How can we predict the success in anti-EGFR therapy?

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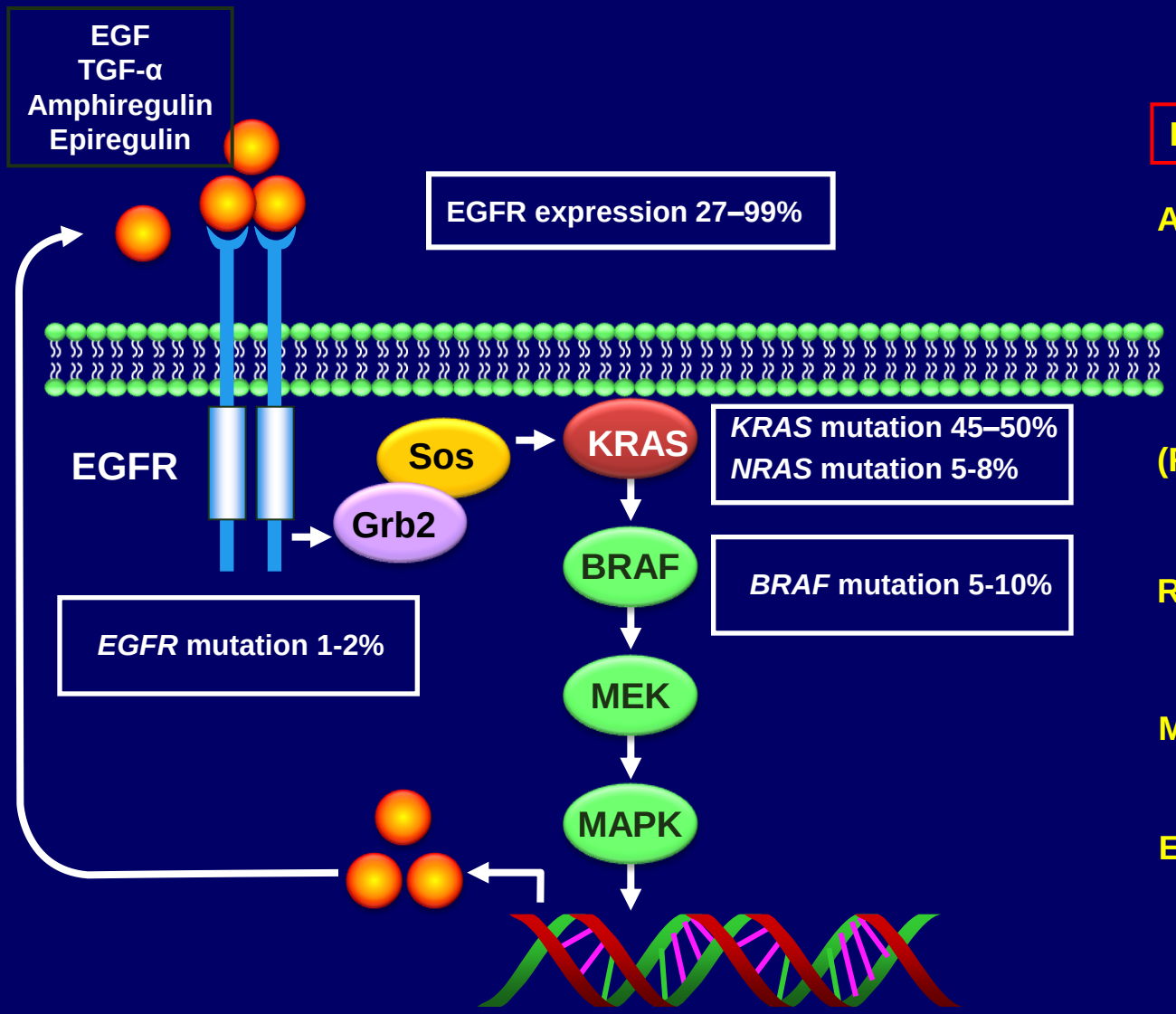
Targeting the EGFR pathway in CRC



Inhibitors

Anti-EGFR MoAbs:
Cetuximab
Panitumumab

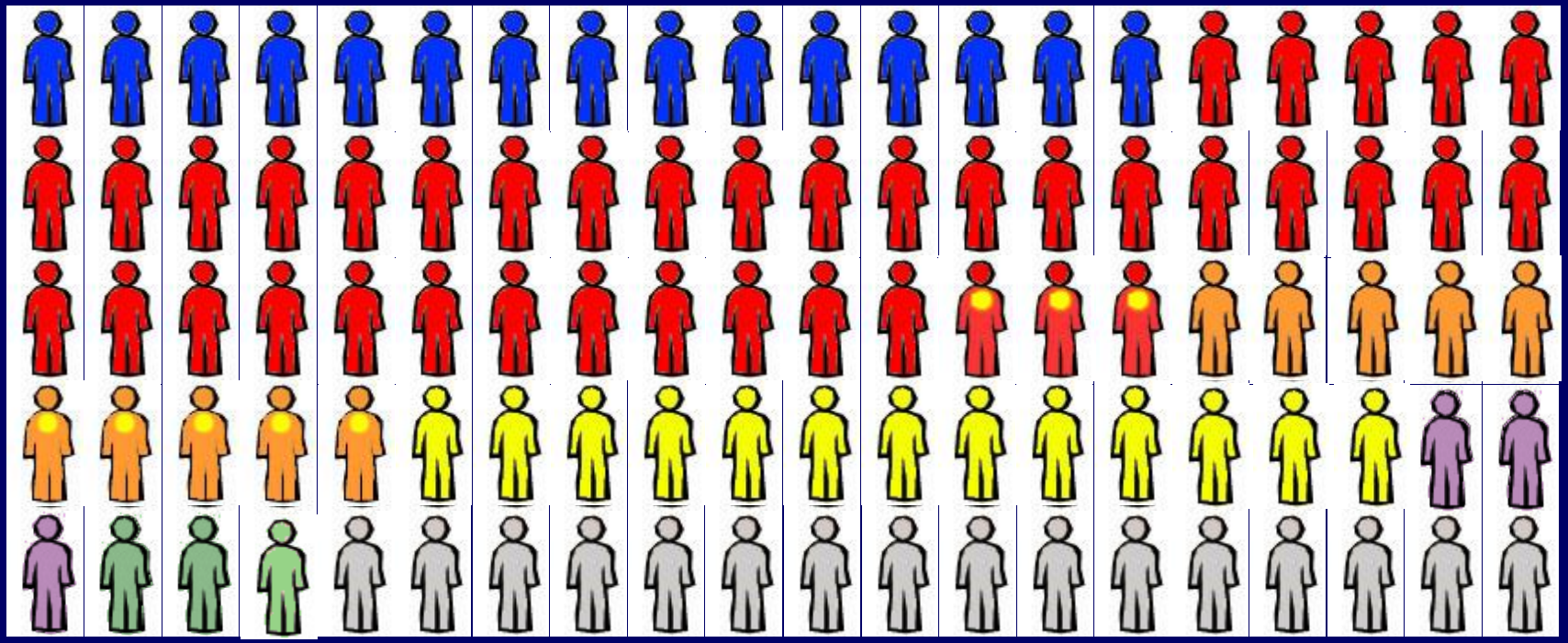
(RAS inh.)

RAF inh.

MEK inh.

ERK inh.

Primary resistance to anti-EGFR therapy in colorectal cancer



Responder (15%)

KRAS-NRAS (35-45%)

BRAF (5-10%)

PIK3CA and/or PTEN (15%)

KRAS/PIK3CA/PTEN

BRAF/PIK3CA/PTEN

HER2 amplification (3%)

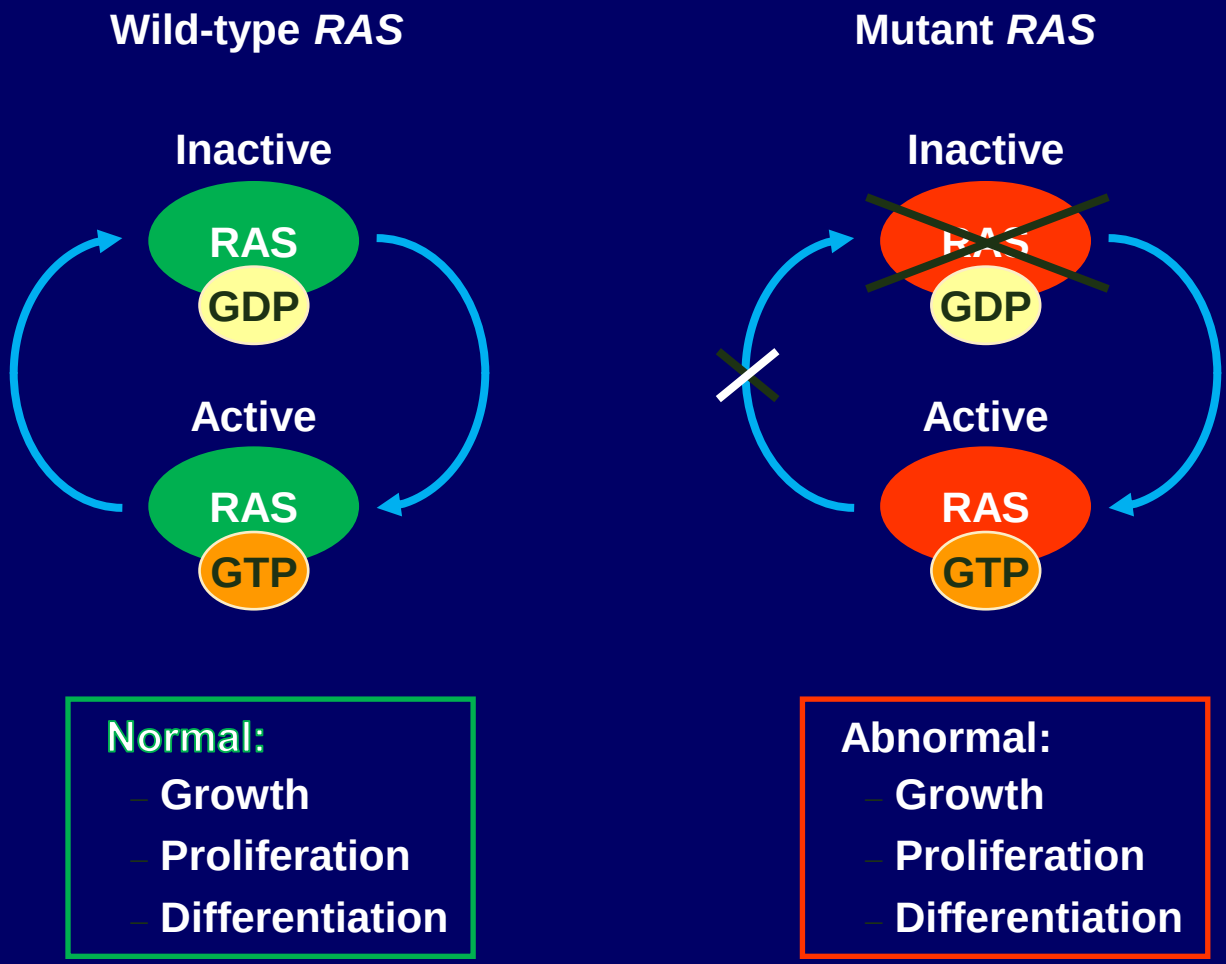
KRAS amplification (1%)

MET amplification (2%)

Non responder (16%)

Modified from Bardelli, J Clin Oncol 2010

RAS mutations induce continuous activation without retro-control



Normal:
- Growth
- Proliferation
- Differentiation

Abnormal:
- Growth
- Proliferation
- Differentiation

Schubbert S, et al. Nat Rev Cancer 2007;7:295–308.

Benefit from anti-EGFRs in the selected population early development late treatment lines

		mPFS (mos)			
	N	Cet	BSC	HR	p
Unselected	572	1.9	1.8	0.68	<0.001
***KRAS* exon 2 wt**	215	3.7	1.9	0.40	<0.001
***KRAS* exon 2 mut**	151	1.8	1.8	0.99	NS

Jonker et al, N Engl J Med 2007
Karapetis et al, N Engl J Med 2008

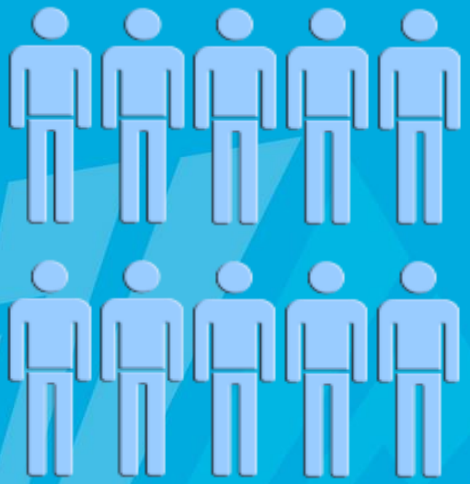
		mPFS (mos)			
	N	Pan	BSC	HR	p
Unselected	463	1.8	1.7	0.54	0.66
***KRAS* exon 2 wt**	243	2.8	1.7	0.45	<0.001
***KRAS* exon 2 mut**	184	1.7	1.7	0.99	NS

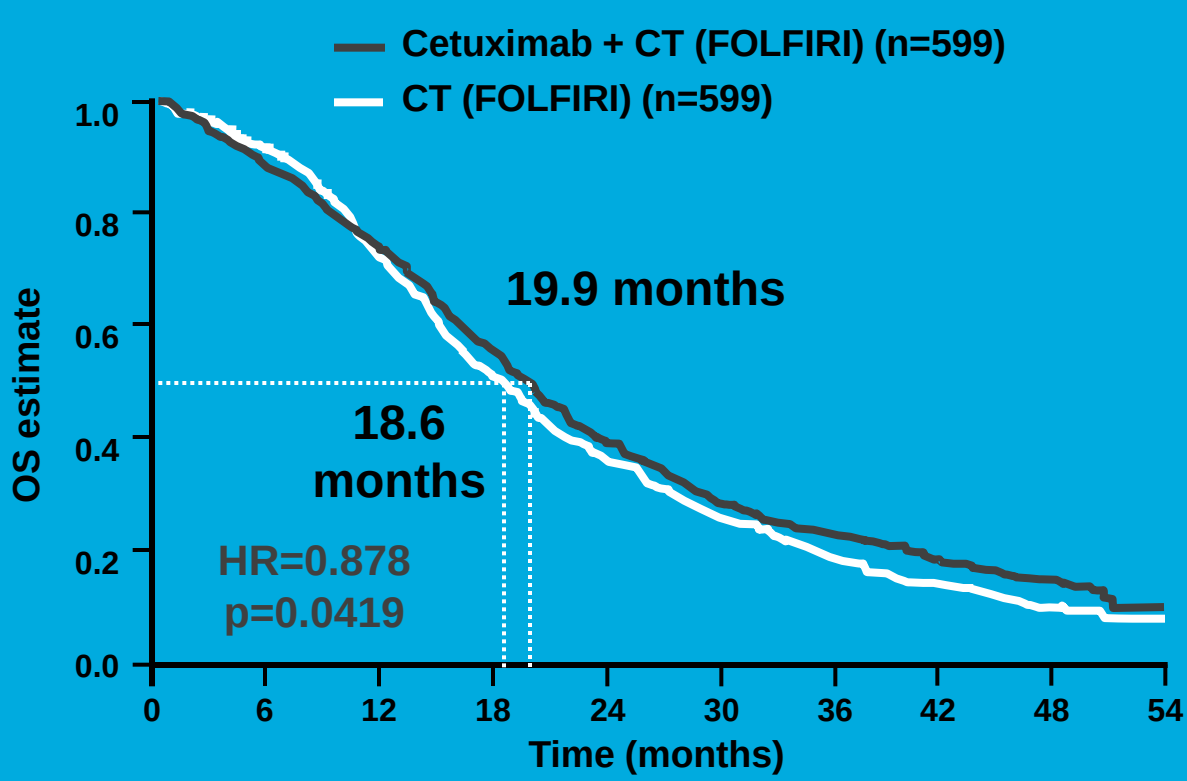
Van Cutsem et al, J Clin Oncol 2007
Amado et al, J Clin Oncol 2008

The magnitude of benefit from anti-EGFR moAbs is amplified in *KRAS* exon 2 wt population

Crystal study in mCRC
no biomarker

Overall patient population

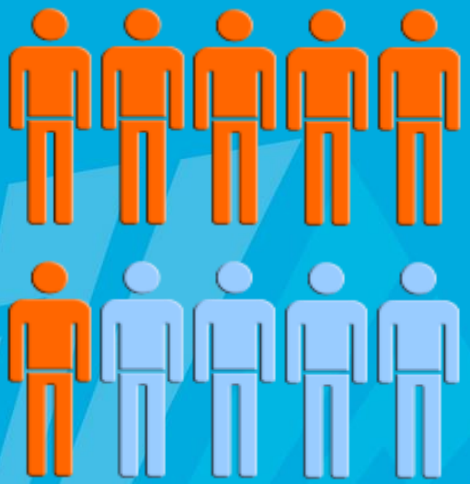




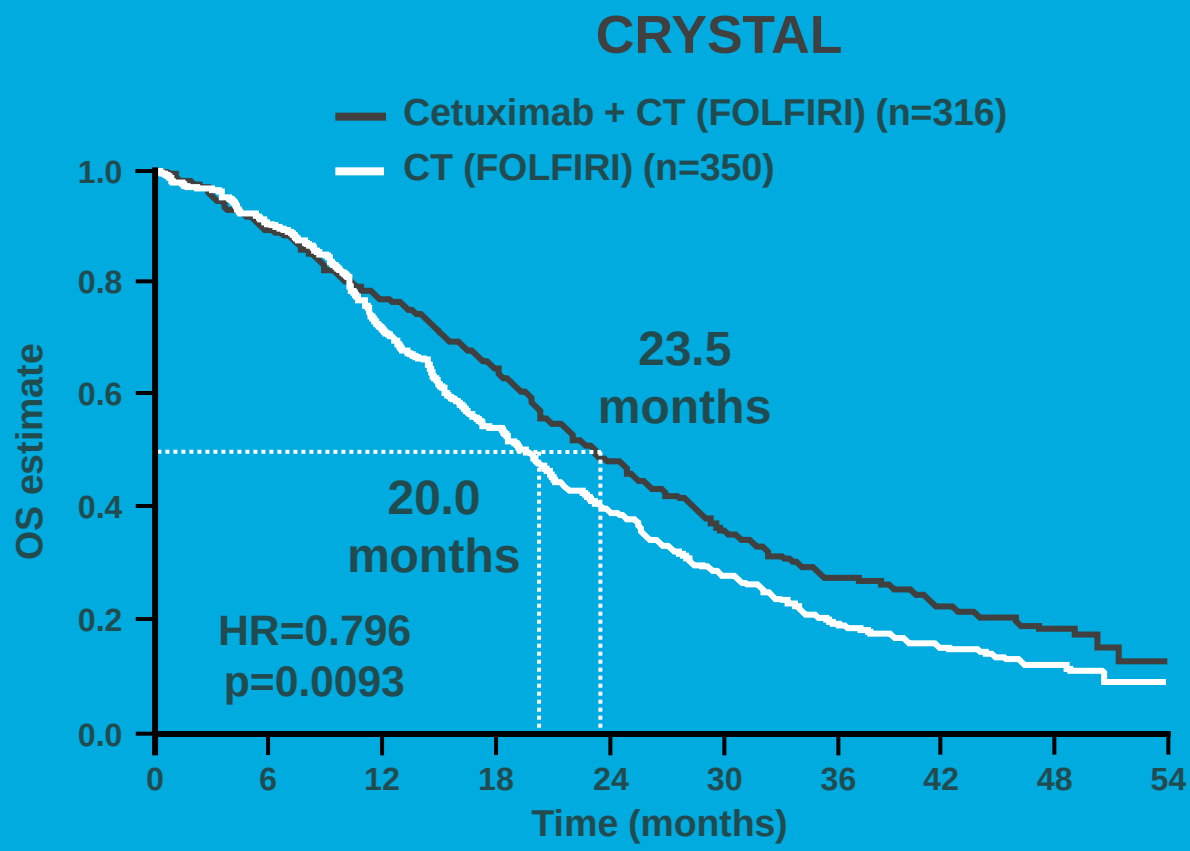
Van Cutsem E, et al. J Clin Oncol 2011;29:2011–2019

Crystal study in mCRC: KRAS (exon 2) status as a biomarker

KRAS wt (exon 2) population



60% of overall population



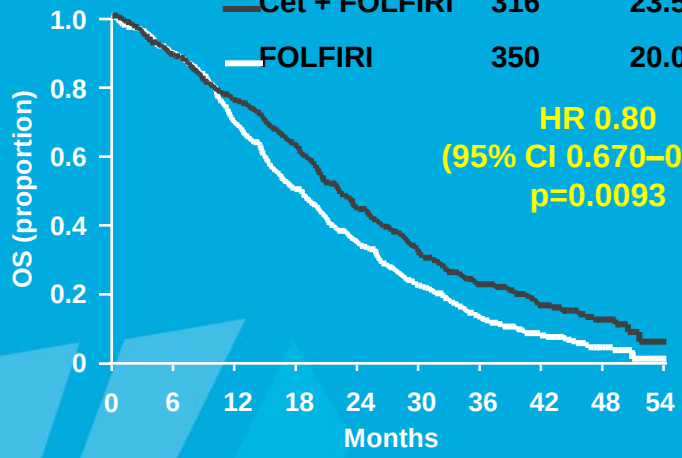
Van Cutsem E, et al. J Clin Oncol 2011;29:2011–2019

Effect of EGFR inhibitor treatment in KRAS (exon 2) wt population: Consistency of data across trials

CRYSTAL[1]

	n	OS, months (95% CI)
Cet + FOLFIRI	316	23.5 (21.2–26.3)
FOLFIRI	350	20.0 (17.4–21.7)

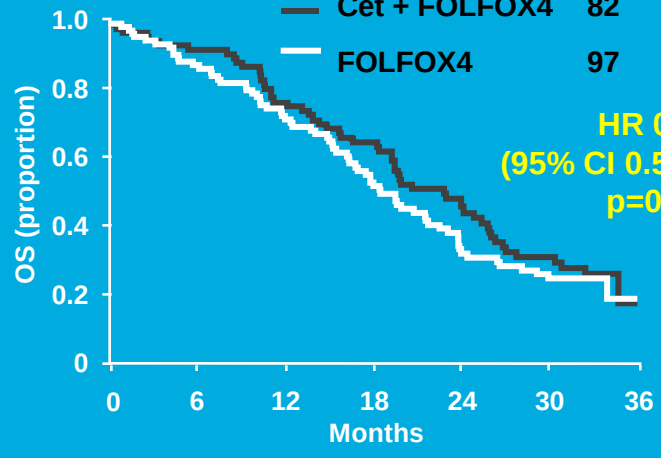
HR 0.80
(95% CI 0.670–0.946)
p=0.0093



OPUS[2]

	n	OS, months (95% CI)
Cet + FOLFOX4	82	22.8 (19.3–25.9)
FOLFOX4	97	18.5 (16.4–22.6)

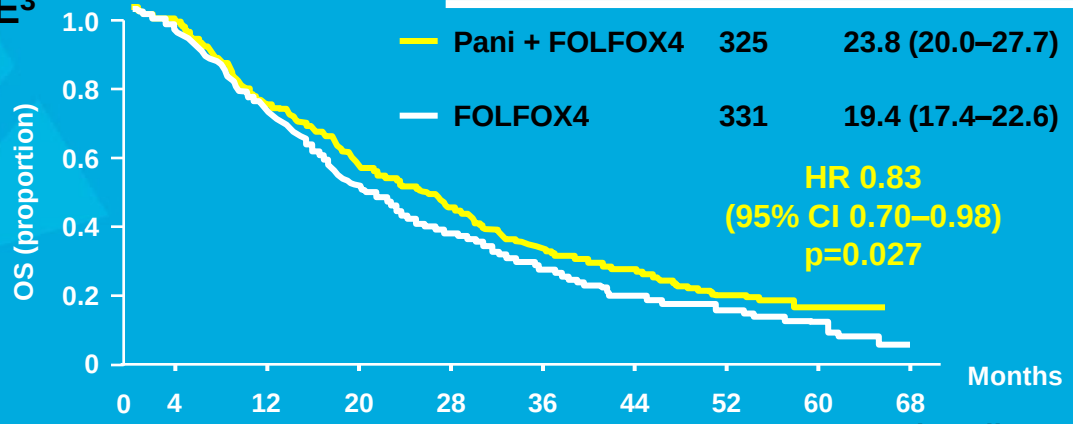
HR 0.86
(95% CI 0.599–1.219)
p=0.39



PRIME[3]

	n	OS, months (95% CI)
Pani + FOLFOX4	325	23.8 (20.0–27.7)
FOLFOX4	331	19.4 (17.4–22.6)

HR 0.83
(95% CI 0.70–0.98)
p=0.027

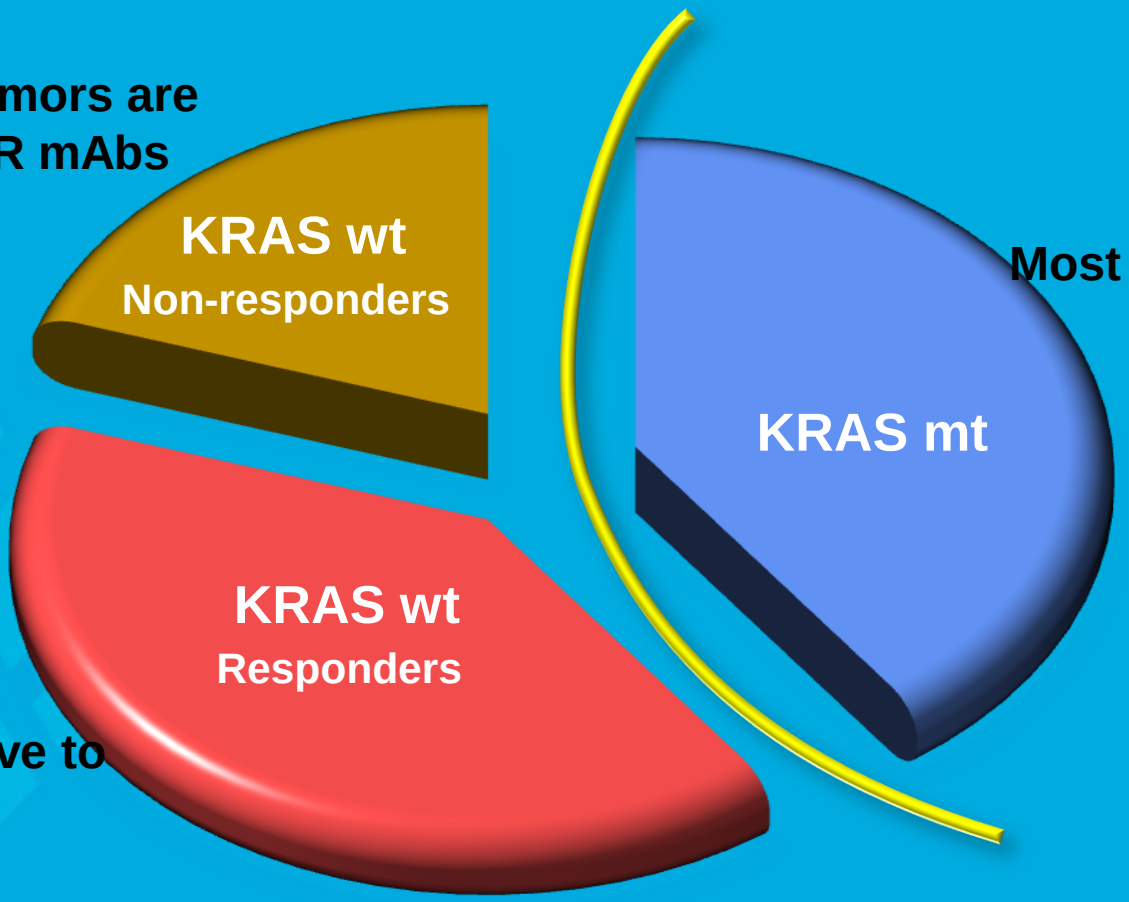


Cetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown[4]

1. Van Cutsem E, et al. J Clin Oncol 2011;29:2011–2019
2. Bokemeyer C, et al. Ann Oncol 2011;22:1535–1546
3. Douillard J-Y, et al. J Clin Oncol 31, 2013 (suppl; abstr 3620)
4. Erbitux SmPC June/2014

KRAS wt or mt status:
until recently the only validated predictive biomarker for anti-EGFR antibodies in mCRC

Some KRAS wt tumors are resistant to EGFR mAbs

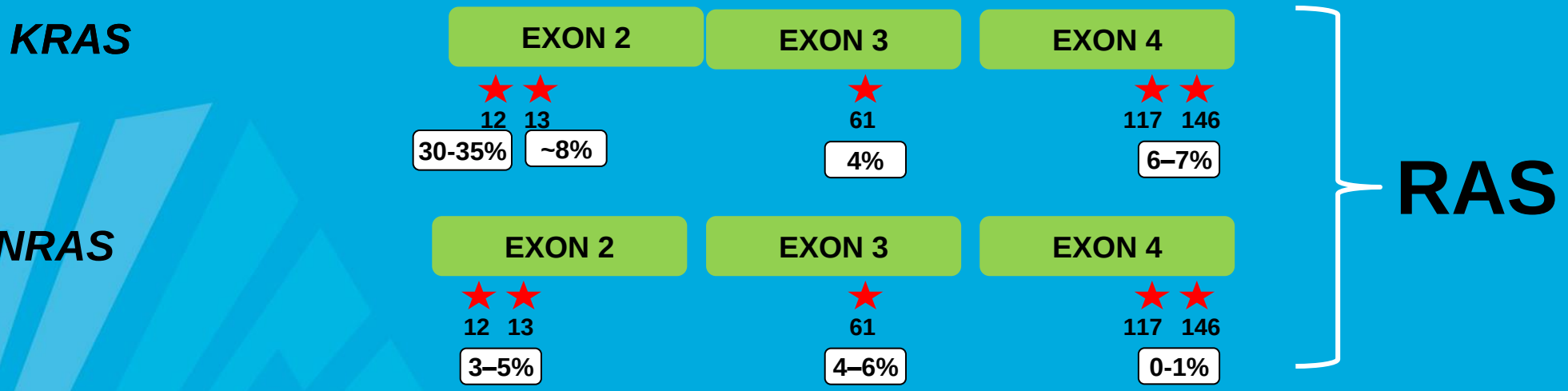


Most KRAS mutant tumors are resistant to EGFR mAbs

Many KRAS wt tumors are responsive to EGFR mAbs

Hotspots of Mutations in *KRAS and NRAS*

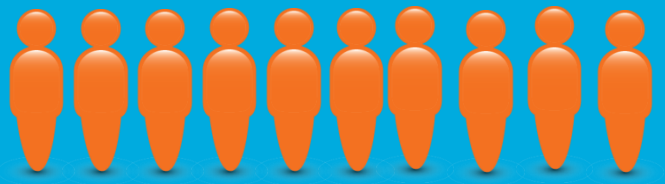
Initially: *KRAS* testing identifies mutations in codons 12 and 13 of exon 2



***KRAS/NRAS* mutations outside *KRAS* exon 2 are now tested before using cetuximab and panitumumab**

CRYSTAL: RAS wt selection extended the PFS benefit with cetuximab + FOLFIRI

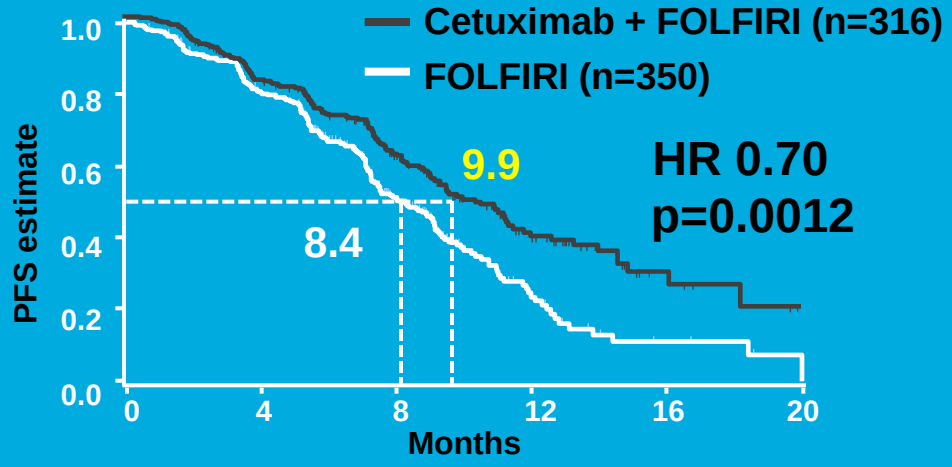
KRAS exon 2 wt population[1]

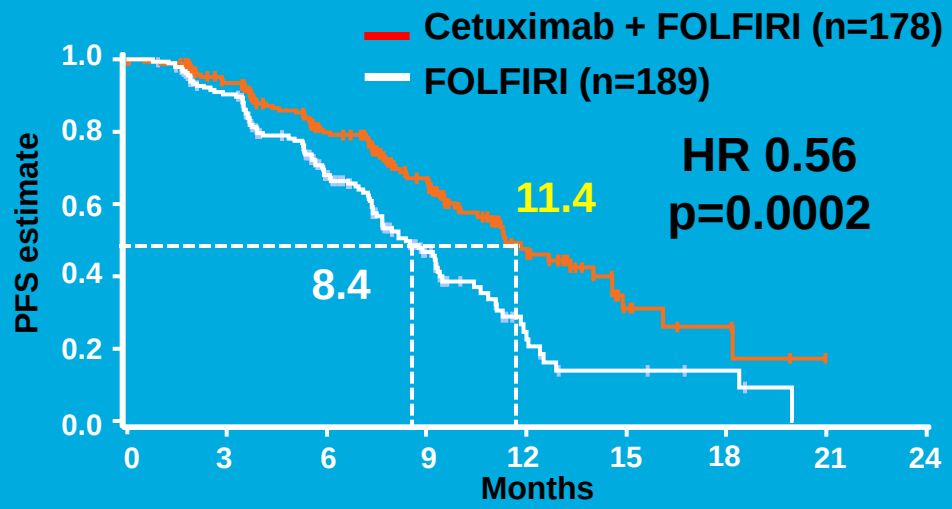


RAS wt population (85%) [2]

367/430 patients with KRAS exon 2 wt tumors evaluated for RAS status were RAS wt

Cetuximab should not be used for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown[3]



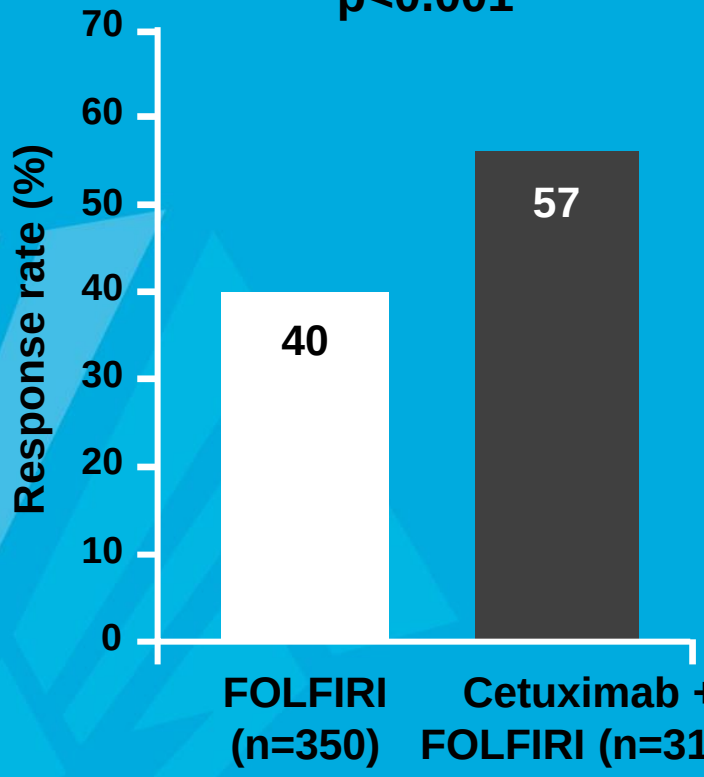


1. Van Cutsem E, et al. J Clin Oncol 2011;29:2011–2019
2. Van Cutsem E, et al. J Clin Oncol 2015
3. Erbitux SmPC June/2014

CRYSTAL: RAS wt selection extended the ORR benefit with cetuximab + FOLFIRI

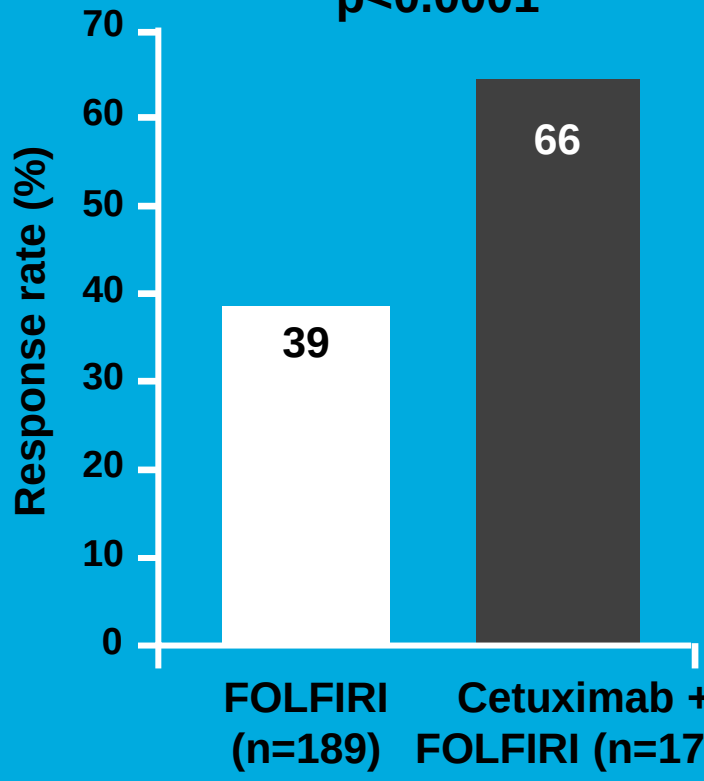
KRAS exon 2 wt[1]

OR 2.069
p<0.001



RAS wt* (subgroup)[2]

OR 3.11
p<0.0001

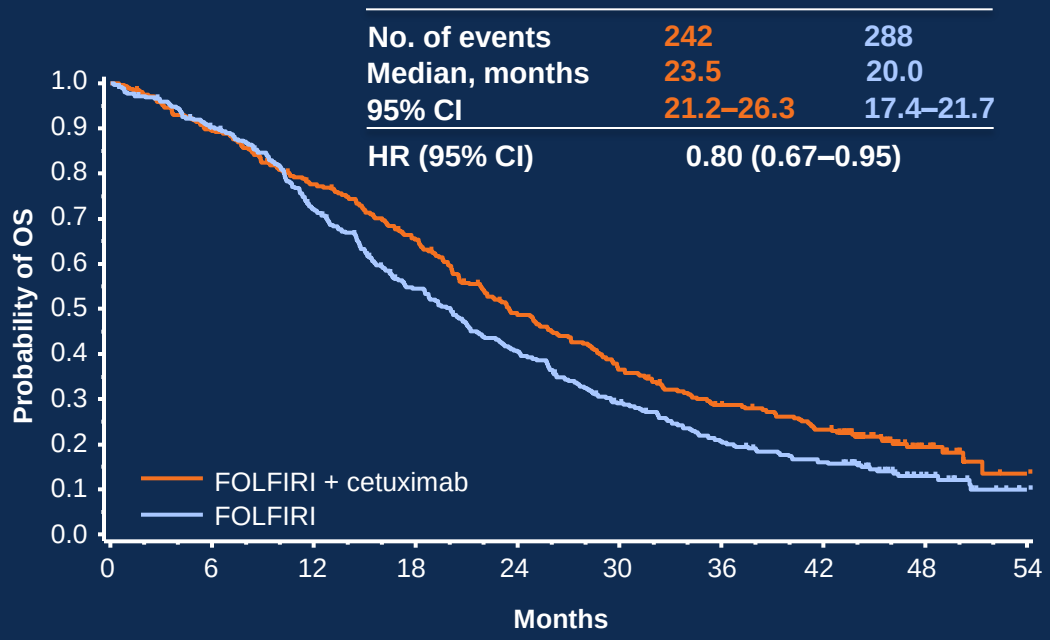


*RAS evaluable in 430/666 (65%) patients with KRAS exon 2 wt mCRC; RAS wt: 367/430 (85%), 5% sensitivity cut-off; cetuximab is not indicated for the treatment of patients with mCRC whose tumors have RAS mutations or for whom RAS tumor status is unknown[3]

1. Van Cutsem E, et al. J Clin Oncol 2011;29:2011–2019
2. Van Cutsem E, et al. J Clin Oncol 2015
3. Erbitux SmPC June/2014

Crystal study: Overall survival

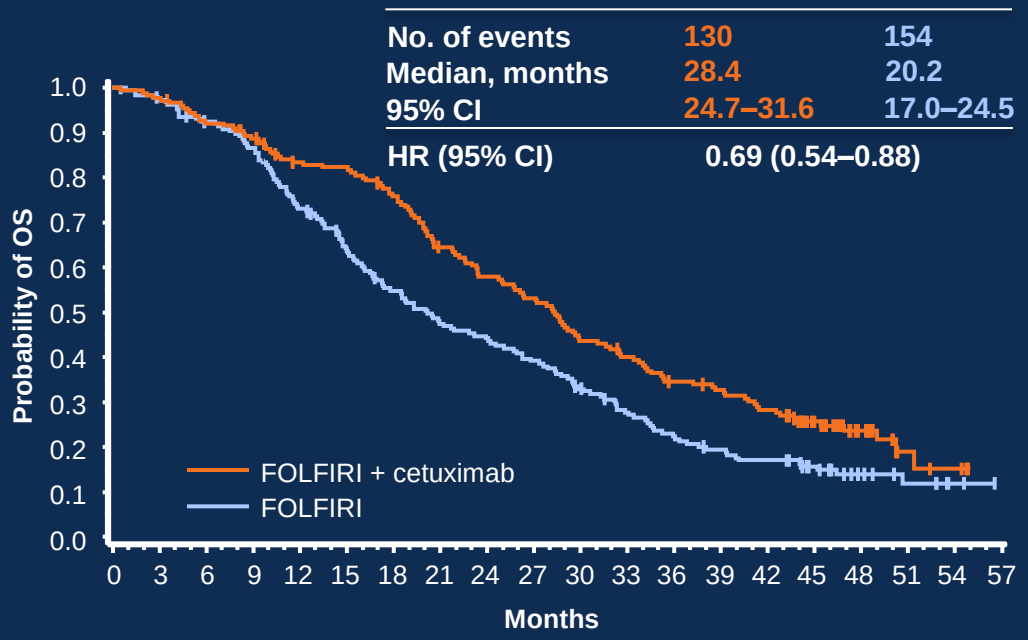
KRAS codon 12/13 wild-type*



Number of patients at risk

316	281	237	198	144	108	82	65	21	4
350	311	246	179	132	92	64	48	18	2

RAS wild-type



Number of patients at risk

178	174	163	155	142	140	128	108	97	89	73	66	56	52	45	29	16	5	3	0
189	182	171	160	135	115	98	85	79	70	58	47	38	32	28	20	10	6	2	0

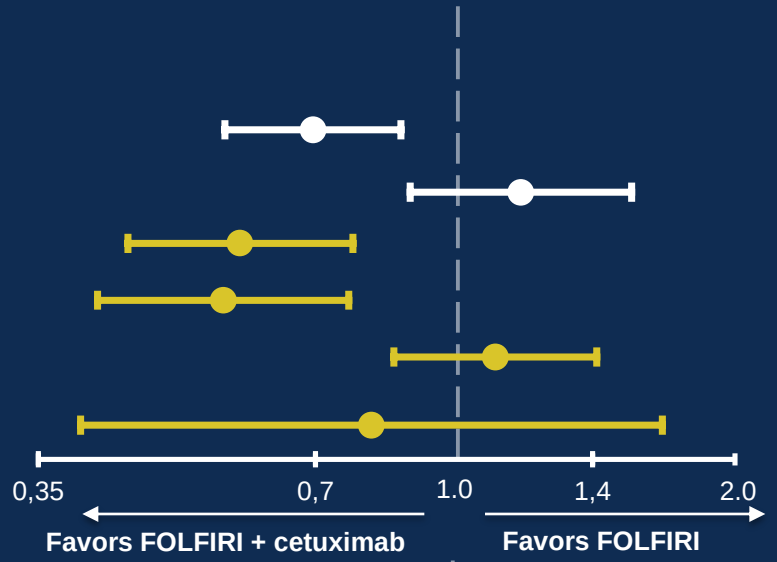
*Van Cutsem E, et al. J Clin Oncol 2011;29:2011-9

E Van Cutsem et al, J Clin Oncol 2015

Crystal study: Efficacy: *RAS* subgroups

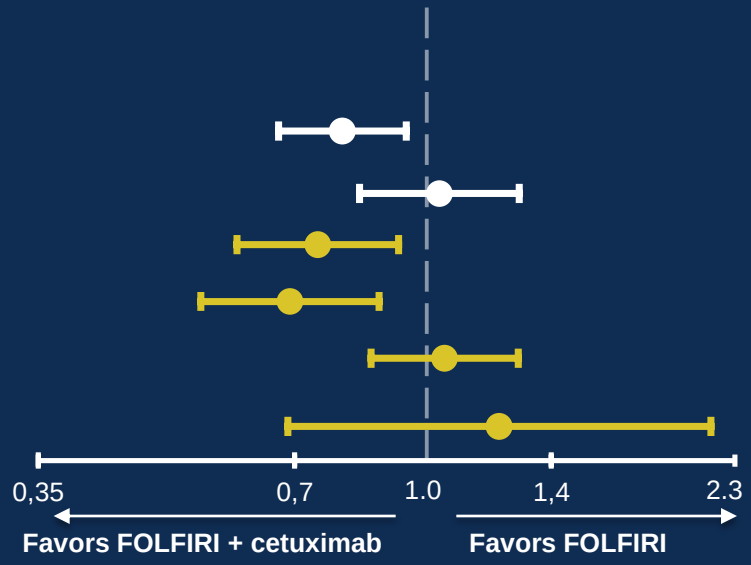
PFS

Subgroup	n	HR (95% CI)
KRAS codon 12/13 WT	666	0.70 (0.56–0.87)
KRAS codon 12/13 MT	397	1.17 (0.89–1.54)
RAS evaluable*	430	0.58 (0.44–0.77)
RAS WT	367	0.56 (0.41–0.76)
Any *RAS* MT†	460	1.10 (0.85–1.42)
Other *RAS* MT*	63	0.81 (0.39–1.67)



OS

Subgroup	n	HR (95% CI)
KRAS codon 12/13 WT	666	0.80 (0.67–0.95)
KRAS codon 12/13 MT	397	1.04 (0.83–1.28)
RAS evaluable*	430	0.75 (0.60–0.93)
RAS WT	367	0.69 (0.54–0.88)
Any *RAS* MT†	460	1.05 (0.86–1.28)
Other *RAS* MT*	63	1.22 (0.69–2.16)



***KRAS codon 12/13 WT; †KRAS codon 12/13 or other RAS MT, mutant; WT, wild-type**

Expanded RAS mutation in PRIME

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Panitumumab–FOLFOX4 Treatment and *RAS* Mutations in Colorectal Cancer

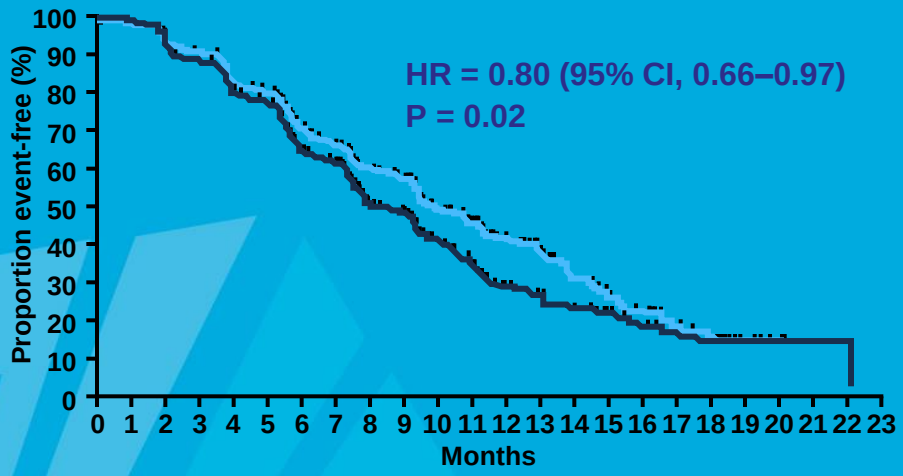
Jean-Yves Douillard, M.D., Ph.D., Kelly S. Oliner, Ph.D., Salvatore Siena, M.D., Josep Tabernero, M.D., Ronald Burkes, M.D., Mario Barugel, M.D., Yves Humblet, M.D., Ph.D., Gyorgy Bodoky, M.D., Ph.D., David Cunningham, M.D., Jacek Jassem, M.D., Ph.D., Fernando Rivera, M.D., Ph.D., Ilona Kocákova, M.D., Ph.D., Paul Ruff, M.D., Maria Błasińska-Morawiec, M.D., Martin Šmakal, M.D., Jean Luc Canon, M.D., Mark Rother, M.D., Richard Williams, M.B., B.S., Ph.D., Alan Rong, Ph.D., Jeffrey Wiezorek, M.D., Roger Sidhu, M.D., and Scott D. Patterson, Ph.D.

N Engl J Med 2013; 369:1023-34

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

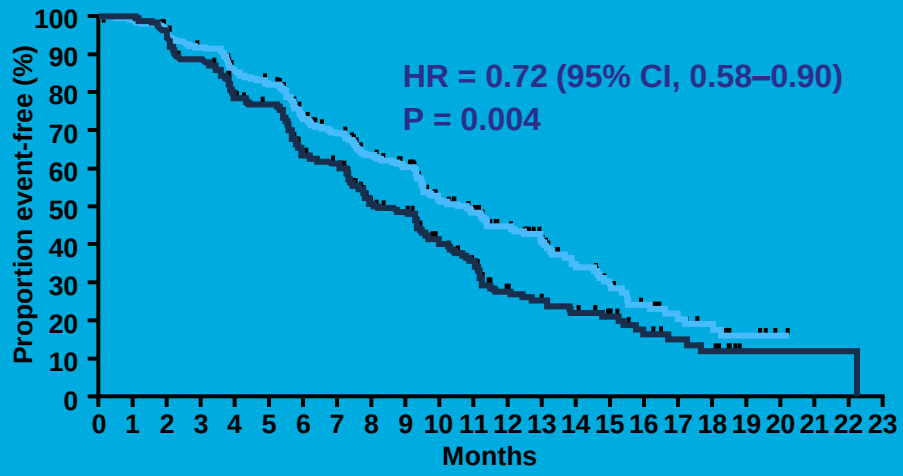
Progression-free survival

Original WT *KRAS* exon 2 testing



	Events n (%)	Median (95% CI) months
Panitumumab + FOLFOX4 (n = 325)	199 (61)	9.6 (9.2–11.1)
FOLFOX4 (n = 331)	215 (65)	8.0 (7.5–9.3)

WT *RAS*



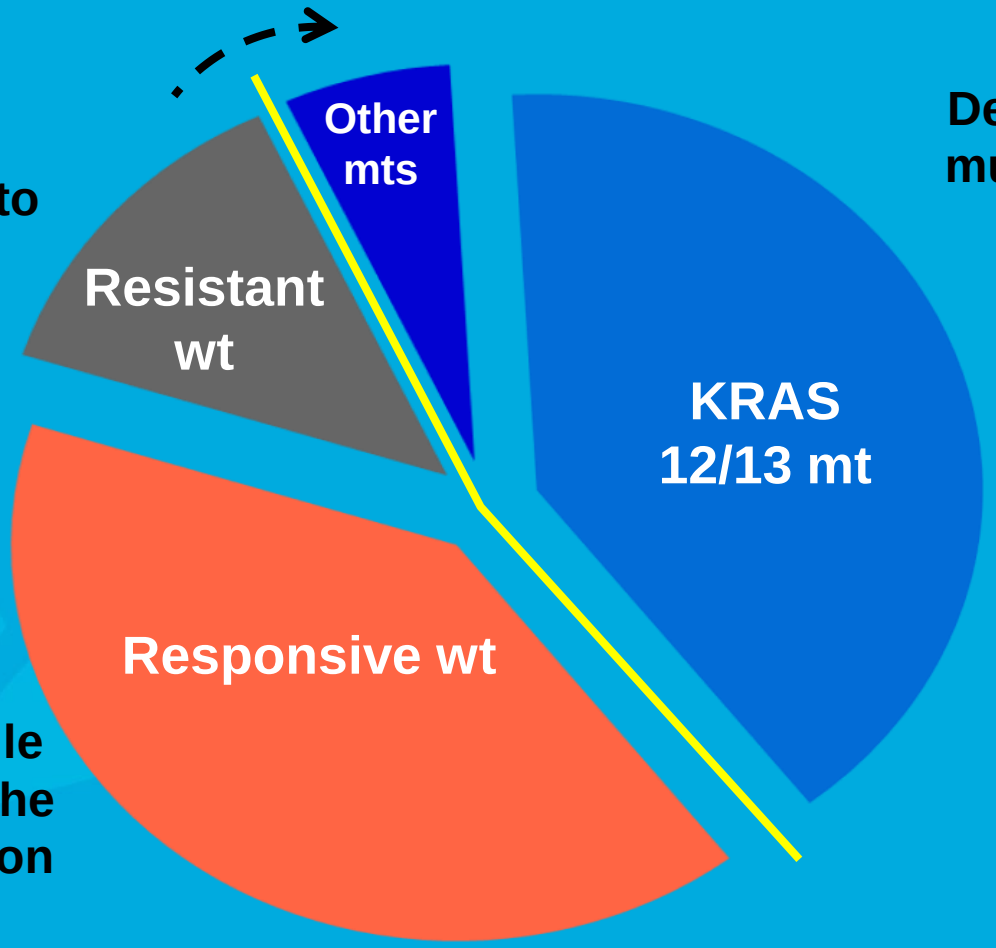
	Events n (%)	Median (95% CI) months
Panitumumab + FOLFOX4 (n = 259)	156 (60)	10.1 (9.3–12.0)
FOLFOX4 (n = 253)	170 (67)	7.9 (7.2–9.3)

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

Douillard JY, et al. N Engl J Med 2013; 369:1023-34,

Excluding additional mutant tumors increases the relative proportion of responsive wt tumors

Increasing relative proportion of wt population responsive to EGFR mAbs



Detection of additional mutant tumors that are resistant to EGFR mAbs

Enhanced benefit profile for EGFR inhibitors in the more selected population

Are all *KRAS* mutations equal?

***KRAS* mutation frequency in patients with CRC: ~40%**

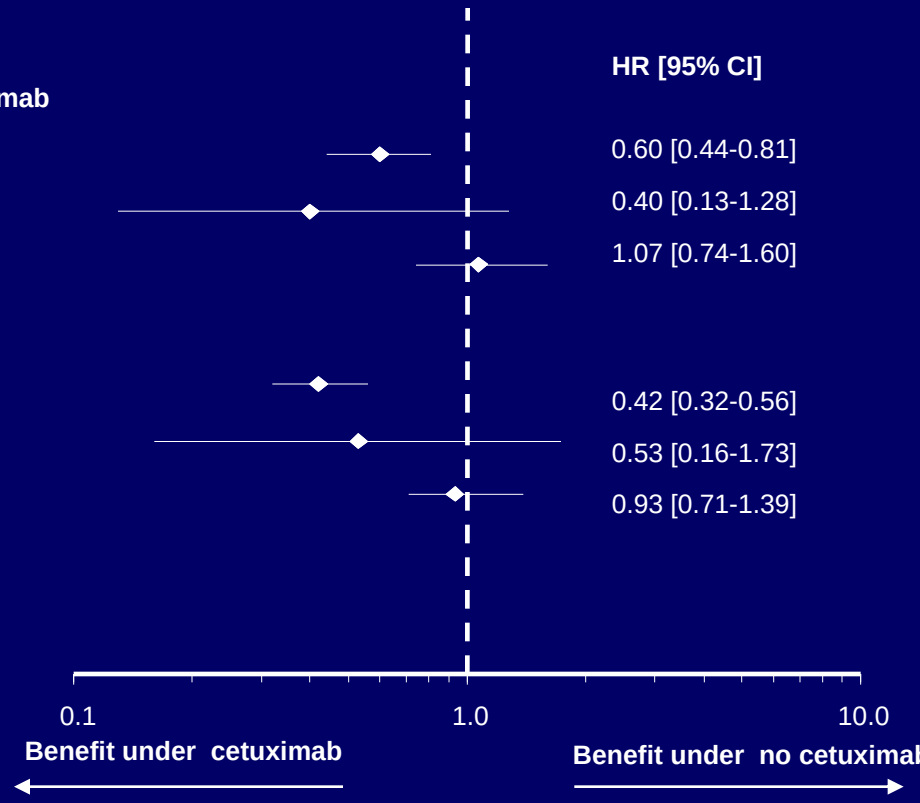
KRAS mutation			
Amino acid substitution	**Nucleic acid substitution**	**Relative Incidence %**	**Absolute Incidence %**
Codon 12 mutations			
Aspartate (G12D)	G35A	32.5	13
Valine (G12V)	G35T	22.5	9
Cysteine (G12C)	G34T	8.8	3
Serine (G12S)	G34A	7.6	3
Alanine (G12A)	G35C	6.4	3
Arginine (G12R)	G34C	0.9	0.4
Codon 13 mutations			
Aspartate (G13D)	G38A	19.5	8
Other mutations		1.8	0.7

Normanno N, et al. Nat Rev Clin Onc 2009;6:519-27

Differential effects of *KRAS* mutations in chemorefractory mCRC

- In patients receiving cetuximab monotherapy PFS and OS was longer for those with *KRAS* G13D mutated tumors vs other *KRAS* mutations[1]
- Patients with *KRAS* G13D mutant tumors have a worse prognosis under BSC[1]

KRAS subset		Median in months [95%CI] Any cetuximab vs. no cetuximab	HR [95% CI]
OS	wt	10.1 [9.4-11.3] vs. 5.0 [4.2-5.5]	0.60 [0.44-0.81]
	G13D mt	7.6 [5.7-20.5] vs. 3.6 [2.2-4.8]	0.40 [0.13-1.28]
	mt-other	5.7 [4.9-6.8] vs. 4.7 [3.6-6.7]	1.07 [0.74-1.60]
PFS	wt	4.2 [3.9-5.4] vs. 1.9 [1.8-2.0]	0.42 [0.32-0.56]
	G13D mt	4.0 [1.9-6.2] vs. 1.7 [1.5-1.7]	0.53 [0.16-1.73]
	mt-other	1.9 [1.8-2.8] vs. 1.8 [1.7-1.9]	0.93 [0.71-1.39]

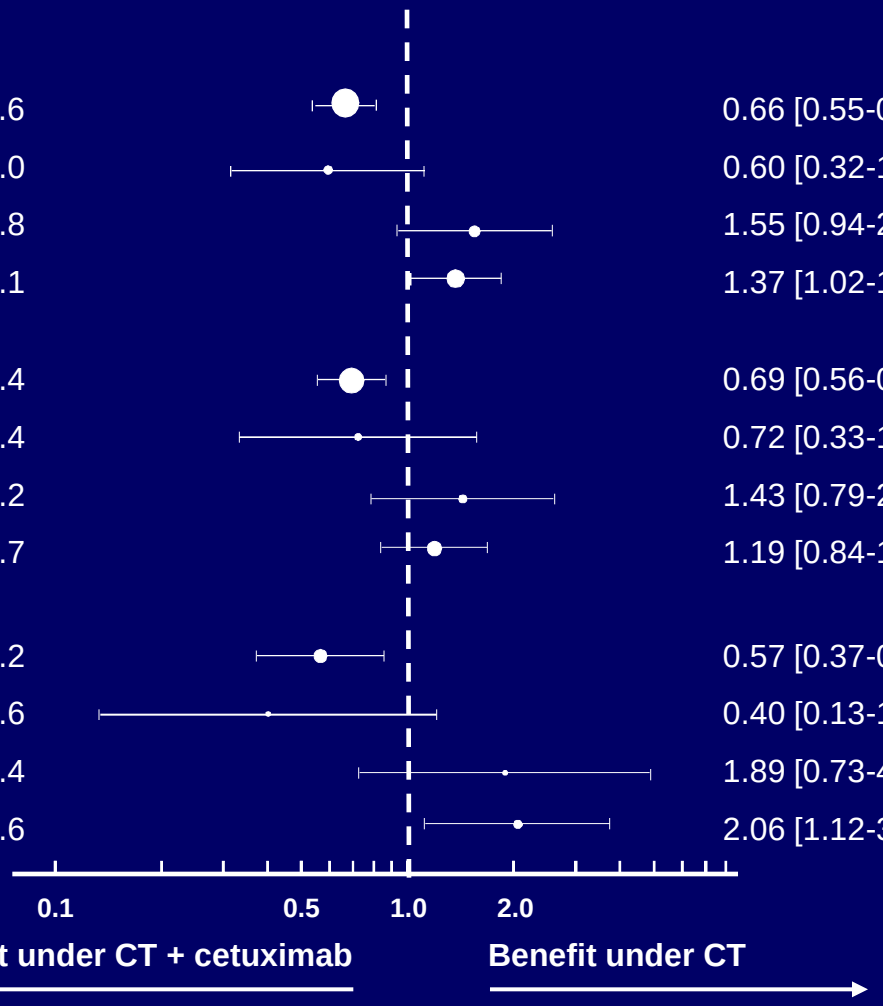


BSC, best supportive care; CT, chemotherapy

[1]De Roock W,, Van Cutsem E, Tejpar S et al. JAMA 2010;304:1812-1820

KRAS mutation status and treatment effect: PFS

Study	Population (*KRAS* mutation)	Median (months) CT + cetuximab vs CT	HR [95% CI]
Pooled analysis	wt (n=845)	9.6 vs 7.6	0.66 [0.55-0.80]
	mt G13D (n=83)	7.4 vs 6.0	0.60 [0.32-1.12]
	mt G12V (n=125)	5.6 vs 8.8	1.55 [0.94-2.56]
	mt other (n=325)	6.7 vs 8.1	1.37 [1.02-1.84]
CRYSTAL	wt (n=666)	9.9 vs 8.4	0.69 [0.56-0.86]
	mt G13D (n=60)	7.5 vs 7.4	0.72 [0.33-1.57]
	mt G12V (n=91)	6.7 vs 8.2	1.43 [0.79-2.59]
	mt other (n=246)	7.1 vs 7.7	1.19 [0.84-1.68]
OPUS	wt (n=179)	8.3 vs 7.2	0.57 [0.37-0.86]
	mt G13D (n=23)	5.7 vs 5.6	0.40 [0.13-1.21]
	mt G12V (n=34)	4.4 vs 9.4	1.89 [0.73-4.86]
	mt other (n=79)	5.5 vs 8.6	2.06 [1.12-3.76]



CT, chemotherapy; mt, mutant; wt, wild-type

Tejpar S,…Van Cutsem E, J Clin Oncol 2012

Mutant KRAS Codon 12 and 13 alleles in mCRC: Panitumumab studies

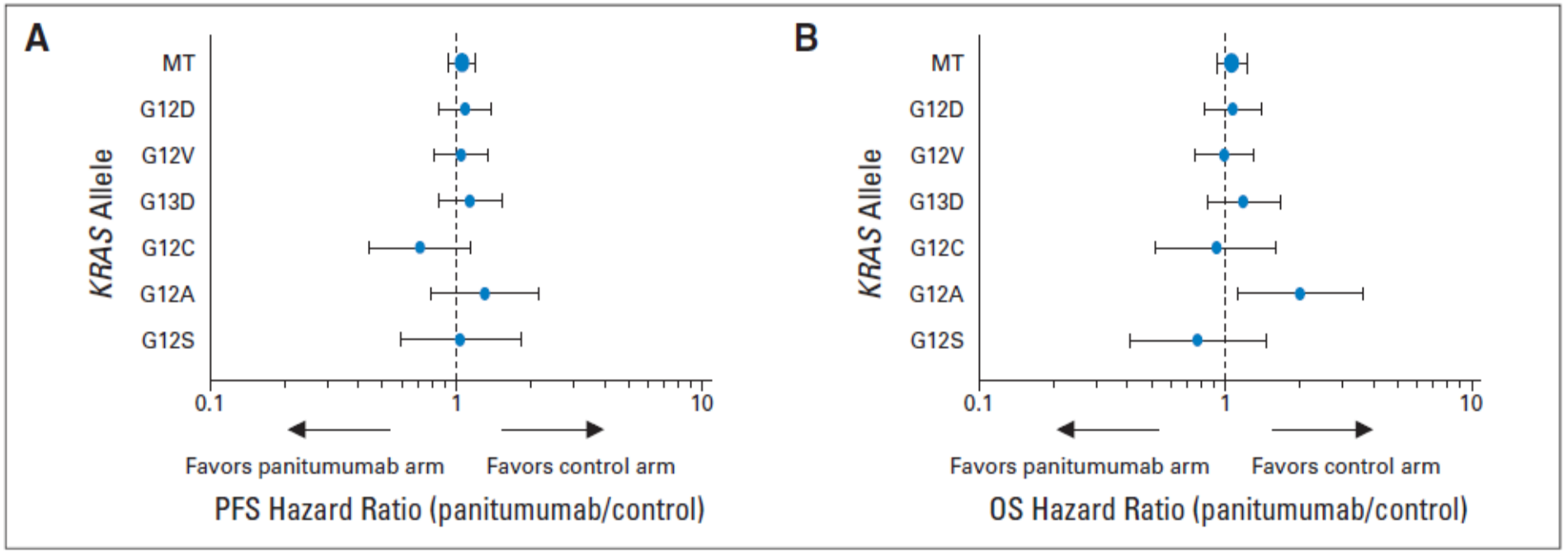


Fig 3. Pooled analysis of studies 20050203, 20050181, and 20020408: Predictive impact of mutant (MT) *KRAS* codon 12 and 13 alleles on (A) progression-free survival (PFS) and (B) overall survival (OS) in patients receiving either control (non–panitumumab-containing) or panitumumab-containing therapy. Point estimates for hazard ratios and their corresponding 95% CIs are plotted for the indicated mutant *KRAS* codon 12 and 13 alleles and are compared with the other mutant *KRAS* codon 12 and 13 alleles as a group.

Peeters M,…. Van Cutsem E et al, J Clin Onc 2012

ICECREAM Study schema

AGITG

refractory mCRC (n=100) either
quad WT (no mut in *KRAS*, *BRAF, NRAF, PIK3CA* ex 20)
OR *KRAS* G13D mutation

RANDOMISATION 1:1
Stratified by:
Mutation status (quad WT vs G13D)
Institution

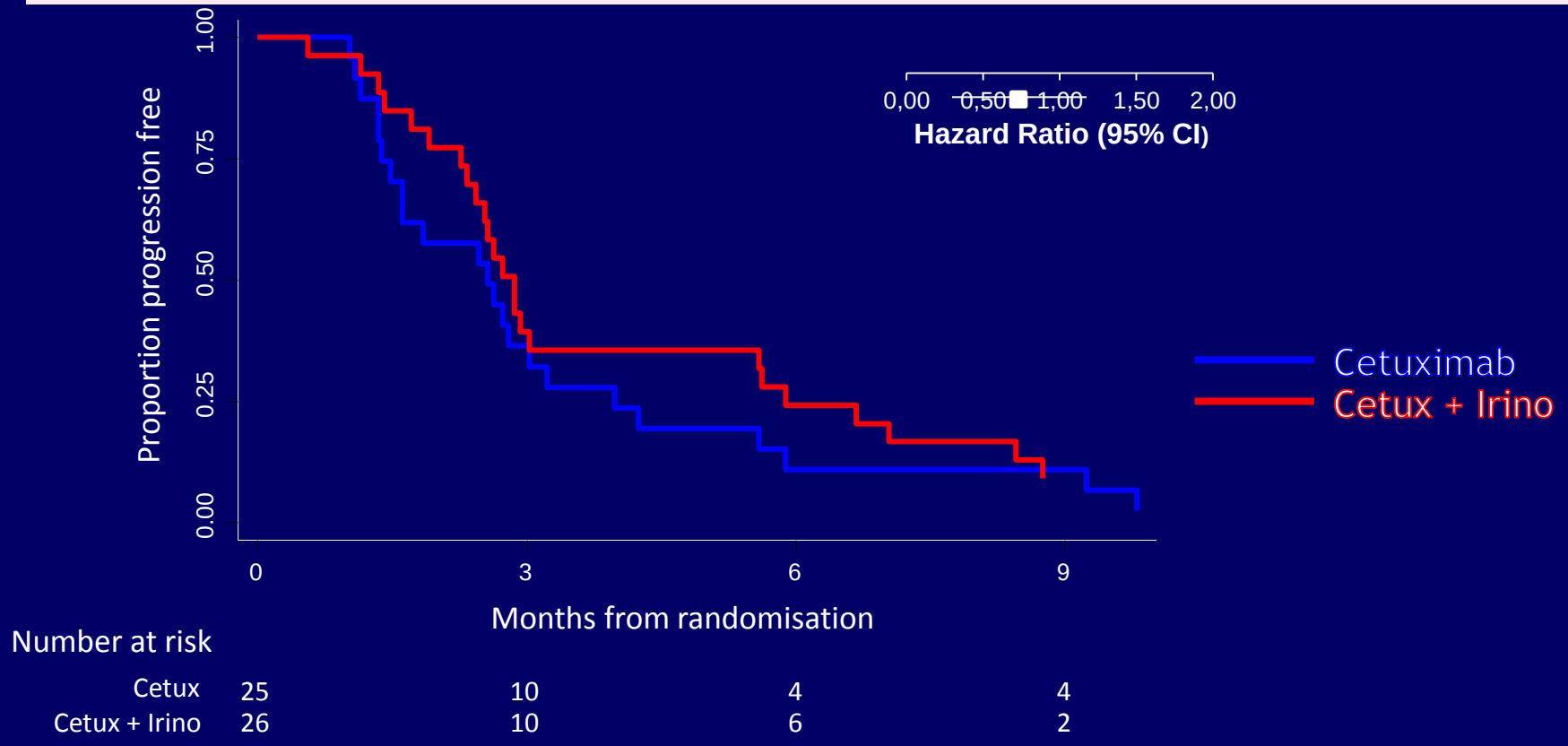
cetuximab
400mg/m^2 loading then
250mg/m^2 weekly

cetuximab + irinotecan
400mg/m^2 loading then
250mg/m^2 weekly
Irinotecan 180mg/m^2 q 14 days

Segelov E et al, ECC/ESMO 2015

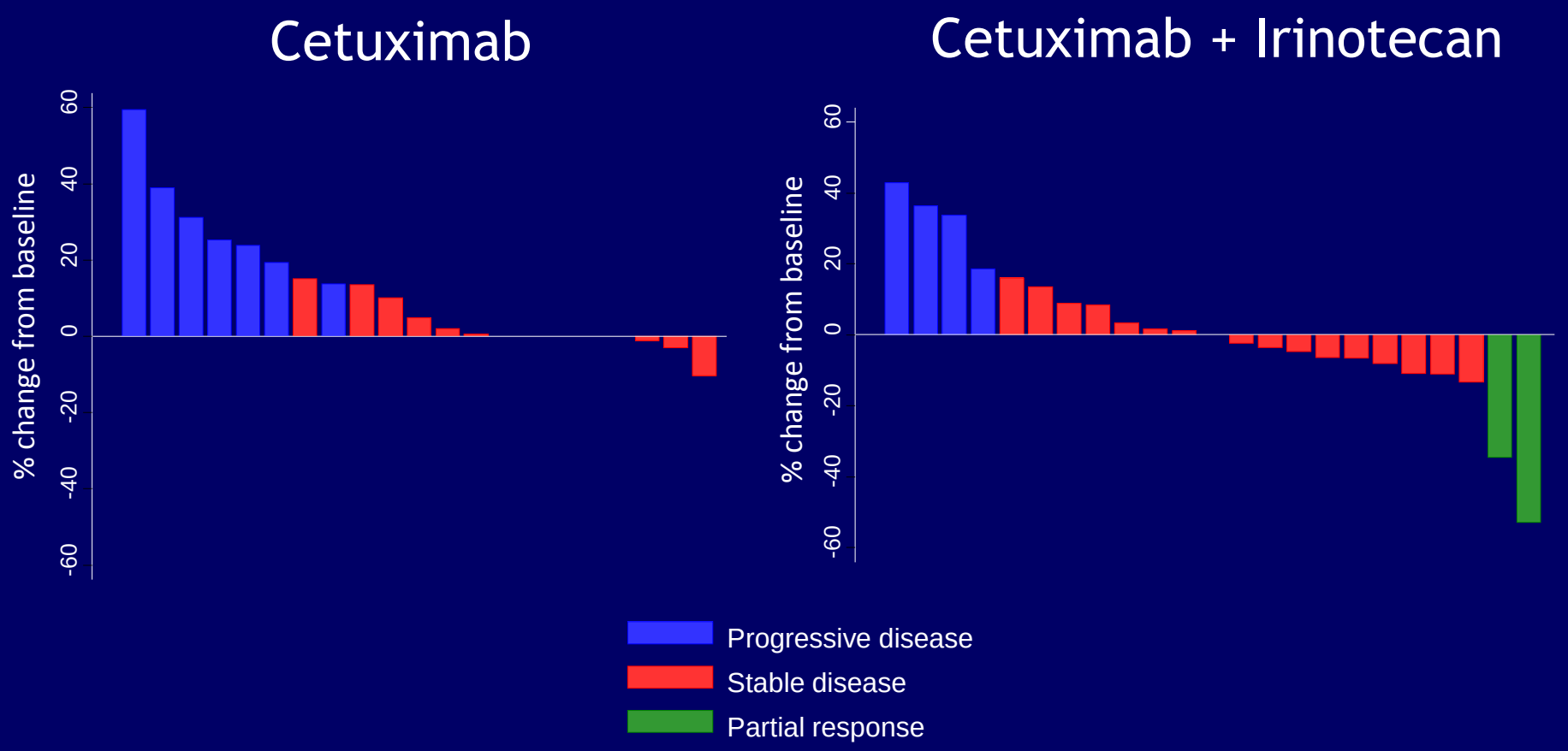
ICECREAM:
G13D: 6 months Progression Free Survival

	Cetuximab	Cetux+ Irino
% event free at 6 m (95% CI)	**10 %** (2-26%)	**23%** (9-40%)



Segelov E et al, ECC/ESMO 2015

ICECREAM
G13D: Maximal tumour response



Segelov E et al, ECC/ESMO 2015

Molecular Pathology and Biomarkers

Recommendation: RAS testing

- ***RAS* is a predictive biomarker for therapeutic choices** involving EGFR antibody therapies in the metastatic disease setting [1, A].
- ***RAS* testing is mandatory prior to treatment** with EGFR-targeted monoclonal antibodies cetuximab and panitumumab [1, A].
- Primary or metastatic colorectal tumour tissue can be used for *RAS* testing (see also *Recommendation 3*).
- ***RAS* analysis** should include at least *KRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and *NRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117).
- **Turnaround time for *RAS* testing** (expanded *RAS* analysis) should be ≤7 working days from the time of receipt of the specimen by the testing laboratory to the time of issuing of the final report, for >90% of specimens.

Molecular Pathology and Biomarkers

Recommendation: BRAF testing

- Tumour ***BRAF* mutation** status should be assessed alongside the assessment of tumour *RAS* mutational status for prognostic assessment and/or potential selection for clinical trials [1, B].

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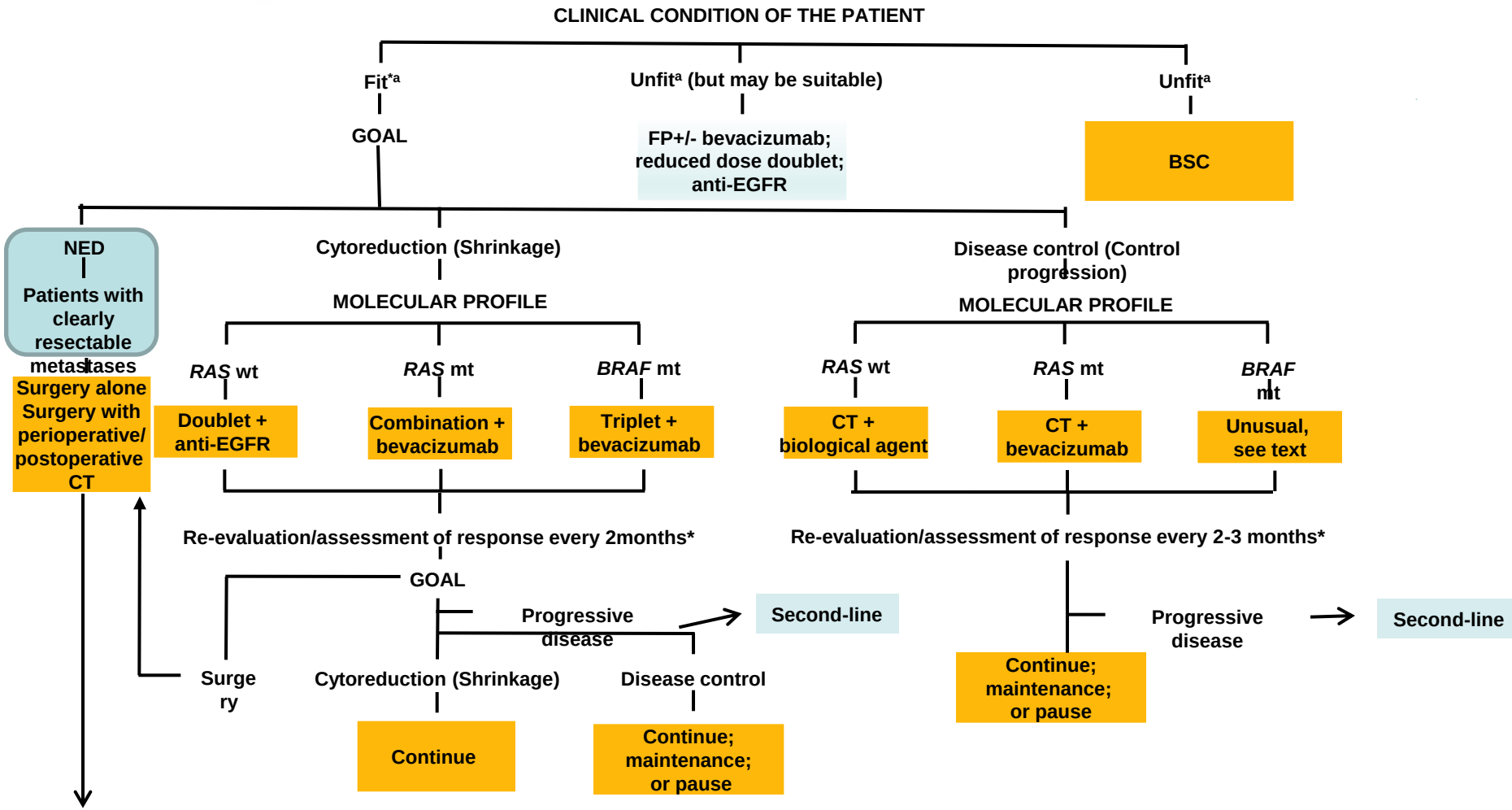
Treatment of metastatic disease



Van Cutsem E, Cervantes A, Arnold D et al, ESMO consensus 2015
@ ESMO/WCGIC Barcelona 2015

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Treatment of metastatic disease

Anti-EGFR´s in later lines

- In *RAS* wild-type and *BRAF* wild-type patients not previously treated with EGFR antibodies cetuximab or panitumumab therapy should be considered
  - Cetuximab and panitumumab equally active as single agents
  - The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients
  - There is no unequivocal evidence to administer the alternate anti-EGFR antibody, if a patient is refractory to one of the anti-EGFR antibodies.

Van Cutsem E, Cervantes A, Arnold D et al, ESMO consensus 2015 @ ESMO/WCGIC Barcelona 2015

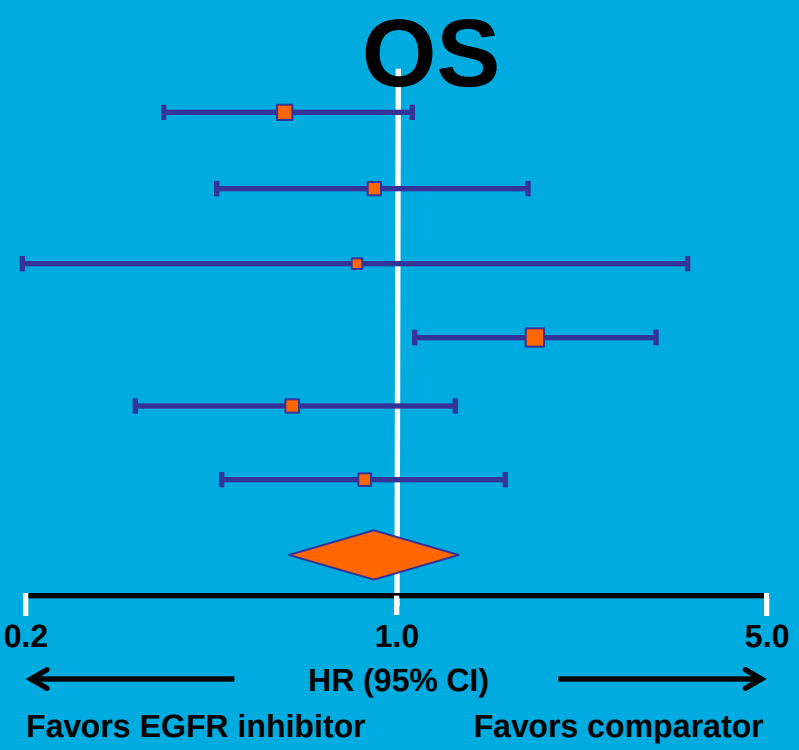
Pietrantonio meta-analysis: OS (BRAF mt)[1]

- No significant benefit in OS demonstrated with anti-EGFR therapy vs standard care in patients with (K)RAS wt/BRAF mt

Trial (n)	Weight, %	OS HR (95% CI)
OPUS/CRYSTAL	20.7	0.62 (0.36–1.06)
PRIME	17.0	0.90 (0.46–1.76)
CO.17	6.0	0.84 (0.20–3.56)
PICCOLO	21.5	1.84 (1.10–3.08)
20050181	16.4	0.64 (0.32–1.28)
FIRE-3	18.5	0.87 (0.47–1.61)
Summary	**100.0**	**0.91 (0.62–1.34)**

Heterogeneity: τ^2=0.11; χ^2=10.09; df=5 (p=0.07); I^2=50%

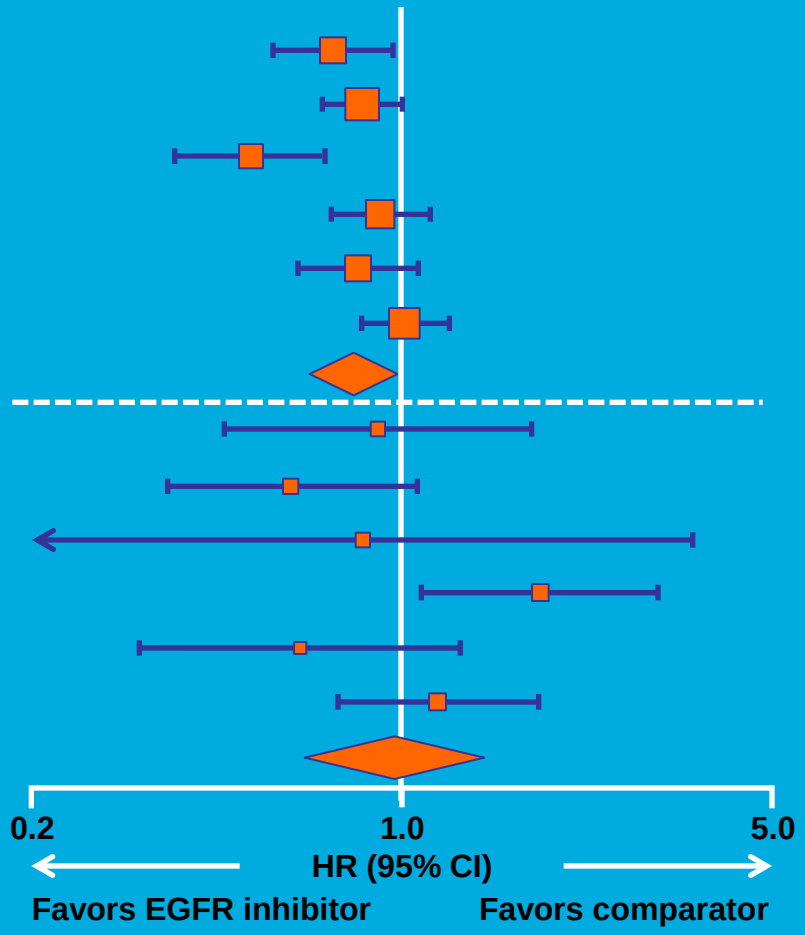
Test for overall effect: Z=0.48 (p=0.63)



1. Pietrantonio F, et al. Eur J Cancer 2015;51:587–594

Rowland et al meta-analysis: Treatment interaction for OS

Subgroup	Trial (n)	HR (95% CI)
RAS wt/ BRAF wt **Test for effect: p=0.009** **Heterogeneity: I^2=64%, p=0.02**	PRIME (n=446)	0.74 (0.57–0.96)
	OPUS/CRYSTAL (n=730)	0.84 (0.71–1.00)
	CO.17 (n=198)	0.52 (0.37–0.71)
	PICCOLO (n=371)	0.91 (0.74–1.13)
	20050181 (n=376)	0.83 (0.64–1.07)
	COIN (n=627)	0.01 (0.84–1.22)
	Summary (n=2748)	0.81 (0.70–0.95)
RAS wt./BRAF mt **Test for effect: p=0.88** **Heterogeneity: I^2=53%, p=0.06**	PRIME (n=53)	0.90 (0.46–1.76)
	OPUS/CRYSTAL (n=70)	0.62 (0.36–1.06)
	CO.17 (n=10)	0.84 (0.20–3.58)
	PICCOLO (n=68)	1.84 (1.10–3.08)
	20050181 (n=45)	0.64 (0.32–1.28)
	COIN (n=102)	1.18 (0.76–1.81)
	Summary (n=351)	0.97 (0.67–1.41)



No significant treatment × BRAF status interaction for OS (p=0.43)

1. Rowland A, et al. Br J Cancer 2015;112:1888–1894

Clinical and molecular correlates

WNT and MYC inhibitors?

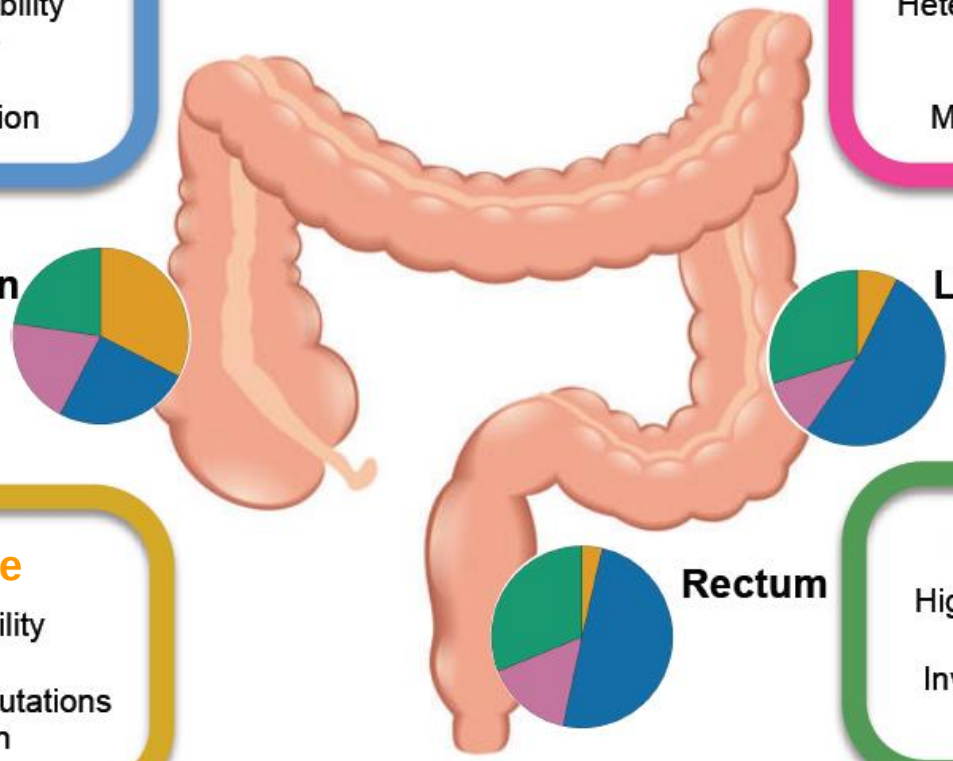
Metabolic inhibitors?

Canonical

High chromosomal instability
Microsatellite stable
CIMP negative
WNT and MYC activation

Metabolic

Heterogeneous chromosomal/ microsatellite status
KRAS mutations
Metabolic reprogramming



MSI - Immune

Microsatellite instability
CIMP high
Hypermutation, *BRAF* mutations
Immune activation

Mesenchymal

High chromosomal instability
TGFb activation
Invasion, matrix remodeling
Angiogenesis

Immune checkpoint inhibitors
Immune regulators
BRAF strategies

TGFb inhibitors
New antiangiogenics
Matrix inhibitors

Dienstmann R. J Clin Oncol 2014

The consensus molecular subtypes of colorectal cancer

CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
MSI, CIMP high Hypermutation	SCN high	Mixed MSI status SCNA low, CIMP low	SCN high
BRAF mutations		*KRAS* mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration TGF beta activation Angiogenesis

CIMP, CpG island methylator phenotype; MSI, microsatellite instability; TGF, transforming growth factor

Guinney J et al, Nature Medicine 2015

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