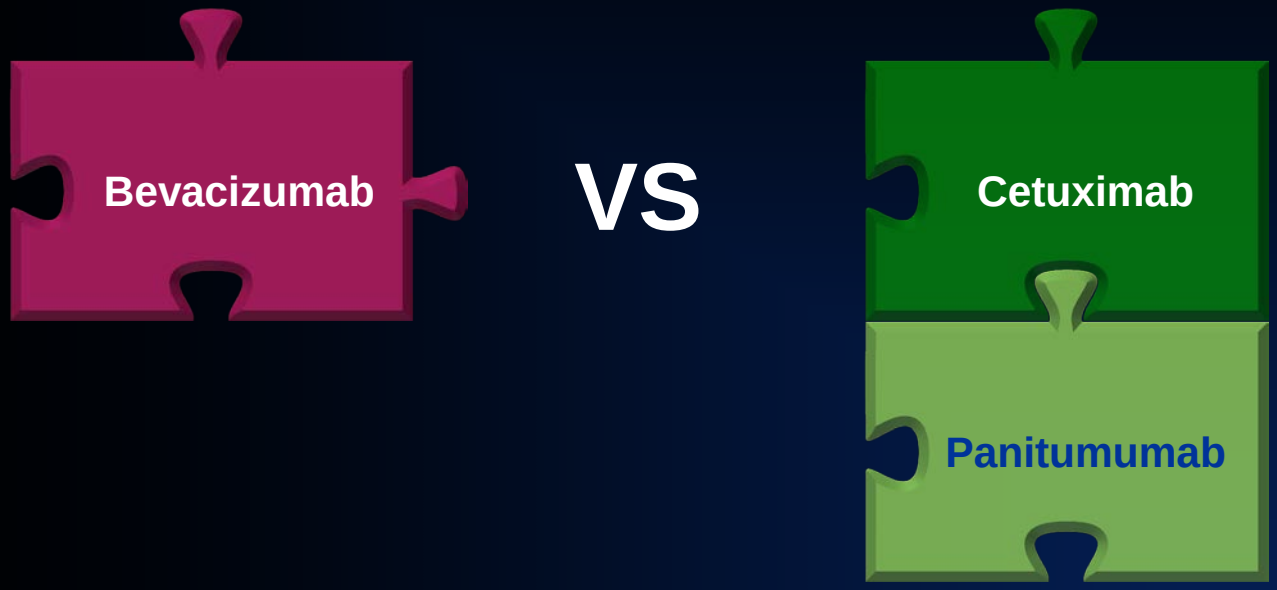
ESMO Personalised Medicine Fact Sheet. www.esmo.org/content/download/34303/682038/file/ESMO-Personalised-Cancer-Medicine-Fact-Sheet.pdf. Last accessed March 20, 2015

Overview of EGFR and VEGFR Growth Signaling Pathways

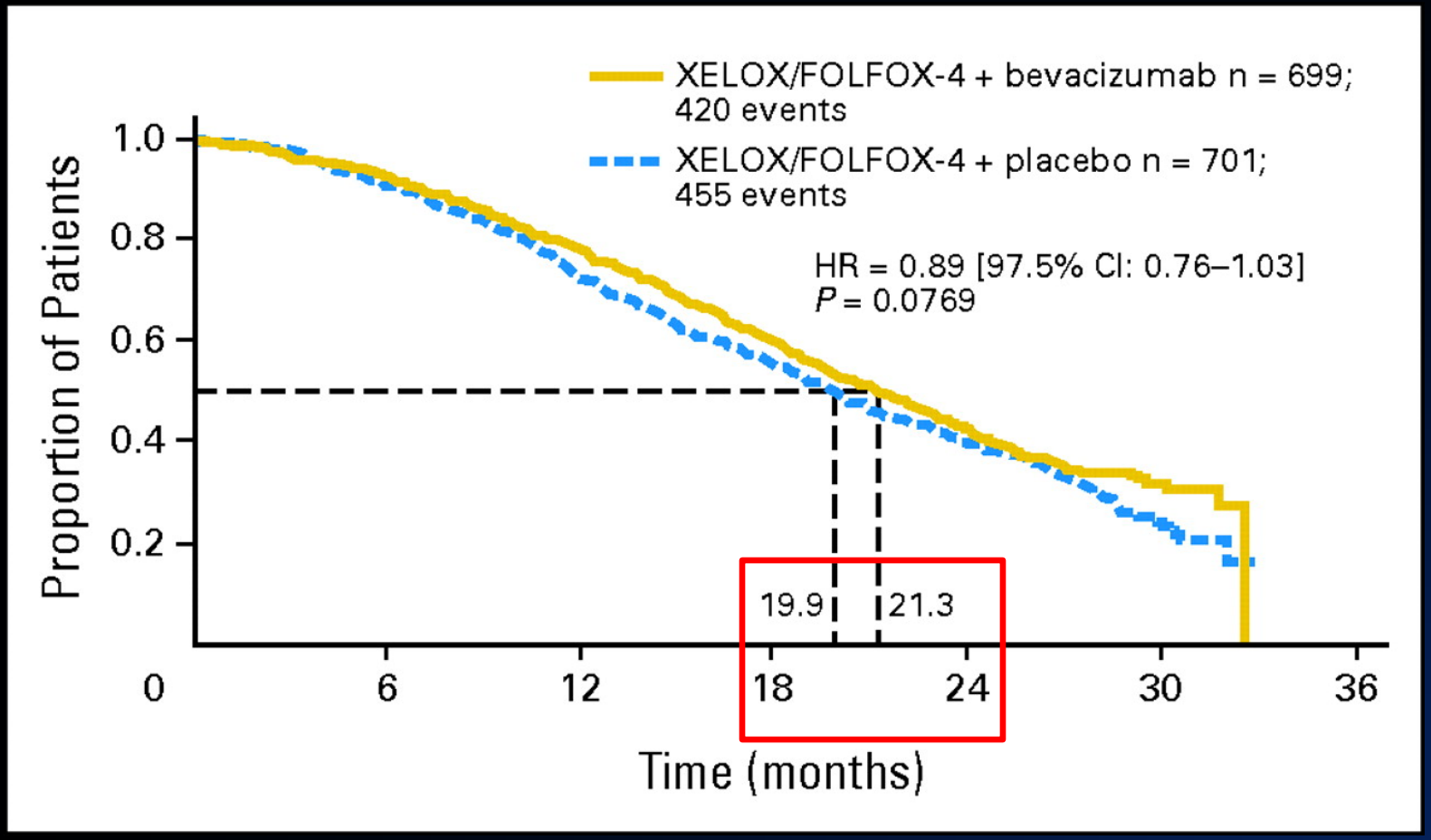


Krasinskas AM. *Patholog Res Int.* 2011;2011:932932; Sitohy B, et al. *Cancer Res* 2012;72:1909-1914; Bendardaf R, et al. *Anticancer Res.* 2008;28:3865-3870; Kitadai Y, et al. *Am J Pathol.* 2006;169:2054-2065; Jayson GC, et al. *J Clin Oncol.* 2005;23:973-981.

Initial choice of biologic agent for 1st line therapy of mCRC

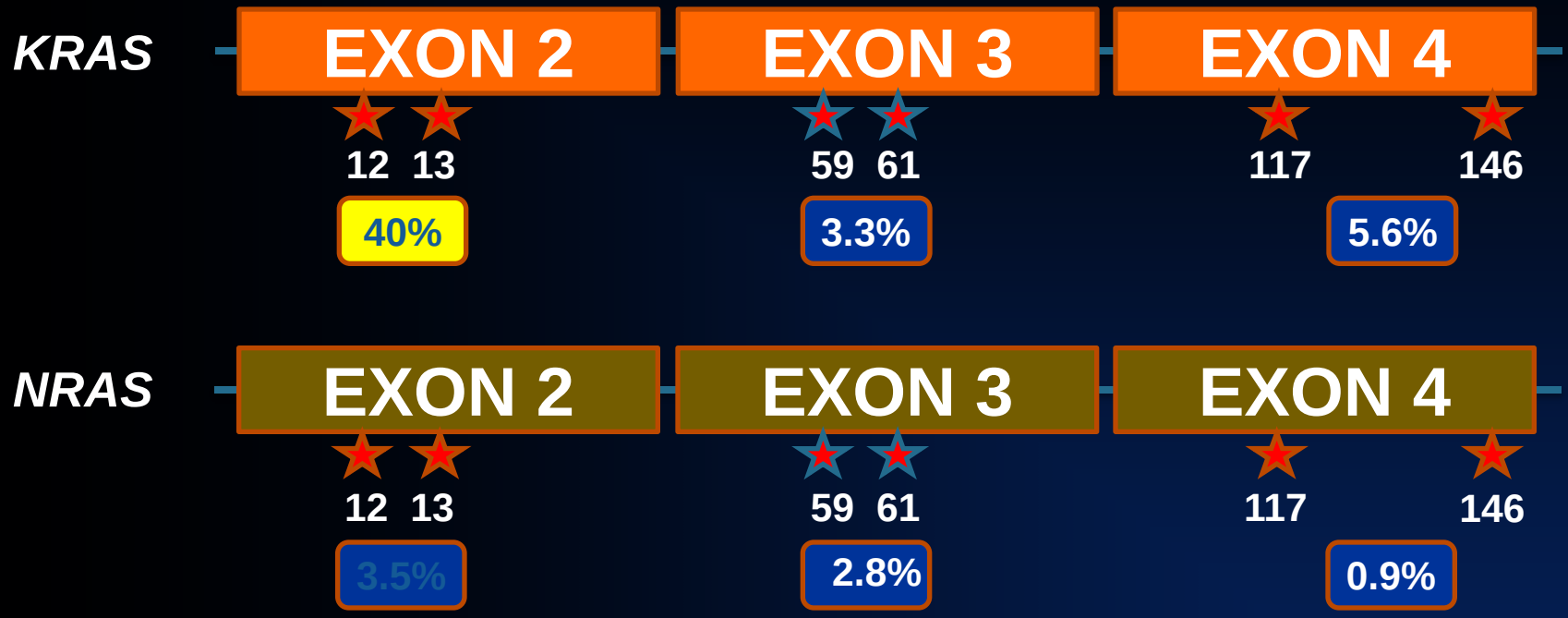


FOLFOX/XELOX and bevacizumab: PFS gain but modest effect on OS



Arnold D, 2008:2006-2012: Discuss perforation, hypertension & bleeding

Spectrum of ras mutations



Progress: Improving patient selection extends the benefit with anti-EGFR therapies

Overall patient population

KRAS exon 2 wt population

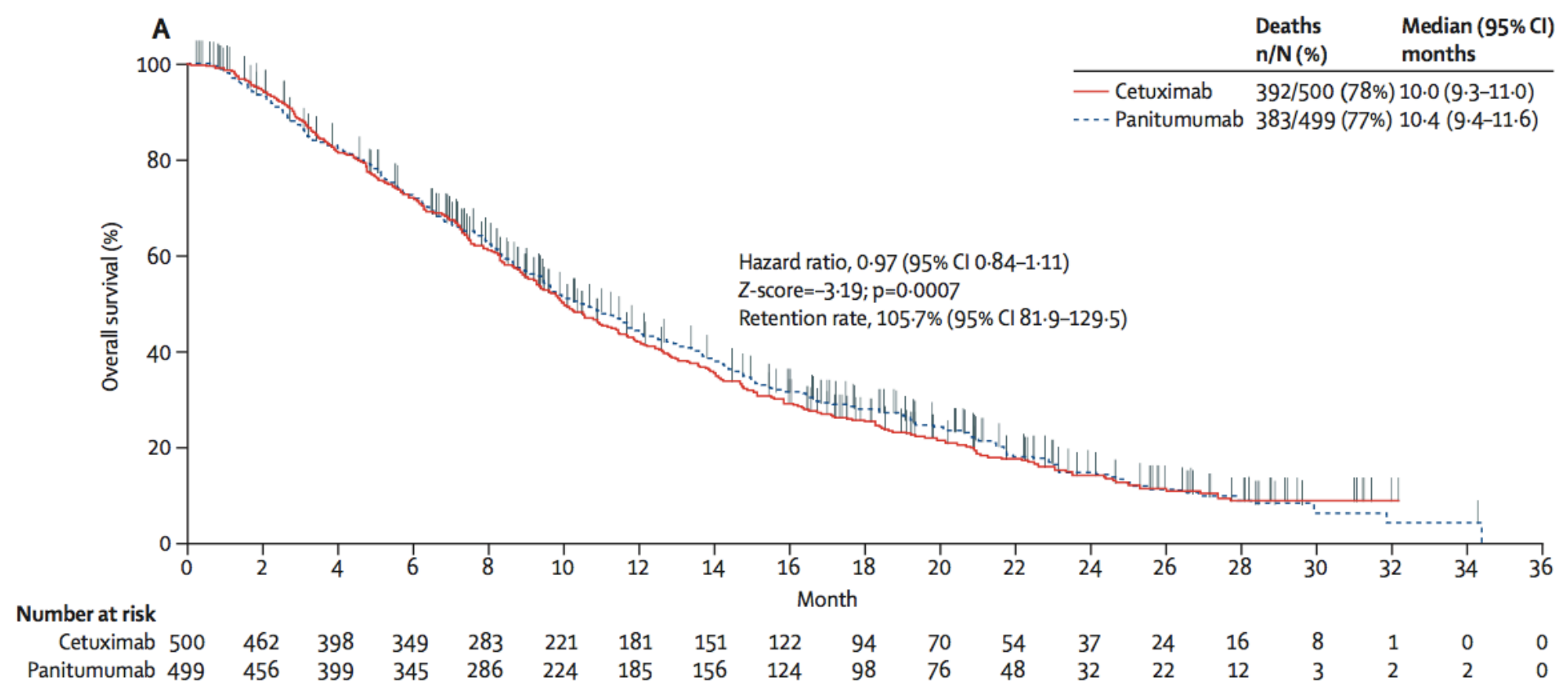
RAS wt population

OS benefit*
CRYSTAL[1,2]
PRIME[3]
FIRE-3[4,5]

PFS benefit*
OPUS[6,7]
PEAK[8]

*Decreased HR in the RAS wt population compared with the KRAS exon 2 wt population or ITT population

ASPECCT panitumumab v cetuximab: OS (non-inferiority)



The Lancet Oncology 15 (6), 569-579

Main differences between panitumumab and cetuximab relate to safety

Adverse Event – n (%)	Panitumumab N=496	Cetuximab N =503
Fatal AE's	29 (5.8)	50 (9.9)
Colon cancer	20 (4.0)	34 (6.8)
Others	9 (1.8)	16 (3.2)
Treatment-related fatal AE's	0 (0)	1 (0.2)
Skin and Subcutaneous tissue AE's		
Any grade	430 (86.7)	440 (87.5)
Grade 3	60 (12.1)	48 (9.5)
Grade 4	2 (0.4)	0 (0)
Serious	1 (0.2)	0 (0)
Hypomagnesemia		
Any grade	143 (28.8)	95 (18.9)
Grade 3	27 (5.4)	10 (2.0)
Grade 4	9 (1.8)	3 (0.6)
Infusion reactions		
Any grade	14 (2.8)	63 (12.5)
Grade 3	1 (0.2)	5 (1.0)
Grade 4	0 (0)	4 (0.8)
Diarrhea		
Any grade	91 (18.3)	89 (17.7)
Grade 3	7 (1.4)	9 (1.8)
Grade 4	3 (0.6)	0 (0.0)

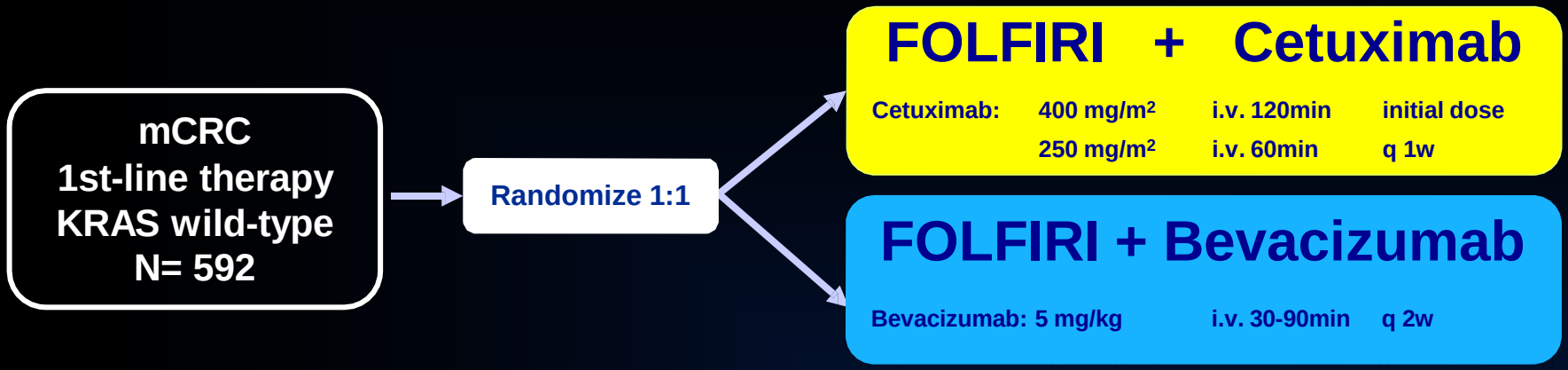
The Lancet Oncology 15 (6), 569-579

First-line Chemotherapy + EGFR Inhibitor Regimens in mCRC: Efficacy Summary From Phase 3 Trials

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

Head to head comparisons of chemotherapy + EGFR inhibitor vs chemotherapy + bevacizumab

FIRE-3 study design



FOLFIRI: 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 endpoint: **Overall response rate (ORR) (inv assessed)**
- 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%

Heinemann et al., Lancet Oncol 2014

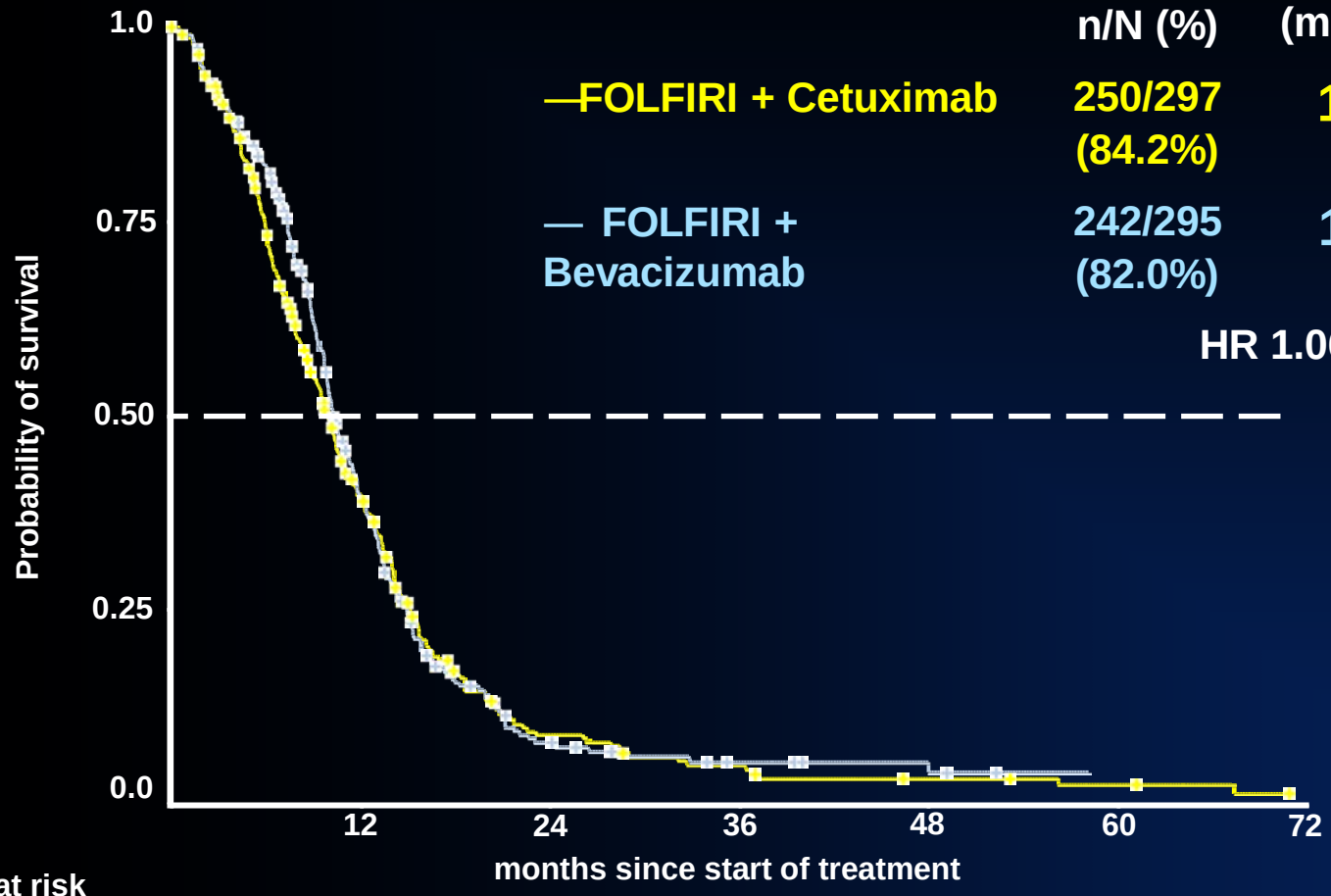
FIRE-3 ORR
Primary Endpoint

	FOLFIRI + Cetuximab		FOLFIRI + Bevacizumab		Odds ratio	p
ORR	%	95%-CI	%	95%-CI		
ITT population (N= 592)	62.0	56.2 – 67.5	58.0	52.1 – 63.7	1.18 0.85-1.64	0.183

p = Fisher's exact test (one-sided)

Heinemann et al., Lancet Oncol 2014

FIRE-3 PFS



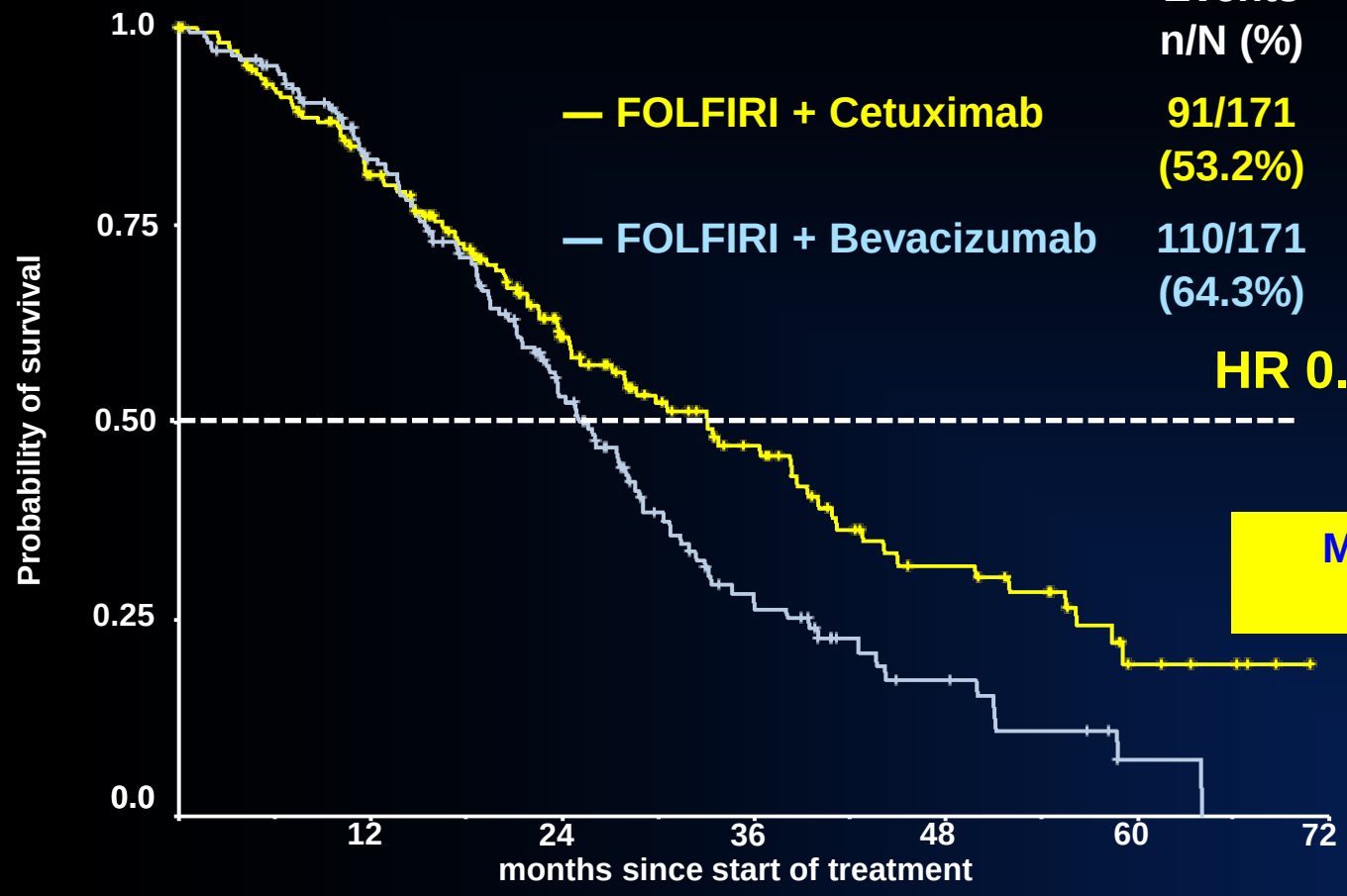
	Events n/N (%)	Median (months)	95% CI
FOLFIRI + Cetuximab	250/297 (84.2%)	10.0	8.8 – 10.8
FOLFIRI + Bevacizumab	242/295 (82.0%)	10.3	9.8 – 11.3

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

umber at risk						
OLFIRI+cetux	297	100	19	10	5	3
OLFIRI+bev	295	99	15	6	4	

Heinemann et al., Lancet Oncol 2014

FIRE-3 ESMO/ECCO Update Overall survival All-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

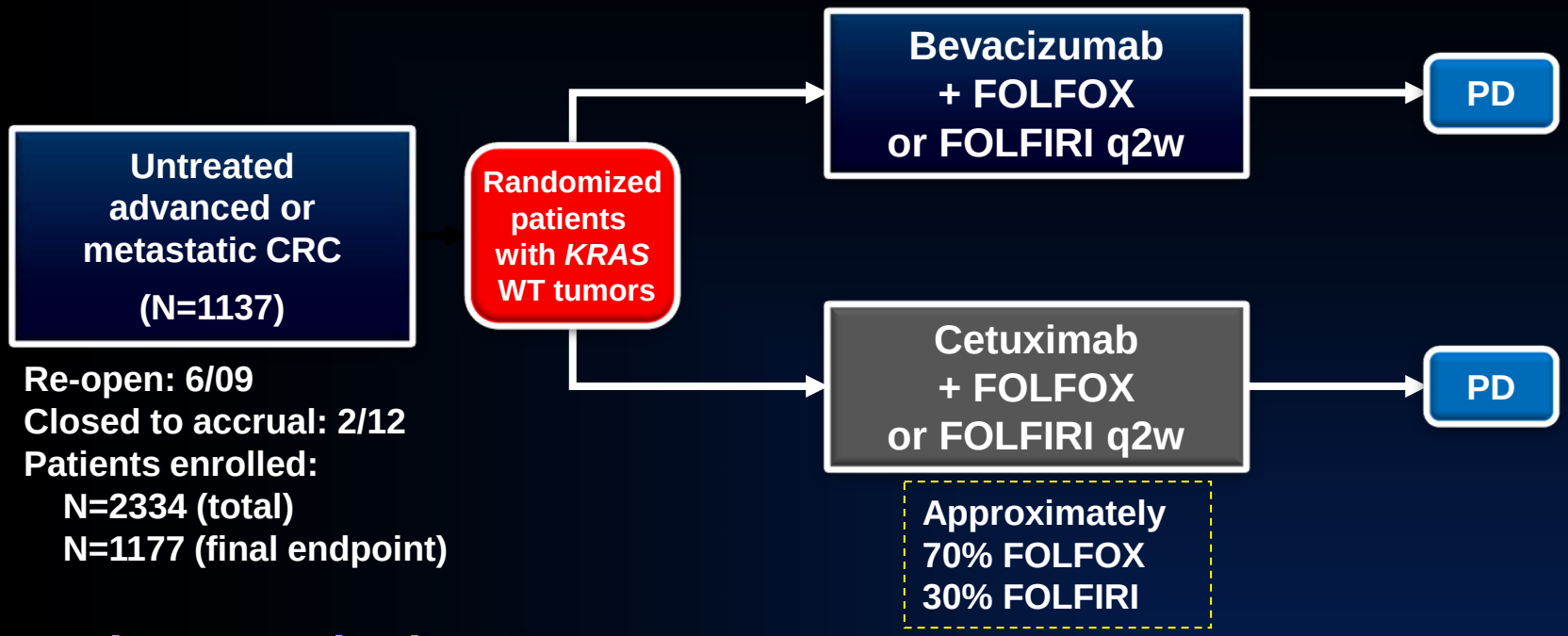
HR 0.70 (95% CI: 0.53 – 0.92)
p (log-rank)= 0.011

Median Δ = 7.5 months

RAS* wild-type: KRAS 61/146; NRAS Exon2, NRAS Exon3

Heinemann et al., Lancet Oncol 2014

CALGB/SWOG 80405: H2H Bevacizumab vs Cetuximab in First-line *KRAS* WT mCRC



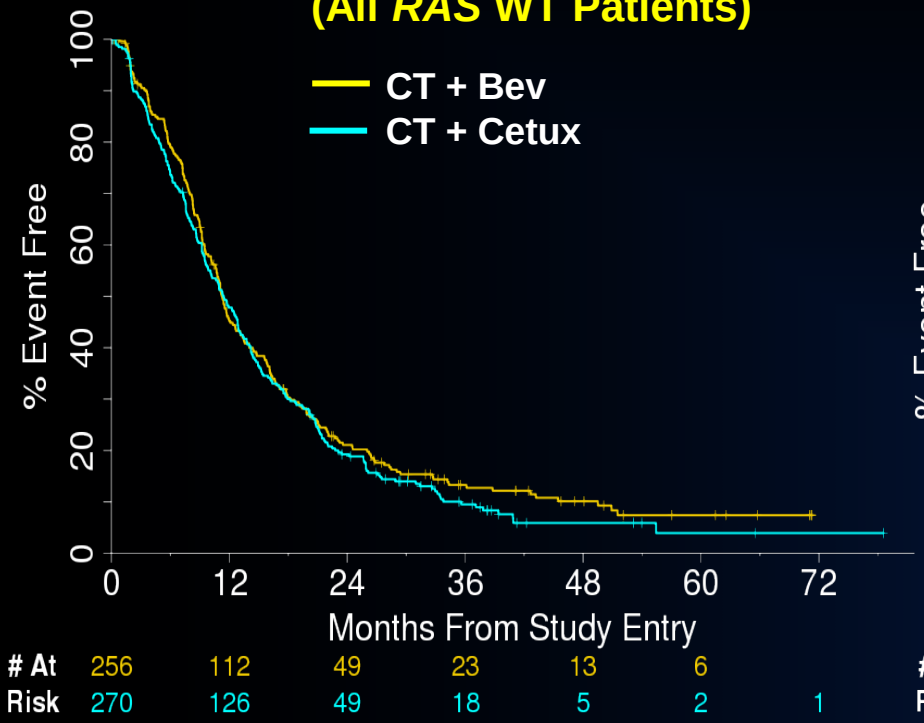
- **Primary endpoint: OS**
  - Superiority trial with 90% power to detect an OS HR of 1.25 (2-sided α=0.05)
- Secondary endpoints: ORR, PFS, TTF, DOR, and safety

H2H=head-to-head; TTF=time to treatment failure.

Venook et al, ASCO 2014. NCT identifier: NCT00265850.

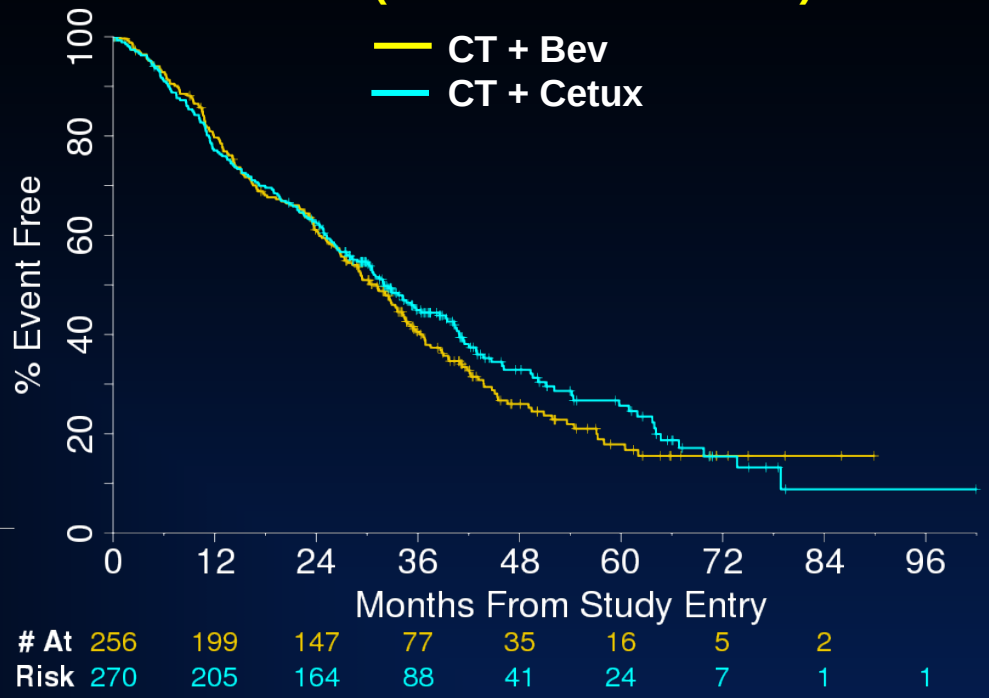
CALGB/SWOG 80405: PFS and OS in All *RAS* WT Patients

Progression-Free Survival (All *RAS* WT Patients)



Arm	N (Events)	mPFS, Mos	HR (95% CI) *P* Value
CT + Bev	256 (221)	11.3 (10.3-12.6)	**1.1 (0.9-1.3)**
CT + Cetux	270 (241)	11.4 (9.6-12.9)	***P*=0.31**

Overall Survival (All *RAS* WT Patients)

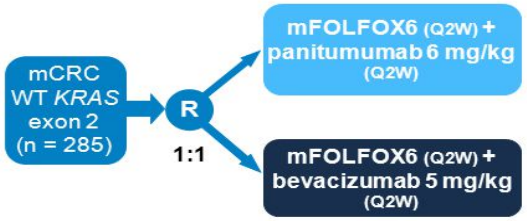


Arm	N (Events)	mOS, Mos	HR (95% CI) *P* Value
CT+ Bev	256 (178)	31.2 (26.9-34.3)	**0.9 (0.7-1.1)**
CT + Cetux	270 (177)	32.0 (27.6-38.5)	***P*=0.40**

Lenz H-J, et al. Presented at: ESMO. 2014 (abstr 501O).

PEAK Study

Phase 2 PEAK study
mFOLFOX6 + panitumumab or bevacizumab in 1st-line treatment of WT *KRAS* exon 2 mCRC



WT *RAS*[1]	Panitumumab + mFOLFOX6 (n = 88)	Bevacizumab + mFOLFOX6 (n = 82)
Median PFS, mo*	13.0	9.5
HR (95% CI) P-value	0.65 (0.44–0.96) P = 0.029	
Median OS, mo†	41.3	28.9
HR (95% CI) P-value	0.63 (0.39–1.02) P = 0.058	
ORR, %* (95% CI)	63.6 (52.7–73.6)	60.5 (49.0–71.2)

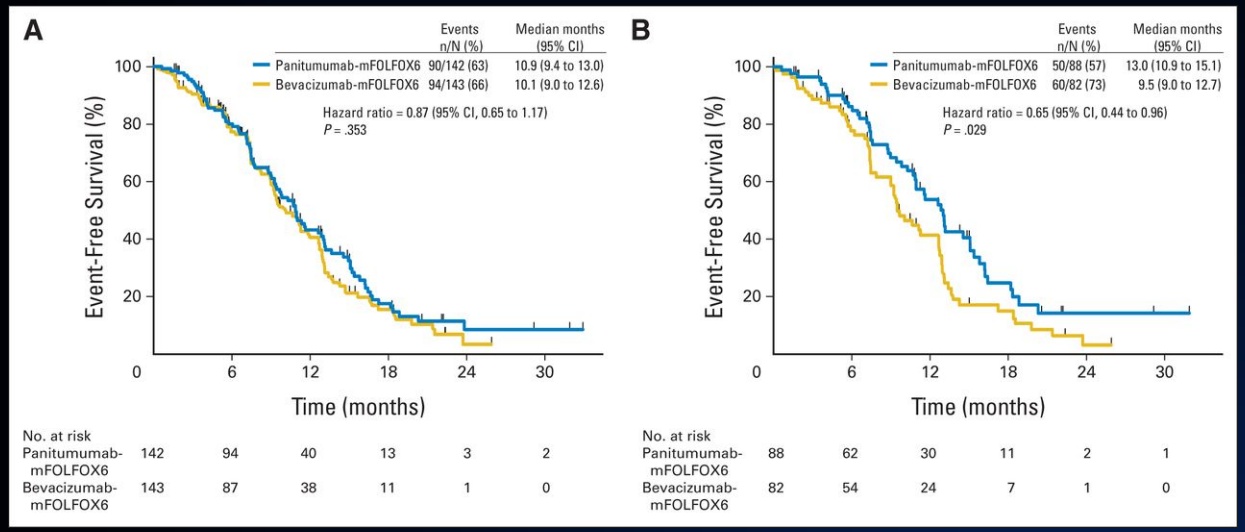
- Primary endpoint: PFS
  - No planned formal hypothesis testing
- Prespecified extended *RAS* analysis

1. Schwartzberg LS, et al. J Clin Oncol 2014;32:2240–7;
Protocol ID: 20070509; ClinicalTrials.gov identifier: NCT00819780.

*Primary analysis; †longer follow-up analysis.
RAS ascertainment rate: 82%.
WT *RAS* = WT *KRAS/NRAS* exons, 2, 3, 4.

Presented by:

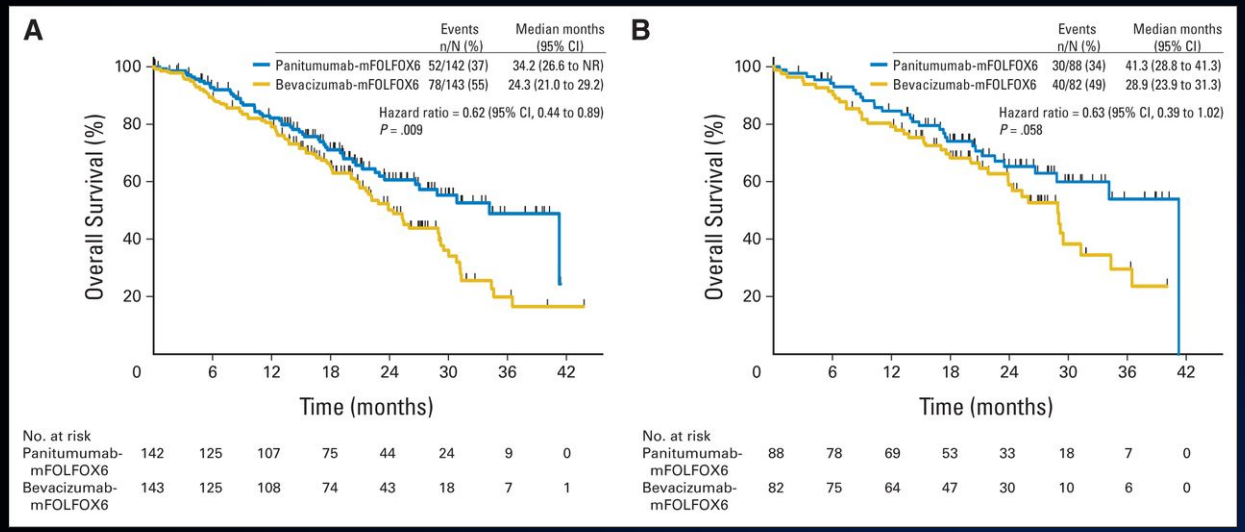
PEAK: Progression-free survival in (A) wild-type (WT) KRAS exon 2 intent-to-treat group and (B) extended WT RAS subgroup.



Lee S. Schwartzberg et al. JCO 2014;32:2240-2247

JOURNAL OF CLINICAL ONCOLOGY ASCO

PEAK: Overall survival in (A) wild-type (WT) KRAS exon 2 intent-to-treat group and (B) extended WT RAS subgroup.

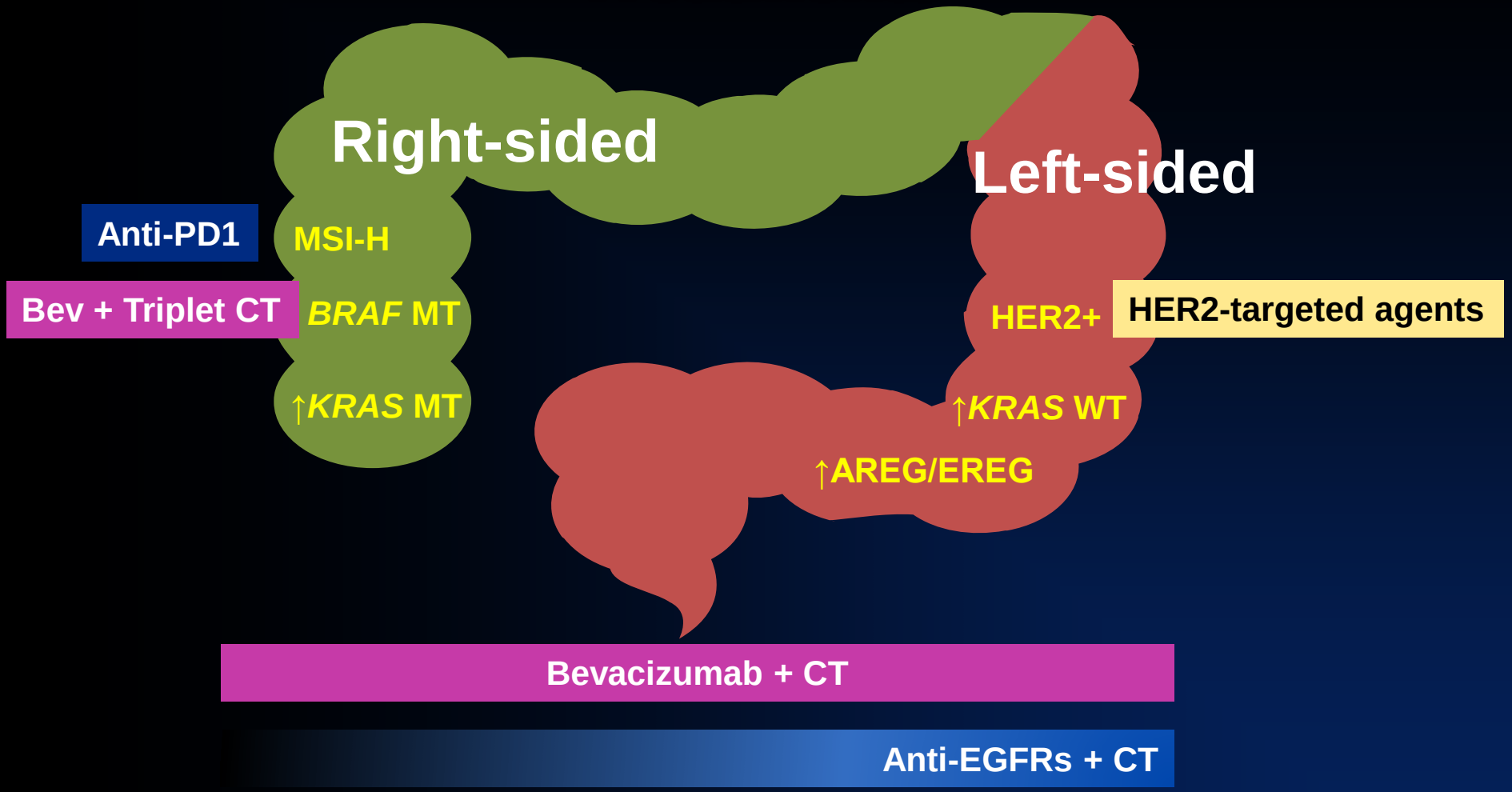


Lee S. Schwartzberg et al. JCO 2014;32:2240-2247

JOURNAL OF CLINICAL ONCOLOGY ASCO

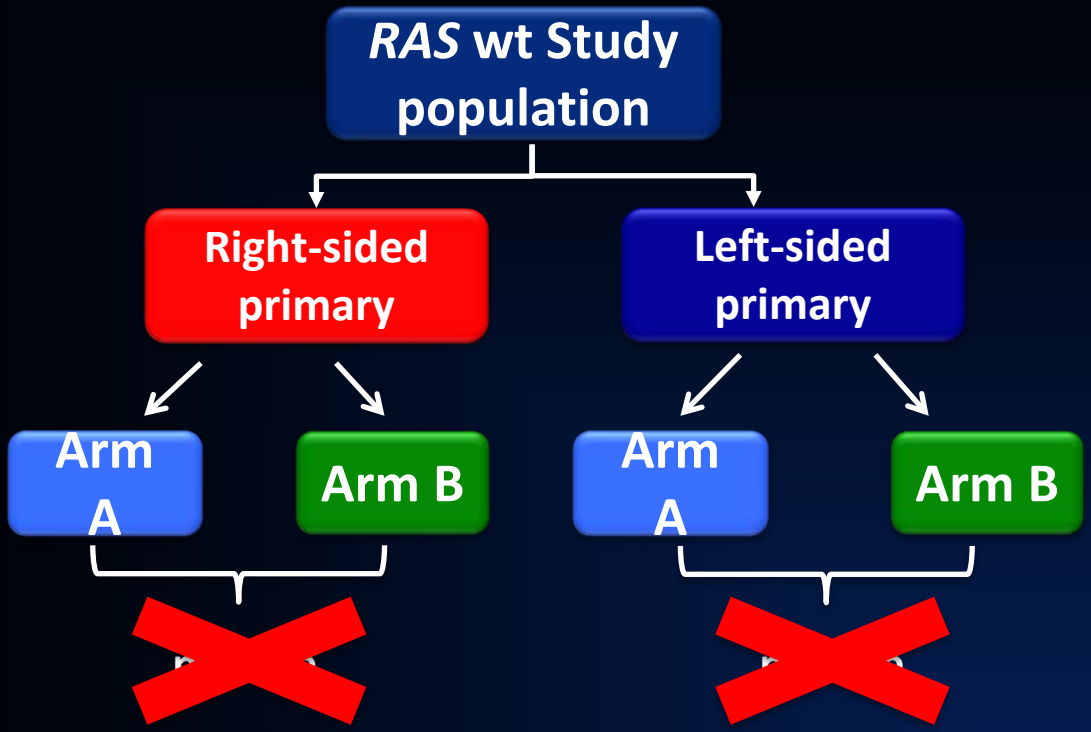
What is the impact of site of primary tumour?

Primary Tumor Location and Potential Treatments

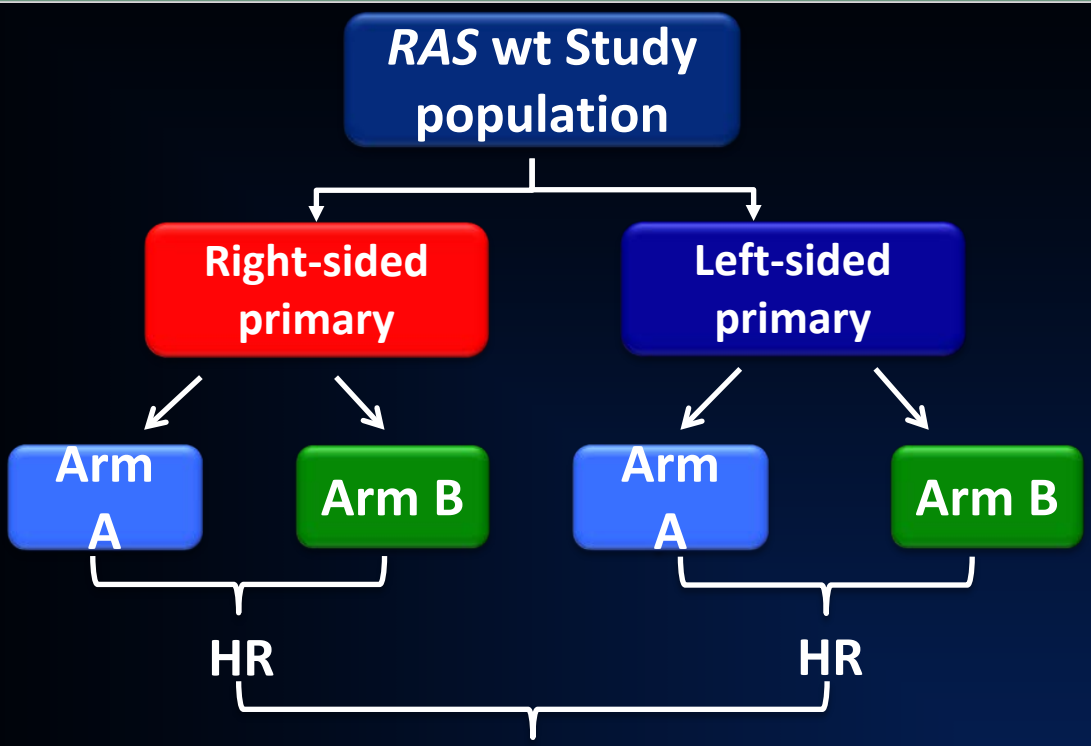


Bufill JA. *Ann Intern Med.* 1990;113:779-788; Missiaglia E, et al. ASCO 2013. Abstract 3526; Brule SY, et al. ASCO 2013. Abstract 3528; The Cancer Genome Atlas Network. *Nature.* 2012490:61-70; Bendardaf R, et al. *Anticancer Res.* 2008;28:3865-3870.

How to interpret subgroup analyses



How to interpret subgroup analyses



If significant (p<0.10) → hypothesis-generating

Right versus Left: summary

1) **Prognostic impact**

Right-sided tumours have worse prognosis

Prognostic impact

JAMA Oncology | Original Investigation

Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer

A Systematic Review and Meta-analysis

Fausto Petrelli, MD; Gianluca Tomasello, MD; Karen Borgonovo, MD; Michele Ghidini, MD; Luca Turati, MD; Pierpaolo Dallera, MD; Rodolfo Passalacqua, MD; Giovanni Sgroi, MD; Sandro Barni, MD

1.437.846 patients in 66 studies (stage I→IV)

HR (left vs right): 0.82 [95%CI: 0.79-0.84], p<0.001

"... Left sided primary tumor location was associated with a significantly reduced risk of death (HR, 0.82; 95% CI, 0.79-0.84; *P* < .001) and this was independent of stage, race, adjuvant chemotherapy, year of study, number of participants, and quality of included studies … "

Right versus Left: summary

1) Prognostic impact

Right-si[illegible]ours have worse prognosis

STRATIFY CLINICAL TRIALS

2) Predictive impact

Predictive impact – bevacizumab

Chemo +/- bevacizumab

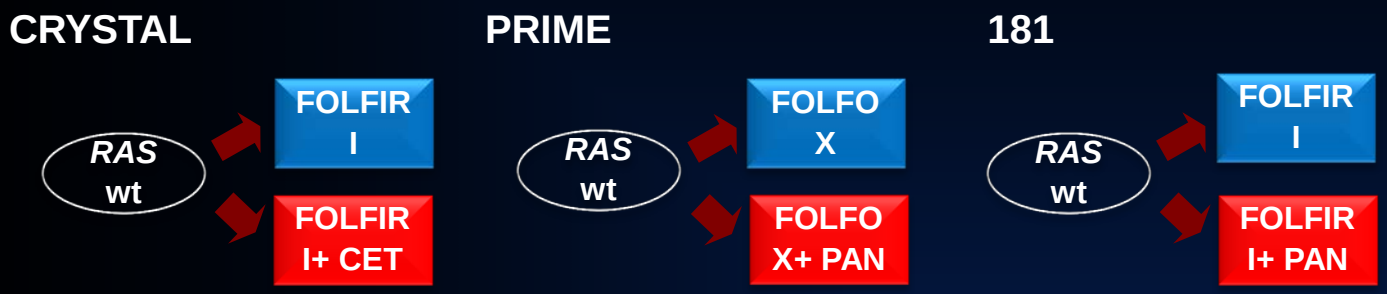
p for interaction OS=0.38; PFS=0.59

p for interaction OS=0.29; PFS=0.62

Loupakis et al, J Natl Can Inst 2015.

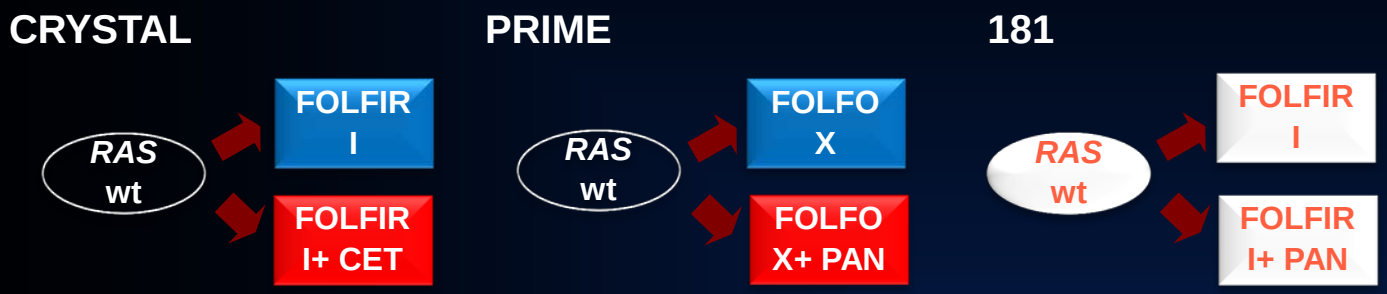
Predictive impact – anti-EGFRs

Chemo +/- anti-EGFR



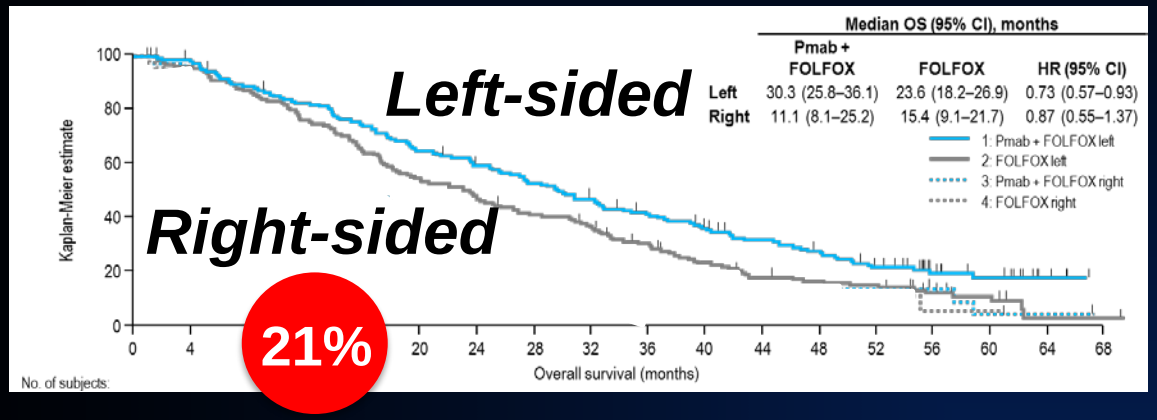
Predictive impact – anti-EGFRs

Chemo +/- anti-EGFR



Right versus Left: PRIME study - OS

PRIME Trial: FOLFOX+PAN vs FOLFOX

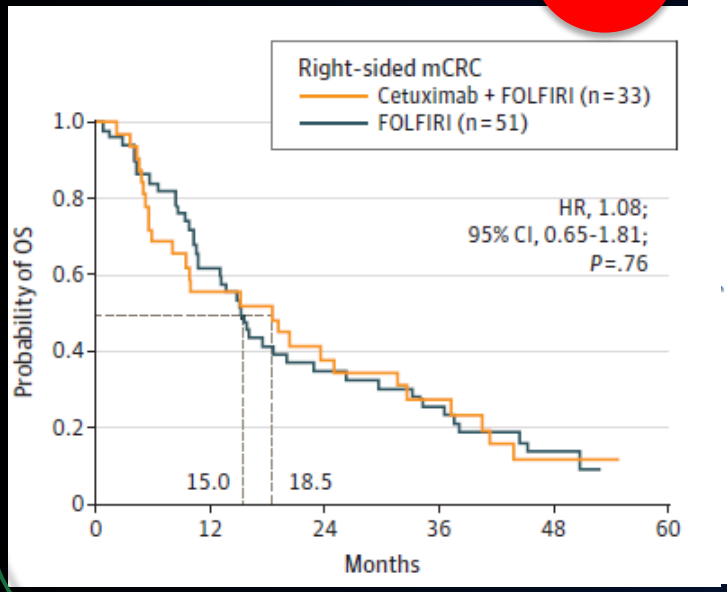


Boeckx et al. Ann Oncol 2017 Apr 25. Epub ahead of print

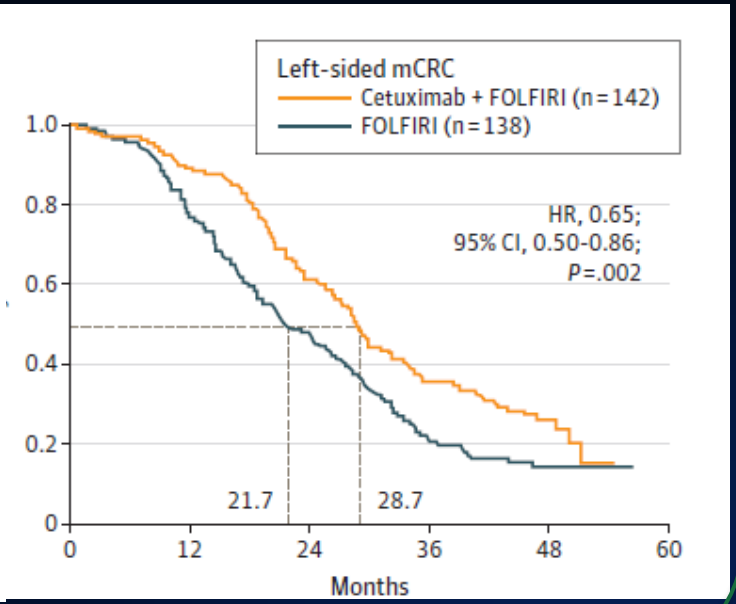
Right versus Left: CRYSTAL study - OS

CRYSTAL Trial: FOLFIRI + cetuximab vs FOLFIRI

Right-sided 23%



Left-sided



p for interaction 0.17

Right versus Left: summary

1) Prognostic impact

Right-sided tumours have worse prognosis

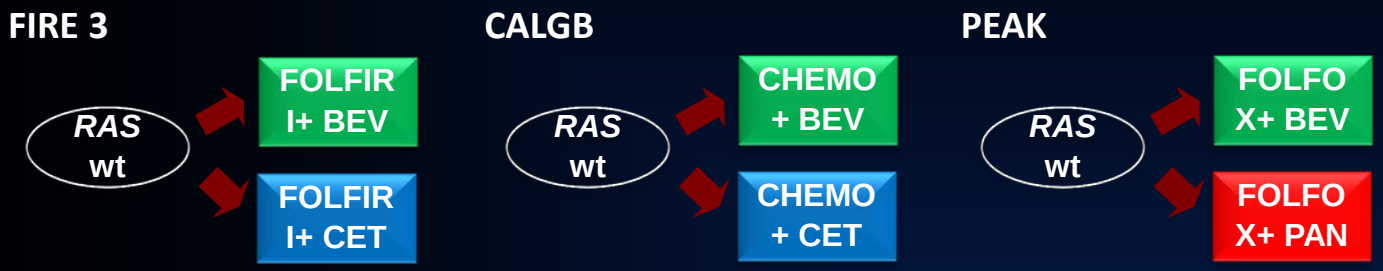
2) Predictive impact

No different benefit from bev for right versus left

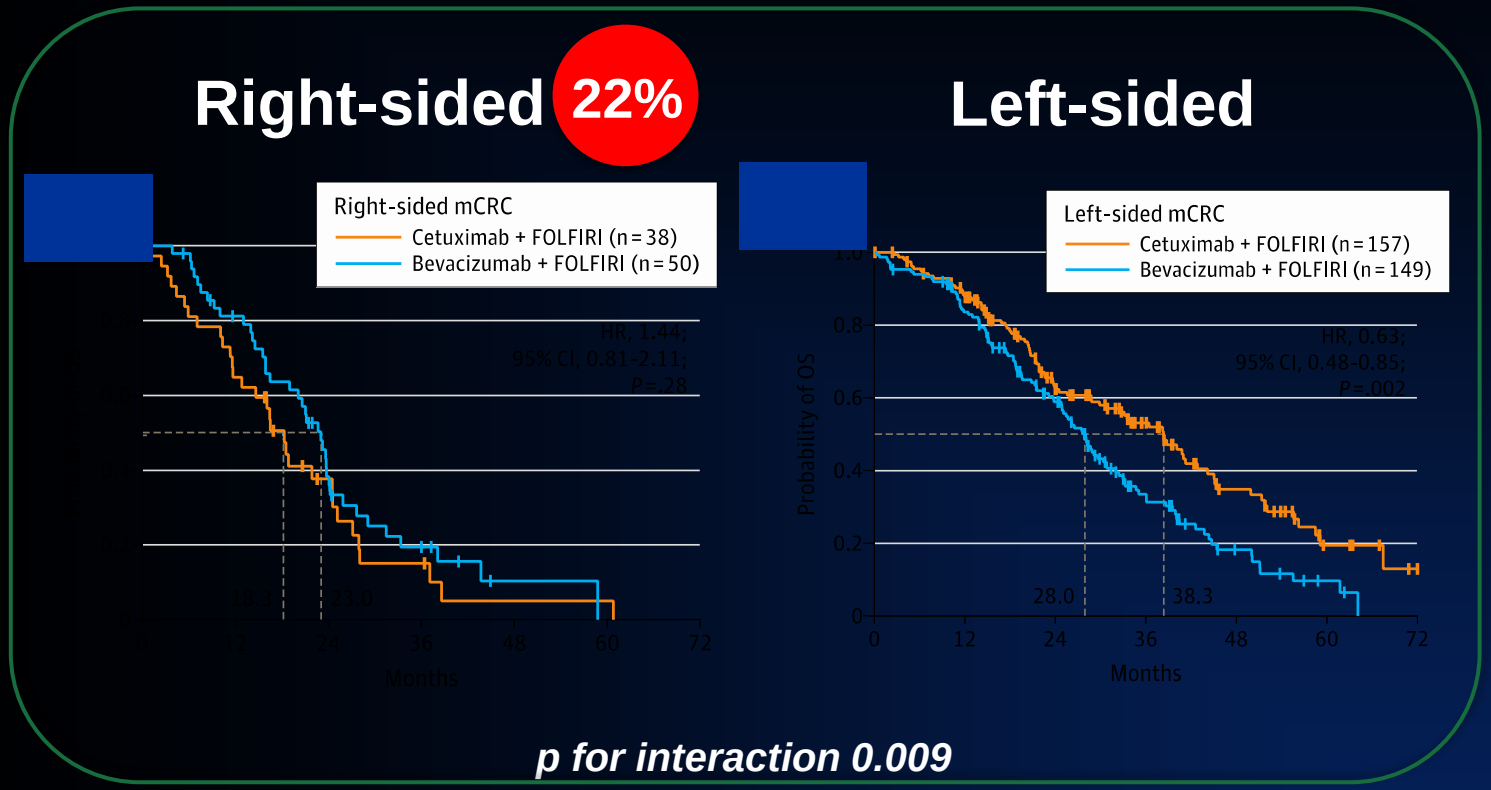
More benefit from anti-EGFRs in left-sided than right-sided mCRC tumours

Predictive impact – bev versus anti-EGFRs

Chemo+anti-EGFR vs Chemo+Bev



Right versus Left: FIRE-3 study - OS



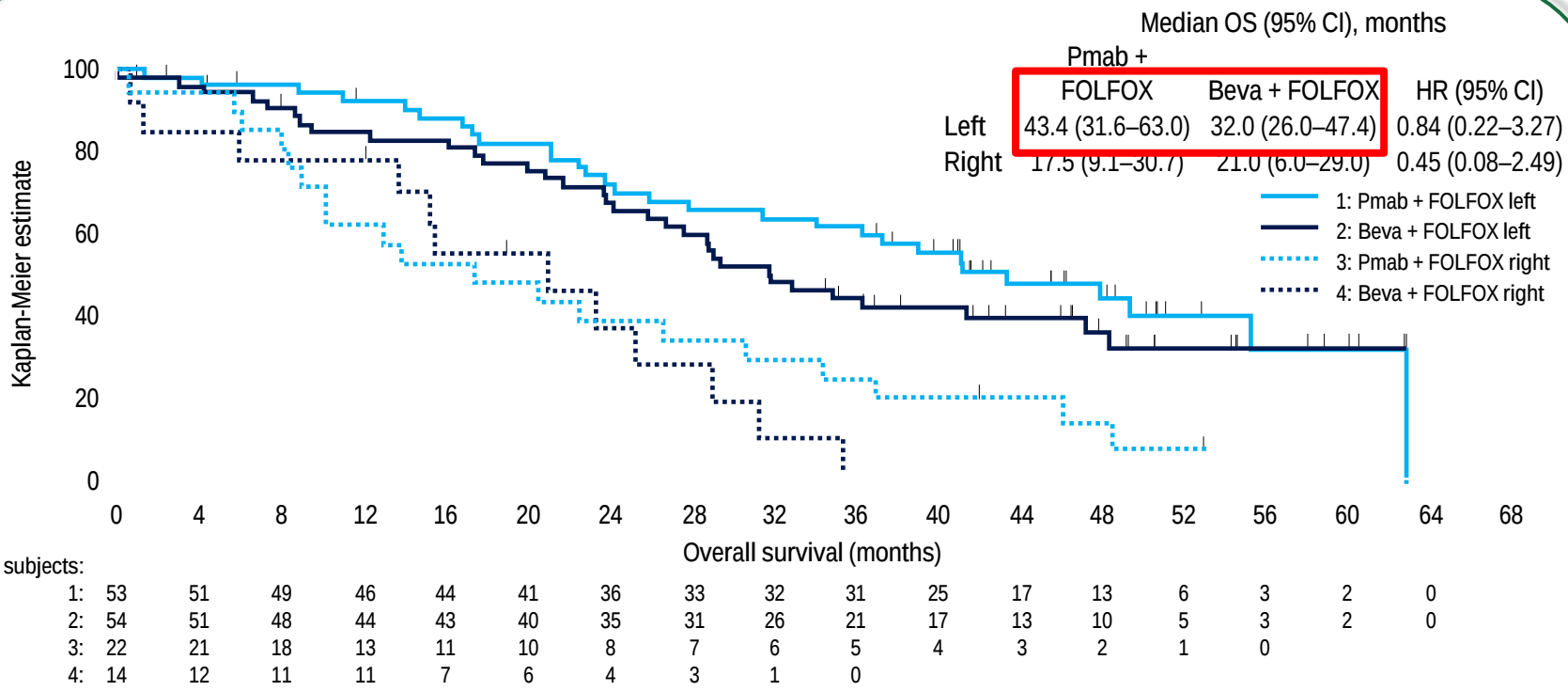
p for interaction 0.009

Right versus Left: CALGB80405 study - OS

31%

p for interaction 0.009

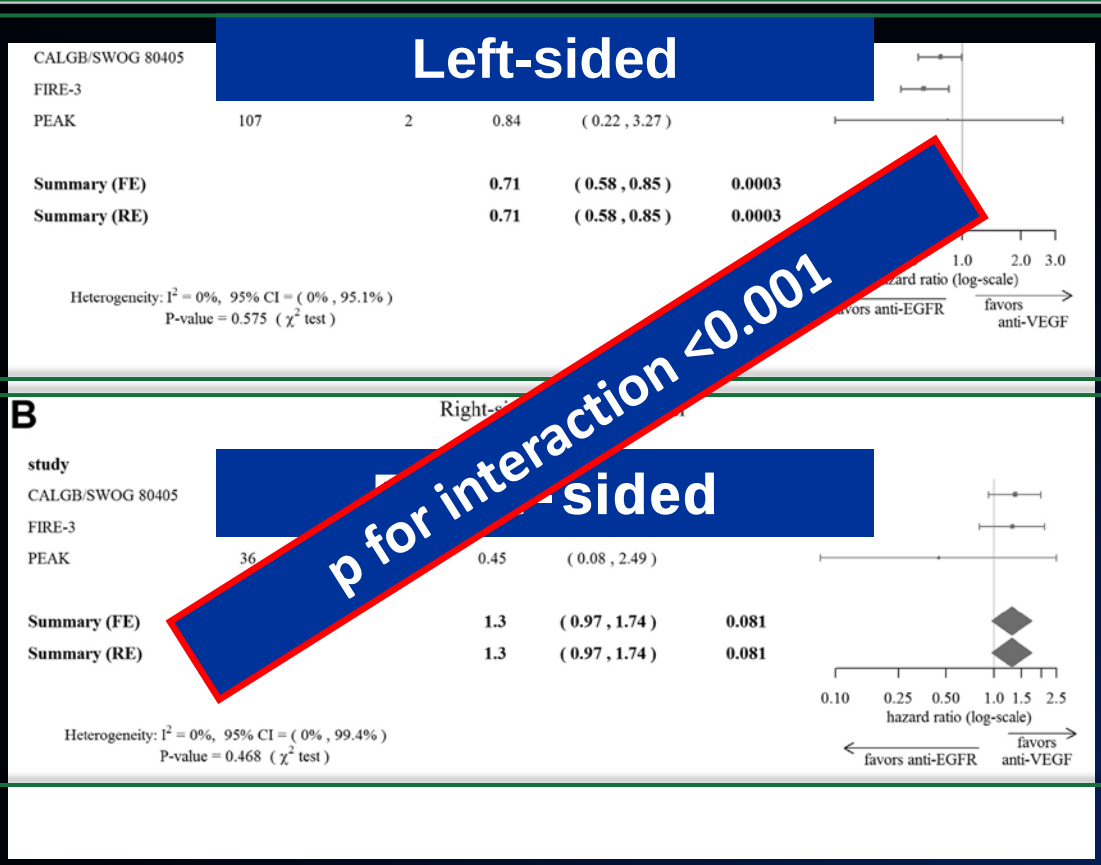
Right versus Left: PEAK – OS



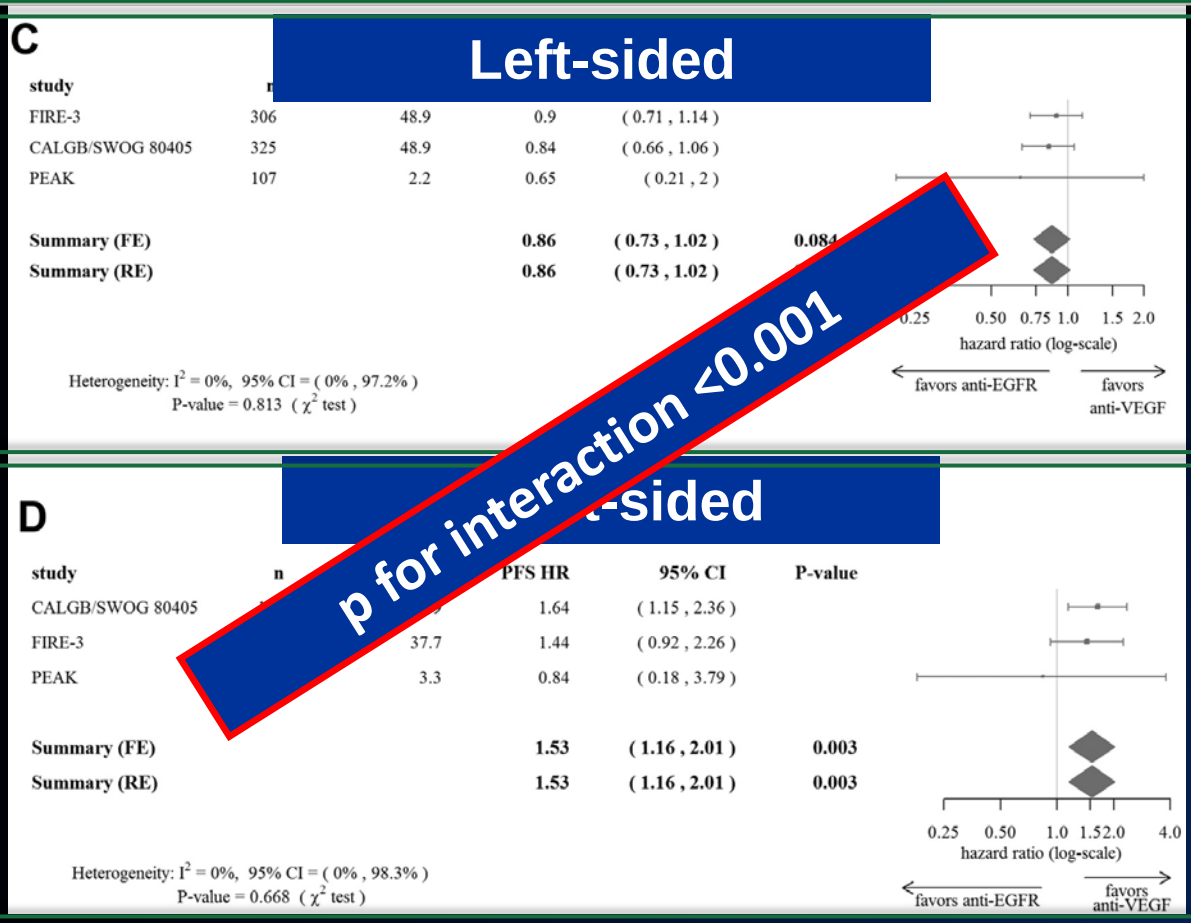
Boeckx ESMO 2016; Peeters et al. Ann Oncol 2017. Apr 25. Epub ahead of print.

Beva, bevacizumab; HR, hazard ratio; OS, overall survival; Pmab, panitumumab

Right versus Left: meta-analysis of H2H trials - OS



Right versus Left: meta-analysis of H2H trials - PFS

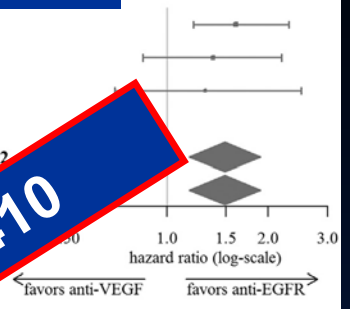


Right versus Left: meta-analysis of H2H trials - response rate

Left-sided

CALGB/SWOG 80405	325	57.7	1.6	(1.2 , 2.3)	
FIRE-3	306	27.3	1.37	(0.85 , 2.19)	
PEAK	107	15.1	1.3	(0.7 , 2.5)	
Summary (FE)			**1.49**	**(1.16 , 1.9)**	**0.002**
Summary (RE)			**1.49**	**(1.16 , 1.9)**	

Heterogeneity: I^2 = 0%, 95% CI = (0% , 88%)
P-value = 0.786 (χ^2 test)

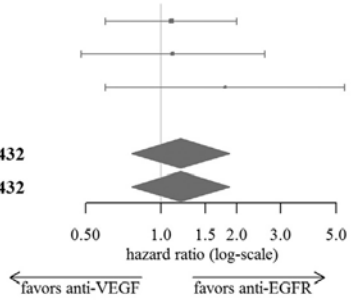


p for interaction =0.410

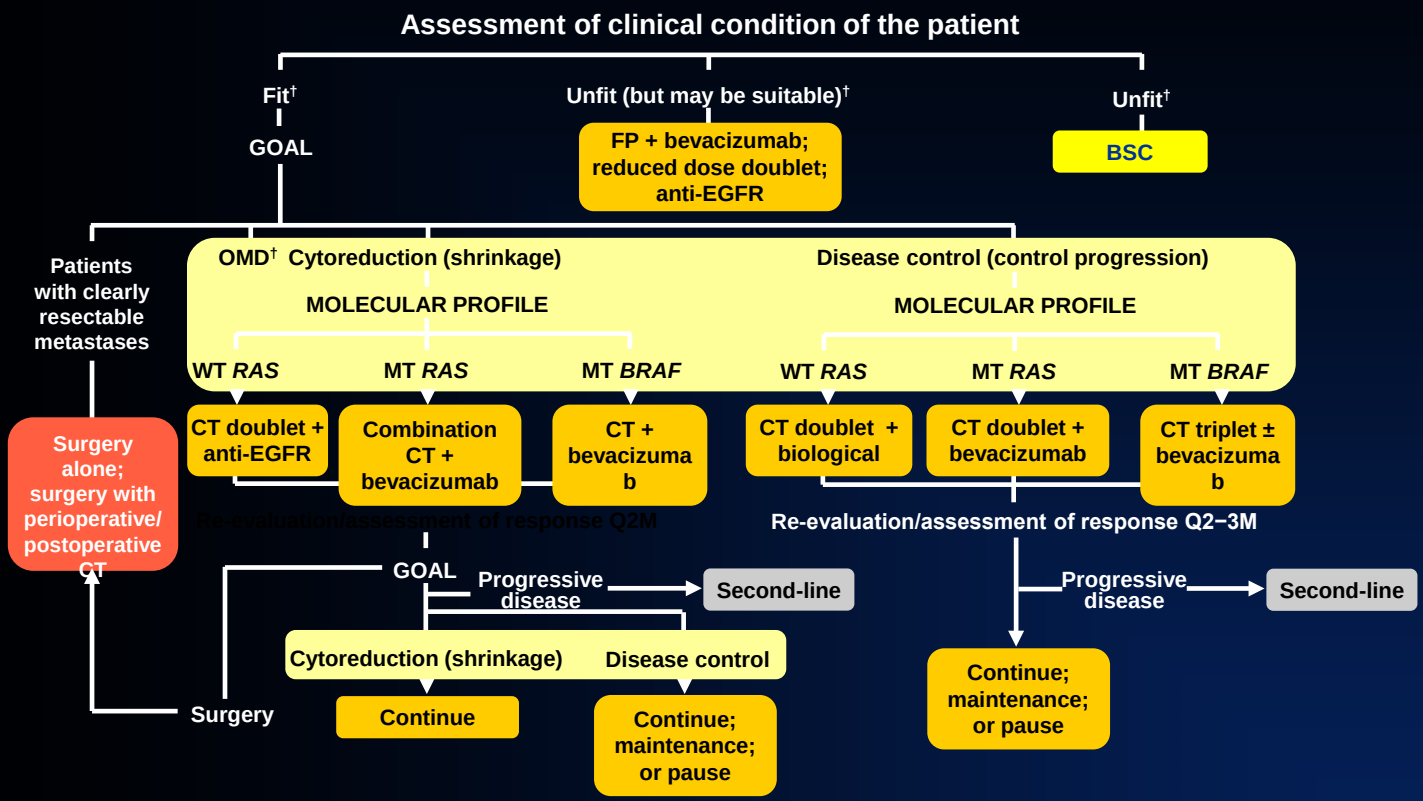
-sided

study	n	RR	95% CI	P-value
CALGB/SWOG 80405	14	1.1	(0.6 , 2)	
FIRE-3		1.11	(0.48 , 2.59)	
PEAK		1.8	(0.6 , 5.4)	
Summary (FE)		**1.2**	**(0.77 , 1.87)**	**0.432**
Summary (RE)		**1.2**	**(0.77 , 1.87)**	**0.432**

Heterogeneity: I^2 = 0%, 95% CI = (0% , 94.2%)
P-value = 0.728 (χ^2 test)



ESMO recommendations: 2016



†Patients assessed as 'fit' or 'unfit' according to medical condition, not due to malignant disease; ‡Separate algorithm.
OMD, oligometastatic disease.

ESMO Recommendations: 2016

Goal / Condition	Molecular	Preferred 1st line regimen
Disease stabilization	all WT	Doublet plus EGFR or Doublet plus beva
	RAS mut	Doublet plus beva
	BRAF mut	FOLFOXIRI +/- beva
Cytoreduction	all WT	Doublet plus EGFR (FOLFOXIRI plus beva)
	RAS mut	Doublet or triplet + beva
	BRAF mut	FOLFOXIRI + beva
"Frail", or chosen sequential treatment	no BRAF !	Cape or FU + beva

After Right vs Left

Goal / Condition	Molecular	Preferred 1st line regimen
Disease stabilization	all WT	**Left: Doublet/EGFR** **Right: Doublet (FOLFOXIRI)/beva**
	RAS mut	(Doublet)/FOLFOXIRI/beva
	BRAF mut	FOLFOXIRI/(Doublet)/beva
Cytoreduction	all WT	**Left: Doublet/EGFR** **Right: FOLFOXIRI/beva** (Doublet/EGFR)
	RAS mut	FOLFOXIRI/beva
	BRAF mut	FOLFOXIRI/beva
"Frail", or chosen sequential treatment	no BRAF !	Capecitabine/beva

Should we consider primary tumour location among other drivers of the first-line therapy?

Candidate predictors of resistance to anti-EGFRs

Different molecular alterations, supported by a strong and sound biologic rationale, have been suggested as predictors of primary resistance to anti-EGFRs

Candidate alterations:

- ***HER2* amplification or mutations**
- ***MET* amplification**
- ***ALK/ROS1/NTRKs* and *RET* fusions**
- **PIK3CA/PTEN/Akt and MAPKs pathways' activating mutations**

BUT…

Up to today their potential impact has been demonstrated only in pre-clinical experiences and retrospective series

Right versus Left: Molecular make-up

BRAF V600E mutation

BRAF-like signature

RAS mutations

PIK3CA mutations

dMMR

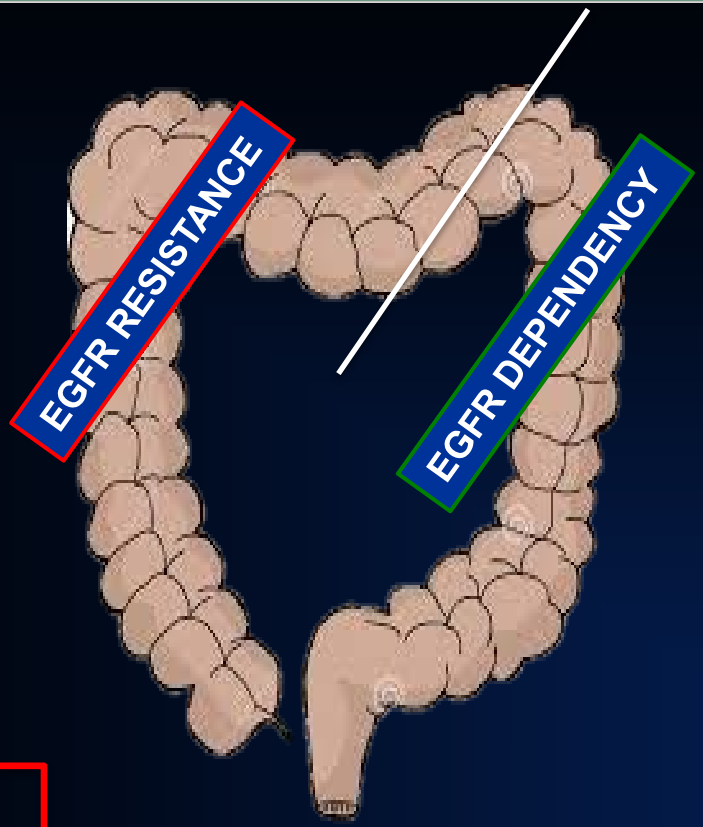
CIMP-high

Low AREG-EREG expression

CMS1(Immune)
miR-31-3p high

EGFR promoter methylation

ALK/ROS1/NTRK rearrangements



HER-2 amplification

High AREG-EREG expression

EGFR amplification

miR-31-3p low

Conclusions

1. Few new classes of therapeutics; refinement of patient selection
2. Data relating to tumour site; improves patient selection
3. Reinforce the use of EGFR antibody therapy in patients with mCRC and left-sided RAS *wt* tumours
4. Patients with right-sided RAS *wt* tumours might be better treated with triplet chemotherapy alone or triplet chemotherapy plus bevacizumab except maybe doublet chemotherapy plus anti-EGFR if the goal is tumour size reduction as the ORRs were higher (but not PFS and OS)
5. Knowledge of site of primary tumor does not replace molecular characterisation