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Clinical applications of molecular markers in colorectal cancer: the impact of *KRAS* and beyond

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EGFR inhibitors: Potential predictive factors

Predictive of efficacy:

- EGFR
  - Immunohistochemistry (IHC) detection
  - Fluorescence in situ hybridization (FISH) detection
  - Gene mutations
  - Gene expression levels
  - Gene polymorphisms
- EGFR ligands

Predictive of lack of efficacy:

- *KRAS* gene mutations
- BRAF gene mutations
- *PI3K* mutations
- Loss of PTEN

Correlation of Response Rate and EGFR Expression

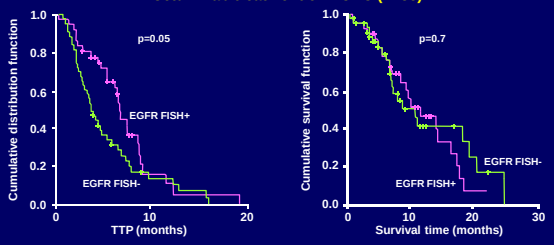
	Cetuximab / irinot. n/N	(%)	Cetuximab n/N	(%)
% EGFR-expressing cells				
≤ 10	25/109	(22.9)	4/56	(7.1)
> 10 - ≤ 20	4/20	(20.0)	5/16	(31.3)
> 20 - ≤ 35	6/27	(22.2)	0/7	(0.0)
> 35	15/62	(24.2)	3/32	(9.4)
EGFR-staining intensity				
faint	11/53	(20.8)	1/21	(4.8)
weak/moderate	22/89	(24.7)	7/55	(12.7)
strong	17/75	(22.7)	4/34	(11.8)

Cunningham D, Verslype C …Van Cutsem E, NEJM 2004

EGFR inhibitors: EGFR expression (FISH)

- Retrospective analyses: EGFR expression by FISH may have predictive value for cetuximab therapy[1,2]
- Major methodological issues for clinical practice

Cetuximab treatment of mCRC (n=85)



1. Cappuzzo F, et al. Ann Oncol 2008;19:717–723; 2. Moroni M, et al. Lancet 2005;6:279–286

EGFR gene copy number

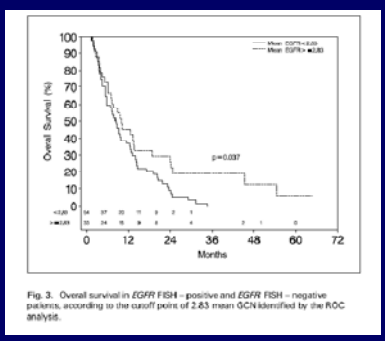


Fig. 3. Overall survival in *EGFR* FISH – positive and *EGFR* FISH – negative patients, according to the cutoff point of 2.83 mean GCN identified by the ROC analysis.

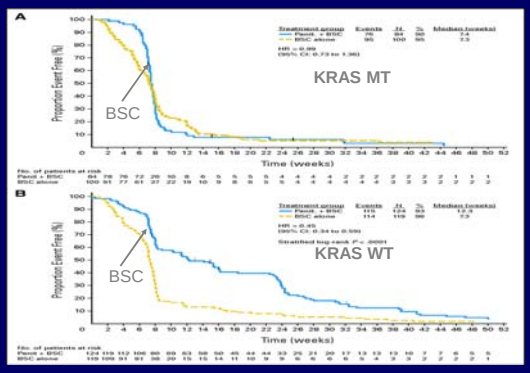
N=87 CRC patients treated with cetuximab

Personeni N, Van Cutsem E, Tejpar S et al, Clin Cancer Res, sept 2008

KRAS data in pretreated mCRC

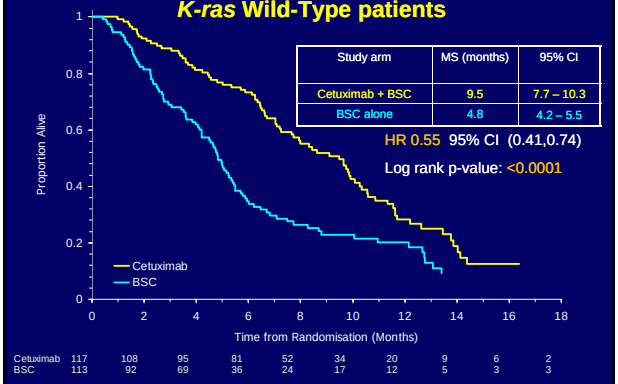
Panitumumab vs BSC in chemorefractory CRC

PFS by treatment within *KRAS* groups



Amado R, Van Cutsem E et al. J Clin Oncol; 26:1626-1634 2008

NCIC CTG C0.17: Overall survival in *K-ras* Wild-Type patients



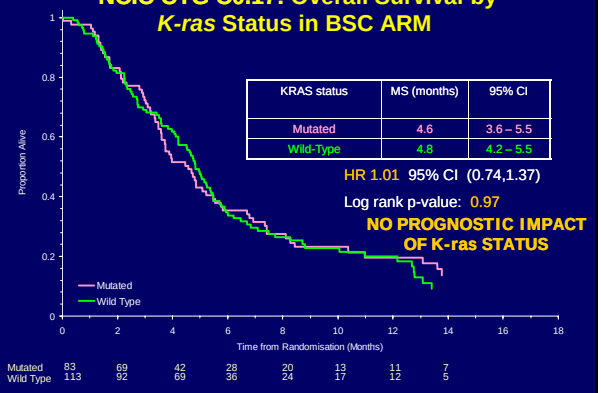
Study arm	MS (months)	95% CI
Cetuximab + BSC	9.5	7.7 – 10.3
BSC alone	4.8	4.2 – 5.5

HR 0.55 95% CI (0.41,0.74)

Log rank p-value: <0.0001

Karapetis C et al, NEJM 2008

NCIC CTG C0.17: Overall Survival by *K-ras* Status in BSC ARM



KRAS status	MS (months)	95% CI
Mutated	4.6	3.6 – 5.5
Wild-Type	4.8	4.2 – 5.5

HR 1.01 95% CI (0.74,1.37)

Log rank p-value: 0.97

NO PROGNOSTIC IMPACT OF K-ras STATUS

Karapetis C et al, NEJM 2008

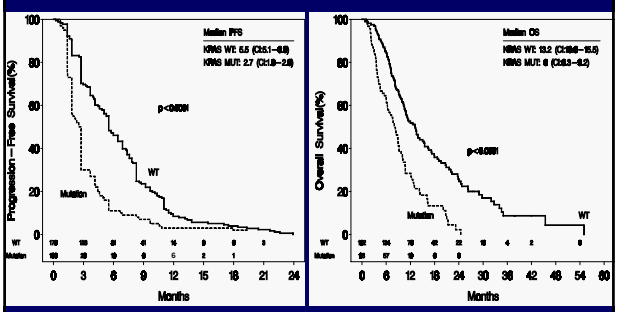
Metaanalysis in chemorefractory CRC

Response to cetuximab-Irinotecan according to *KRAS* status (n=281)

Response	n	*KRAS* mutation (n)	KRAS WT (n)
Complete response (CR)	3	0 (0)	3 (1.6)
Partial response (PR)	74	0 (0)	74 (40.6)
Stable disease (SD)	107	41 (41.4)	66 (36.3)
Progressive disease (PD)	97	58 (58.6)	39 (21.5)

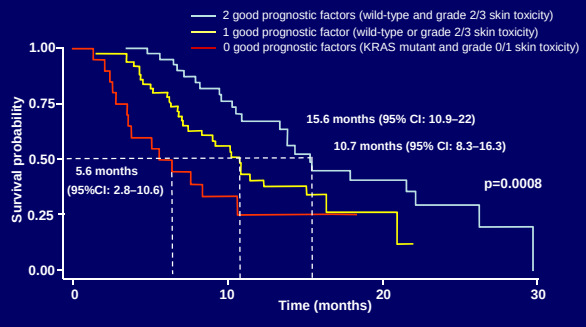
Di Fiore F, Van Cutsem E, Tejpar S et al, WCGIC Barcelona, Ann Oncol, 2008 abstract O-018

Metaanalysis in chemorefractory CRC PFS and OS according to *KRAS* status



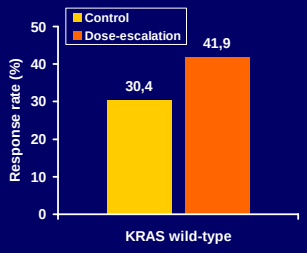
Di Fiore F, Van Cutsem E, Tejpar S et al, WCGIC Barcelona, Ann Oncol, 2008 abstract O-018

Overall survival according to *KRAS* mutation and skin toxicity



Lièvre A, Laurent-Puig P et al. J Clin Oncol 2008

EVEREST Study: Relating *KRAS* status to efficacy: Response – *KRAS* wild-type patients



	Control (n=23)	Dose-escalation (n=31)
CR	0%	0%
PR	30.4%	41.9%
SD	39.1%	41.9%
PD	21.7%	16.1%
NE	8.7%	0%
RR	30.4%	41.9%

p=0.396

S Tejpar, Van Cutsem E et al, Proc ASCO 2008 and WCIGC 2008

EVEREST Study: Relating KRAS status to efficacy: Response – KRAS mutant patients

	Control (n=20)	Dose-escalation (n=12)
CR	0%	0%
PR	0%	0%
SD	45.0%	33.3%
PD	35.0%	58.3%
NE	20.0%	8.3%
RR	0%	0%

S Tejpar, Van Cutsem E et al, Proc ASCO 2008 and WCIGC 2008

KRAS data in first line treatment of mCRC

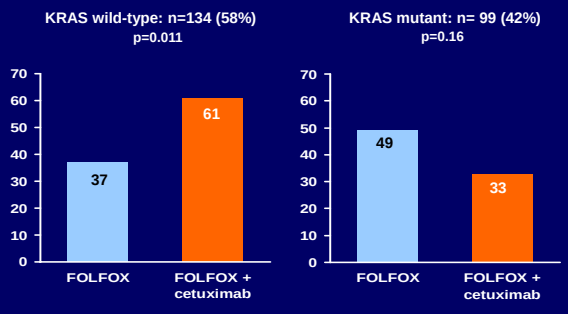
CRYSTAL study: Summary of efficacy data

	ITT		KRAS wild-type		KRAS mutant	
	FOLFIRI (n=599)	cetuximab + FOLFIRI (n=599)	FOLFIRI (n=176)	CETUXIMAB + FOLFIRI (n=172)	FOLFIRI (n=87)	Cetuximab + FOLFIRI (n=105)
RR (%)	39	47	43	59	40	36
	p=0.0038[a]		p=0.0025[a]		p=0.46[a]	
mPFS (months)	8.0	8.9	8.7	9.9	8.1	7.6
Hazard ratio	0.85		0.68		1.07	
	p=0.048		p=0.017		p=0.75	
mOS (months)	18.6	19.9	21.0	24.9	17.7	17.5
Hazard ratio	0.93		0.84		1.03	
	p=0.30		p=0.22		p=0.85	

[a]Cochran–Mantel–Haenszel test

Van Cutsem E, et al. Ann Oncol 2008;19(Suppl. 8):viii4 [Update to 710]
Van Cutsem E, et al. J Clin Oncol 2008;26(Suppl.)[Abstract no. 2]

OPUS study: FOLFOX ± cetuximab: Role of *KRAS* status in response rate

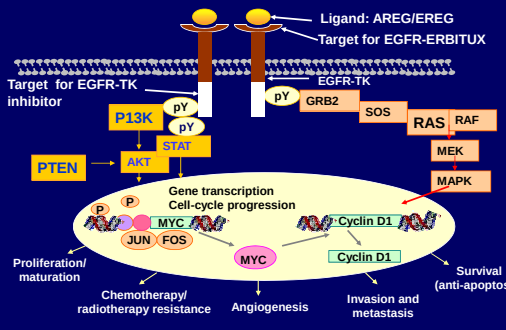


Bokemeyer C, et al. J Clin Oncol dec 2008

Analysis of multiple markers

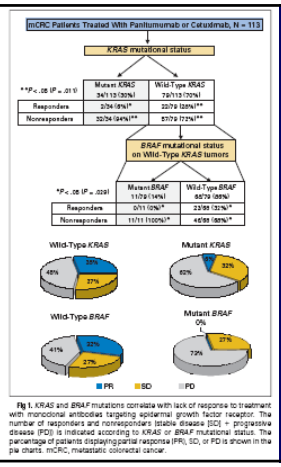
- Testing for multiple prognostic indicators may increase predictive power for response to treatment
  - PTEN loss
  - EGFR ligands
  - PI3K mutations
  - BRAF mutations
  - EGFR gene copy number
  - DUSP
  - ….

EGFR signaling pathway: A rationale for tailored therapy

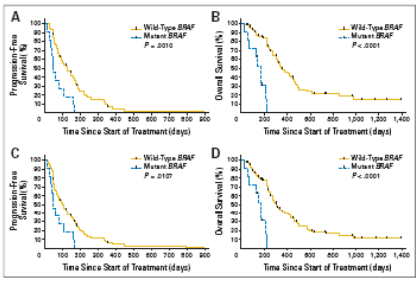


AREG, amphiregulin
EREG, epiregulin

Meyerhardt JA, Mayer RJ. N Engl J Med 2005;352:476–487;
Venook A. Oncologist 2005;10:250–261



Di Nicolantonio et al, JCO dec 2008



Di Nicolantonio et al, JCO dec 2008

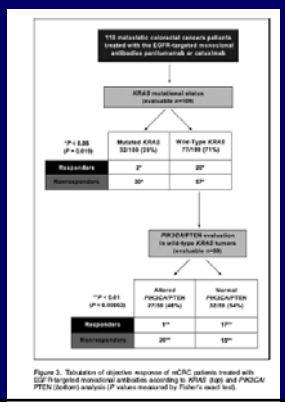
PTEN in CRC: ACTIVITY

	N=55 (4 not evaluable)	
	PTEN + n=33	PTEN - n=22
Responders *(8 RECIST + 5 SD6)*	12 (36%)	1 (5%)
NOT Responders	21 (64%)	21 (95%)

Responders vs NOT Responders
Fisher's Exact Test: p=0.008
PFS: 4.7 vs 3.3 mo – p=0.005
Survival: 11.2 vs 10.7 mo NS

F Loupakis et al, Proc ASCO 2008

PIK3CA in chemorefractory CRC



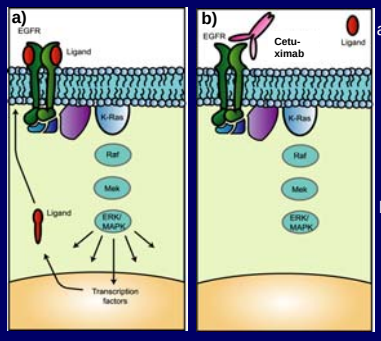
Santore-Bianchi et al, Cancer Research 2009, march 1, online

PIK3CA in chemorefractory CRC

Experimental Design: We analysed the *PIK3CA* and *KRAS* mutation status in a large group (n=200) of chemorefractory metastatic colorectal cancers (mCRC) treated with cetuximab (Erbitux®) in monotherapy or in combination with irinotecan, and correlated the mutation status with outcome.
Results: Twenty-three (12%) out of the 200 samples carried one of the *PIK3CA* mutations included in our assay. We found no correlation between the presence of a *PIK3CA* mutation and impaired response to cetuximab.
Conclusions: Our findings do not provide any evidence for a strong role of *PIK3CA* mutations as a single marker in determining response to cetuximab in chemorefractory metastatic colorectal cancer.

Prenen H, Van Cutsem E, Tejpar S et al, Clin Cancer Research in press 2009

Role of EGFR ligands in CRC



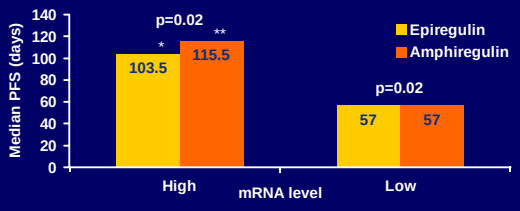
a) Increased expression of epiregulin (EREG) and/or amphiregulin (AREG) may aid tumor growth and survival via an autocrine loop through EGFR[1]

b) May characterize EGFR-dependent tumors more sensitive to cetuximab[1]

Khambata-Ford S, et al. J Clin Oncol 2007;25:3230–3237

EGFR ligand expression may predict increased PFS with cetuximab

- **Median PFS with cetuximab is significantly longer when EGFR ligand expression is high; a similar significant relationship exists with DCR[1]**



n=110, cetuximab monotherapy; DCR, disease control rate

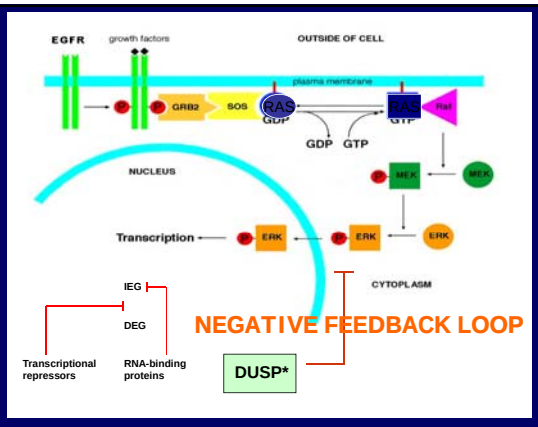
*p=0.002 vs low; **p=<0.0001 vs low

Khambata-Ford S, et al. J Clin Oncol 2007;25:3230–3237

Epiregulin expression associated with PFS and OS in KRAS mt and wt tumors

KRAS status	Epiregulin expression	Median PFS (weeks)	Median OS (weeks)	
All	<0.5233	12	26	p<0.001
	>0.5233	30	45.9	
	Overall	18	36	
Wild-type	<0.5233	12	31.6	p<0.001
	>0.5233	36	65.4	
	Overall	24	44.3	
Mutant	<0.5233	12	22.9	
	>0.5233	12	29.1	
	Overall	12	24.3	

Tejpar S, Van Cutsem E et al. ASCO GI 2008 (Abstract No. 411)



*Dual-specificity phosphatases

Adapted from http://oregonstate.edu/instruction/bb492/fignames/ras3.html

Conclusions

- There is a significantly higher DUSP4 & 6a mRNA expression in the KRAS MUT as a group compared to WT primary CRC.
- However, as expected from cell line data, heterogeneity exists: in the KRAS MUT there are 3 distinct clusters of DUSP4 expression.

De Roock W, Van Cutsem E, Tejpar S et al, ASCO GI 2009

2009 Gastrointestinal Cancers Symposium
SCIENCE AND MULTIDISCIPLINARY MANAGEMENT OF GI MALIGNANCIES

Conclusions

- **The activity of anti-EGFR antibodies in metastatic colorectal cancer is confined to KRAS wild type patients**
  - **Chemorefractory CRC**
    - **Single agents cetuximab/panitumumab**
    - **Combination cetuximab/irinotecan**
  - **First line treatment of cetuximab in combination with standard cytotoxic combinations**
- **Other predictive markers have to be validated**
- **New studies should build on these marker data**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