

K-Ras mutational status and response to EGFR inhibitors for treatment of advanced CRC



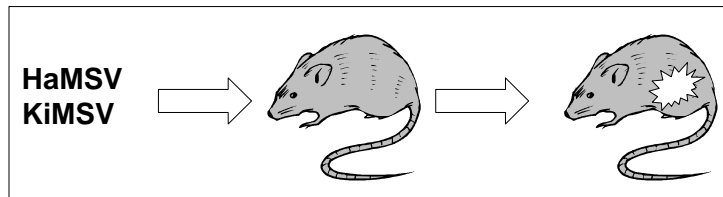
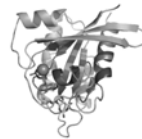
Monica Bertagnolli, MD

CRA Continuing Education, November 2008

The Ras Oncogene

Kirsten and Harvey: 1964

Identification of a virus that
produced tumors in mice



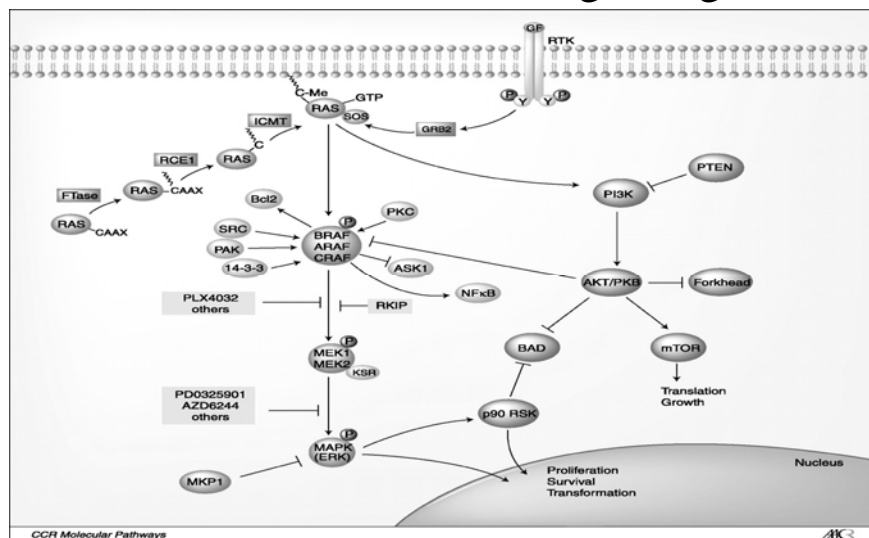
- 100% of mice developed tumors in weeks
- Rapid development of sarcomas and erythroleukemias

Harvey (1964) Nature 204:1104; Somers and Kirsten Science 1967;40:1053

Ras Family of Proteins

- Monomeric G proteins (H-Ras, K-Ras and N-Ras)
- Cycle between GDP bound “off” state and GTP bound “on” state
- Act as “molecular switches” linking extracellular signals through membrane receptors to intracellular signals
- Respond to activation of membrane-associated receptors for cell growth and survival

Ras: Downstream Signaling



Sebolt-Leopold, J. S. Clin Cancer Res 2008;14:3651-3656

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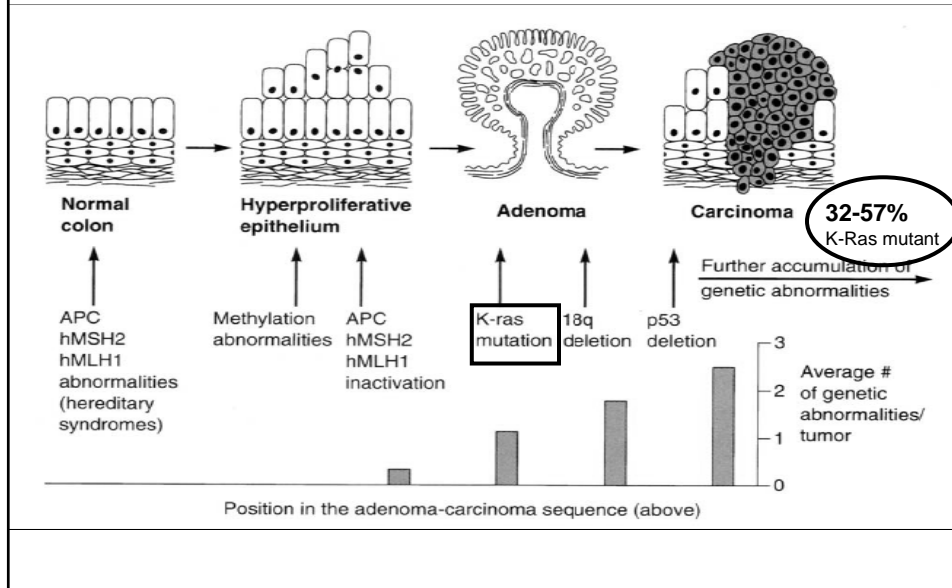
K-Ras Mutations and GAP Dysfunction

- Single amino acid change causes constant stimulation in the absence of growth factors
 - Most commonly mutated codons 12, 13 and 61 with destruction of GTPase activity or prevention of GAP binding
 - Blocks GAP induced hydrolysis of GTP to GDP
 - Locked in “on” state
- GAP dysfunction also maintains the “on” state
 - NF1-GAP/neurofibromin - tumor suppressor gene
 - P120-GAP

Ras is Mutated in 30% of Human Cancers

Pancreatic carcinoma	72-90%
Cholangiocarcinoma	55%
Colon adenocarcinoma	32-57%
Thyroid carcinoma	30%
Seminoma	40%
Embryonal rhabdomyosarcoma	35%
Acute myelogenous leukemia	35%
Myeloblastic syndromes	30%
Lung carcinoma	15-50%

CRC: Adenoma-Carcinoma Sequence

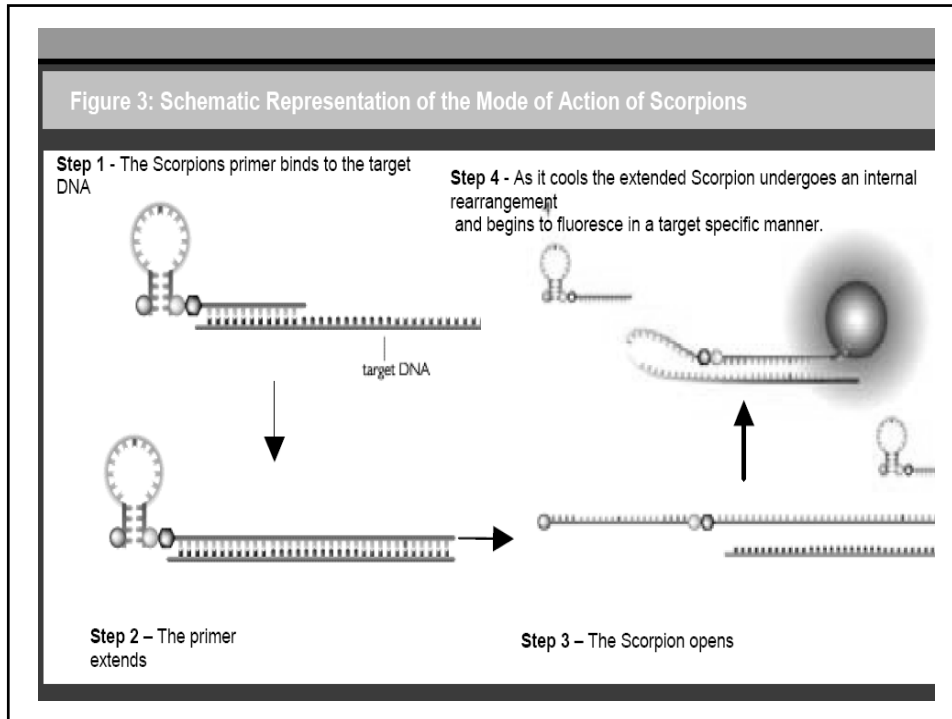


Detecting tumor K-Ras mutations

Single base substitutions that render GTPase domain insensitive to inactivation by GAP

- Gly 12 Asp
- Gly 12 Ala
- Gly 12 Val
- Gly 12 Ser
- Gly 12 Arg
- Gly 12 Cys
- Gly 13 Asp

- DNA extracted from tumor (FFPE, cell-free DNA)
- Mutational analysis by sequencing (various methods) or mutant allele specific amplification
- Detection threshold:
 - 1% of mutant DNA in a background of wild-type genomic DNA

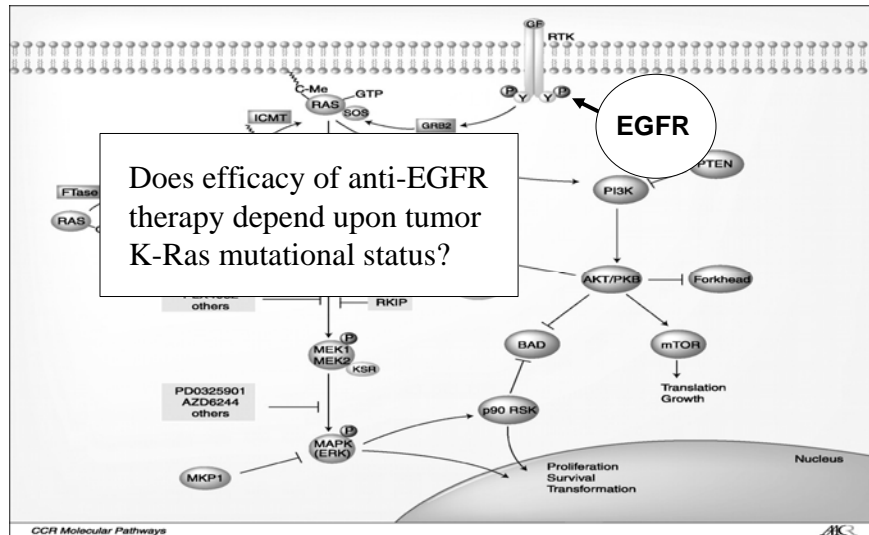


Prognostic implications of tumor K-Ras status

Smakman et al; Biochem Biophys Acta 2005; 1756:103

- Stage I-IV CRC; 24 studies with >100 patients (range 100-3439)
 - Mutation rate 24-69%
- Association between K-Ras status and stage:
 - Yes: 7; No: 13; N/A: 4
- Association between K-Ras status and DFS:
 - Yes: 3; No: 3; N/A: 18

Ras: Downstream Signaling



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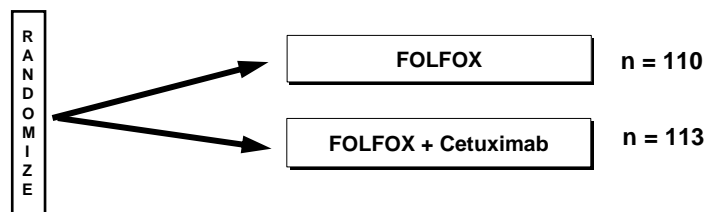
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Retrospective studies supporting K-ras and lack of anti-EGFR response

Reference	Treatment	No. of patients (wt:mt)	Objective response n (%)	
			Wild-type	mutant
A Lièvre, et al. (<i>J Clin Oncol</i> 2008)	Cetuximab ± CT	114 (78:36)	34 (44%)	0 (0%)
S Benvenuti, et al. (<i>Cancer Res</i> , 2007)	Panitumumab or cetuximab or Cetuximab + CT	48 (32:16)	10 (31%)	1 (6%)
W DeRoock, E Van Cutsem S Tejpar (<i>Ann Oncol</i> 2008)	Cetuximab or Cetuximab + irinotecan	113 (67:46)	27 (41%)	0 (0%)
D Finocchiaro, et al. (<i>ASCO Proceedings</i> , 2007)	Cetuximab ± CT	81 (49:32)	13 (26%)	2 (6%)
F Di Fiore, et al. (<i>Br J Cancer</i> , 2007)	Cetuximab + CT	59 (43:16)	12 (28%)	0 (0%)
S Khambata-Ford, et al. (<i>J Clin Oncol</i> , 2007)	Cetuximab	80 (50:30)	5 (10%)	0 (0%)
RG Amado, et al. (<i>J Clin Oncol</i> , 2008)	Panitumumab	208 (124:84)	21 (17%)	0 (0%)

Emerging data:
Randomized phase II/III studies

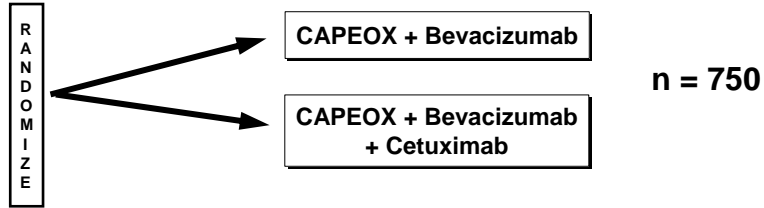
OPUS



	FOLFOX		FOLFOX + Cetuximab	
	Response Rate	PFS	Response Rate	PFS
Wild-type K-ras (n = 134)	37%	7.2 m	61%	7.7 m
Mutant K-ras (n = 99)	49%	8.6 m	33%	5.5 m

Bokemeyer ASCO 2008; JCO 28: May 20 suppl; abstr 4000.

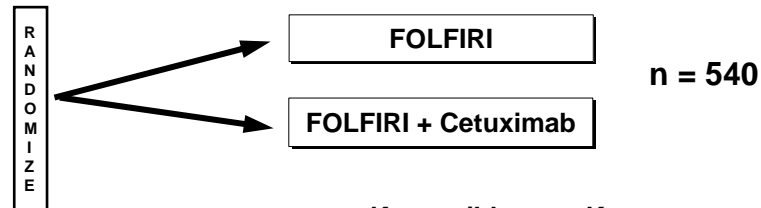
CAIRO2



	All patients	K-ras wildtype	K-ras mutant
CAPEOX + Bevacizumab	10.7 m	10.7 m	12.5 m
CAPEOX + Bevacizumab + Cetuximab	9.6 m	10.5 m	8.6 m
P value	0.02	0.1	0.04

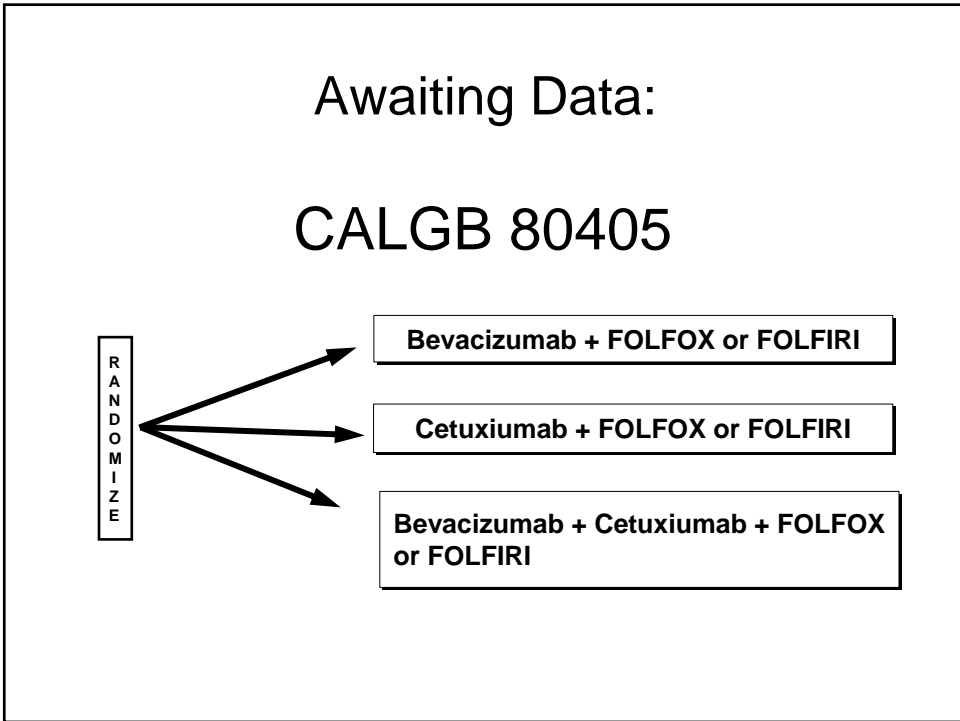
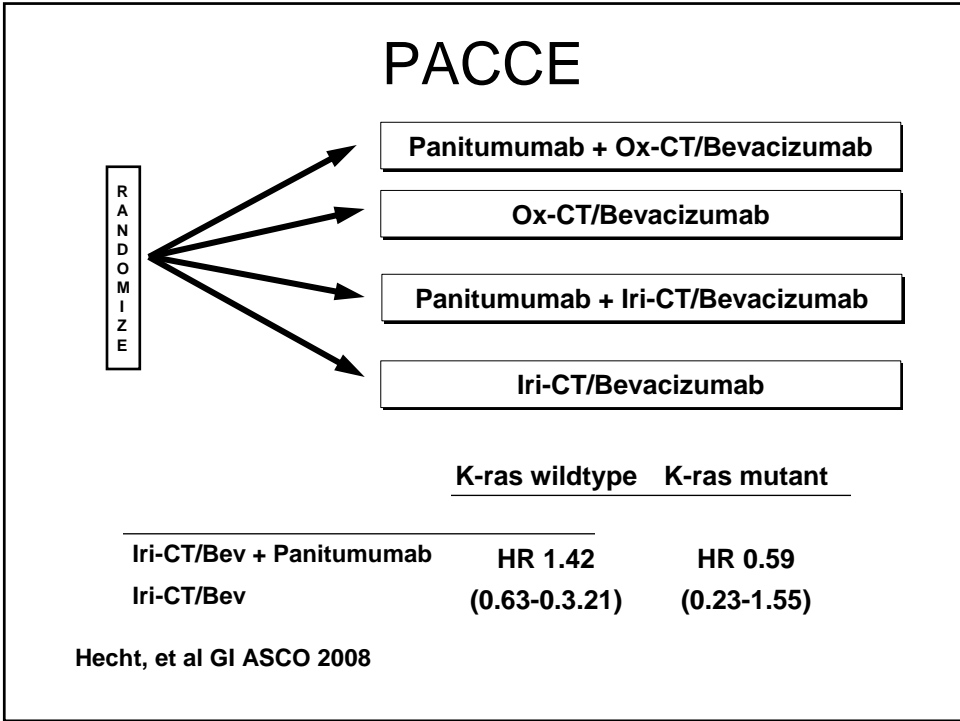
Punt ASCO 2008; JCO 28: May 20 suppl; abstr 4011

CRYSTAL



	K-ras wildtype	K-ras mutant
FOLFIRI	HR 0.68	HR 1.07
FOLFIRI + Cetuximab	(0.051-0.934)	(0.71-1.61)
P value	0.017	0.75

Van Cutsem ASCO 2008; JCO 28: May 20 suppl; abstr 2.



Conclusions:

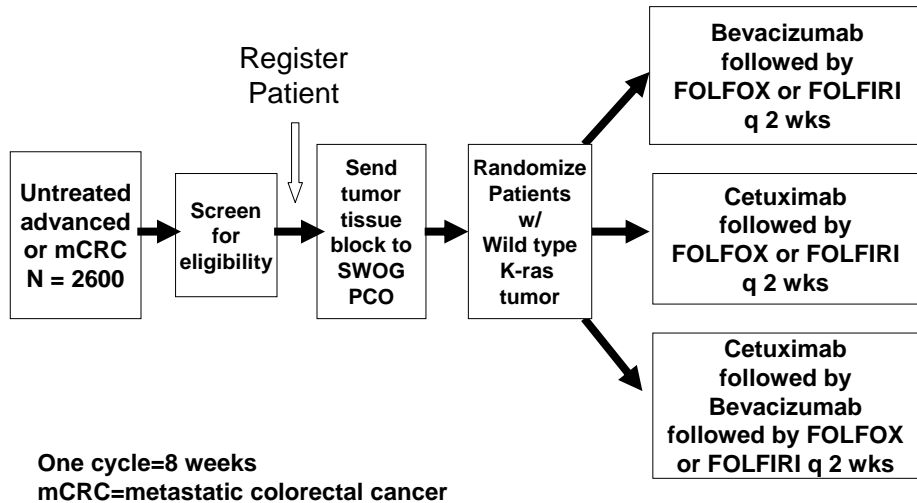
- Monoclonal antibodies against EGFR are active in metastatic colorectal cancer
- Patients whose tumors contain mutant K-Ras do not benefit from cetuximab or panitumumab, either single agent or in combination with cytotoxic chemotherapy
- The relationship between tumor K-Ras mutational status and response to bevacizumab (or other RTK inhibitors) is currently unknown

Important issues for CALGB

- Need to restrict enrollment to CALGB 80405 to patients with K-Ras wildtype tumors
- Perform retrospective analysis to determine whether there are differences in treatment outcome between patients with K-Ras wildtype and mutant tumors
 - For the bevacizumab + CT arm
 - For the bevacizumab + cetuximab + CT arm
- Identify promising regimens for testing in patients with K-Ras mutant advanced CRC

CALGB/SWOG 80405 Study Design

Open-label Phase III Study



THANK YOU!

Denise Collins
Jeff Meyerhardt
Raphael Amado