Personalized Medicine in Colorectal Cancers

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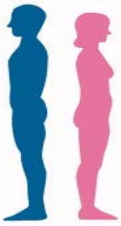
Cancer statistics, 2013

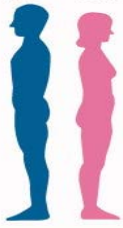
Estimated New Cases*

	Males			Females	
Prostate	241,740	29%	Breast	226,870	29%
Lung & bronchus	116,470	14%	Lung & bronchus	109,690	14%
Colon & rectum	73,420	9%	Colon & rectum	70,040	9%
Urinary bladder	55,600	7%	Uterine corpus	47,130	6%
Melanoma of the skin	44,250	5%	Thyroid	43,210	5%
Kidney & renal pelvis	40,250	5%	Melanoma of the skin	32,000	4%
Non-Hodgkin lymphoma	38,160	4%	Non-Hodgkin lymphoma	31,970	4%
Oral cavity & pharynx	28,540	3%	Kidney & renal pelvis	24,520	3%
Leukemia	26,830	3%	Ovary	22,280	3%
Pancreas	22,090	3%	Pancreas	21,830	3%
All Sites	**848,170**	**100%**	**All Sites**	**790,740**	**100%**



Estimated Deaths

	Males			Females	
Lung & bronchus	87,750	29%	Lung & bronchus	72,590	26%
Prostate	28,170	9%	Breast	39,510	14%
Colon & rectum	26,470	9%	Colon & rectum	25,220	9%
Pancreas	18,850	6%	Pancreas	18,540	7%
Liver & intrahepatic bile duct	13,980	5%	Ovary	15,500	6%
Leukemia	13,500	4%	Leukemia	10,040	4%
Esophagus	12,040	4%	Non-Hodgkin lymphoma	8,620	3%
Urinary bladder	10,510	3%	Uterine Corpus	8,010	3%
Non-Hodgkin lymphoma	10,320	3%	Liver & intrahepatic bile duct	6,570	2%
Kidney & renal pelvis	8,650	3%	Brain & other nervous system	5,980	2%
All Sites	**301,820**	**100%**	**All Sites**	**275,370**	**100%**



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CA: A Cancer Journal for Clinicians
Volume 62, Issue 1, pages 10-29, 4 JAN 2013 DOI: 10.3322/caac.20138
http://onlinelibrary.wiley.com/doi/10.3322/caac.20138/full#fig1

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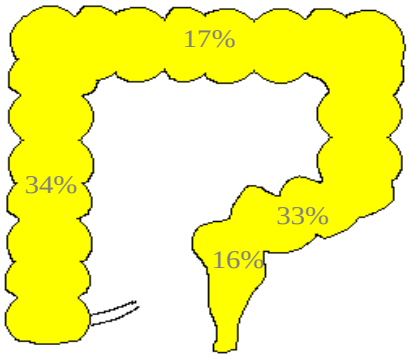
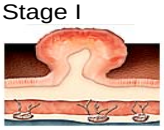
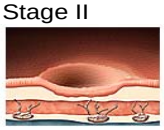
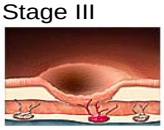
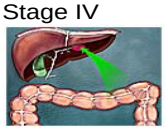
Location of Colorectal Cancers



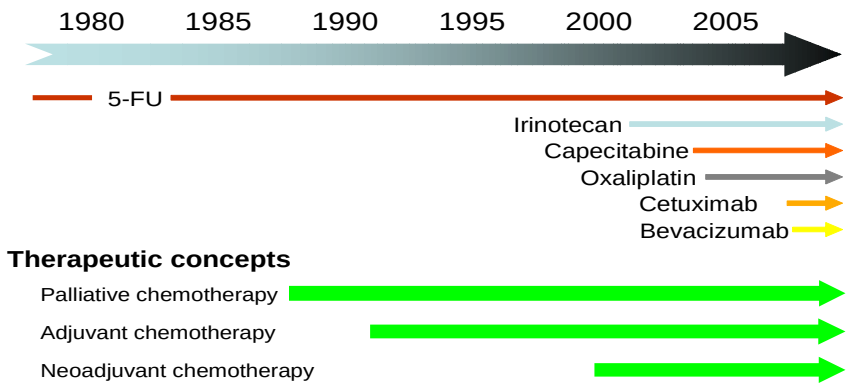
1992 data indicating proximal shift since 1986, supporting effectiveness of screening

AJCC Staging Guidelines for CRC

	Stage I	Stage II	Stage III	Stage IV
Disease development				
Staging	T1, N0, M0 T2, N0, M0	A: T3, N0, M0 B: T4, N0, M0	A: T1-2, N1, M0 B: T3-4, N1, M0 C: Any T, N2, M0	Any T, Any N, M1
Definition	Invades submucosa (T1)/ muscular propria (T2)	Invades subserosa, nonperitonealized pericolic/perirectal tissues (T3) invades other organs or structures/visceral peritoneum (T4)	Involves 1-3 (N1) or more (N2) lymph nodes	Involves distant metastases
Usual treatment	Surgery	Surgery ± chemotherapy	Surgery + chemotherapy	Chemotherapy ± surgery

AJCC Cancer Staging Manual, Sixth Edition.
National Comprehensive Cancer Network *Clinical Practice Guidelines in Oncology:* Colon Cancer. v.1.2004.
Image adapted from http://www.exactsciences.com/pregen26/professionals/about_hnpcc/_index.htm#: Accessed 1/16/04.

Advances in the Treatment of Colorectal Cancer



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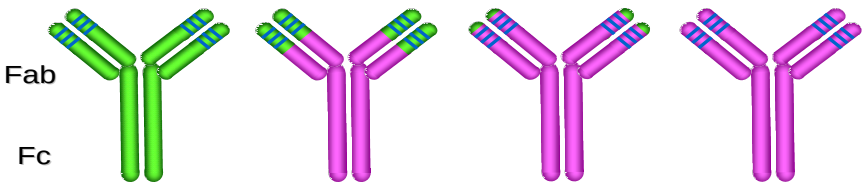
Therapeutic Antibodies



Murine mAb (suffix = "**o**mab")

Chimeric Ab (suffix = "**xi**mab")

Humanized Ab (suffix = "**zu**mab")

Human Ab (suffix = "**u**mab")

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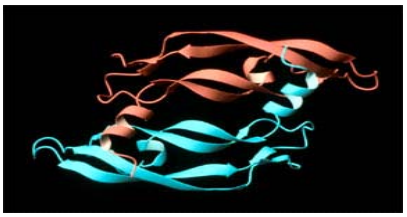
Bevacizumab

- Humanized Monoclonal antibody to vascular endothelial cell growth factor (rhuMAb-VEGF)
- Binds and inhibit VEGF
  - Protein plays a critical role in tumor angiogenesis



Biomarkers for Personalized Medicine

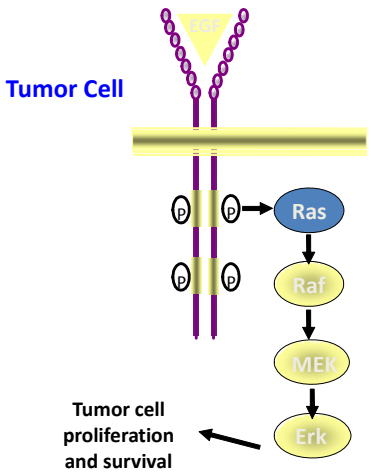
- **Prognostic Markers:** anticipates the likely outcome of an illness
- **Predictive Markers:** anticipate the likelihood a tumor will respond to a drug

Biomarkers in GI Cancers Overview

- **Currently accepted and in practice**
  - Her-2-neu: Amplification or over expression
  - *K-ras* gene: Mutation
- **Strong evidence but not conclusive**
  - *BRCA* gene mutations
  - DPC4
  - MSI, TS, ERCC
- **Earlier in development**
  - Expression: VEGF-A isoforms
  - SNP: VEGFR
  - Mutations: PI3K

KRAS Mutations in CRC

- KRAS pathway links EGFR to cell proliferation and survival
- Activating mutations in KRAS could block EGFR signaling
  - Mediate resistance to EGFR inhibitors
- KRAS mutations occur in 35%-45% of CRC
- Raf mutations occur in 10-15%
- Mutations rarely occur in both KRAS and Raf



Yarden. *Nat Rev Mol Cell Biol.* 2001;2:127; Van Cutsem. *ASCO.* 2008 (abstr 2); Bokemeyer. *ASCO.* 2008 (abstr 4000
Amado. *J Clin Oncol.* 2008;26:1626; Tejpar. *ASCO.* 2008 (abstr 4001); Eberhard. *J Clin Oncol.* 2005;23:5900

Retrospective Studies: KRAS Interaction With EGFR Inhibitors

Study	Regimen	N (% mKRAS)	RR	
			WT	Mutant
Lievre, 2008	Cetuximab	114 (32)	44	0
De Roock, 2008	CT + Cetuximab	113 (41)	41	0
Tejpar, 2008	Irinotecan + Cetuximab	89 (36%)	37	0
Tabernero, 2008	Cetuximab	48 (41)	28	0
Di Fiore, 2007	CT + Cetuximab	59 (37)	12	0
Finocchiaro, 2007	Cetuximab CT	81 (40)	27	6
Khambata-Ford, 2007	Cetuximab	80 (38)	10	0
Amado, 2008	Panitumumab	208 (40)	17	0

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Lievre. *J Clin Oncol.* 2008;26:374; De Roock. *Ann Oncol.* 2008;19:508; Tejpar. *ASCO.* 2008 (abstr 4001); Tabernero. *A* 2008 (abstr 435); Di Fiore. *Br J Cancer.* 2007;96:1166; Finocchiaro. *ASCO.* 2007 (abstr 4021); Khambata-Ford. *J Clin O* 2007;25:3230; Amado. *J Clin Oncol.* 2008;26:1626.

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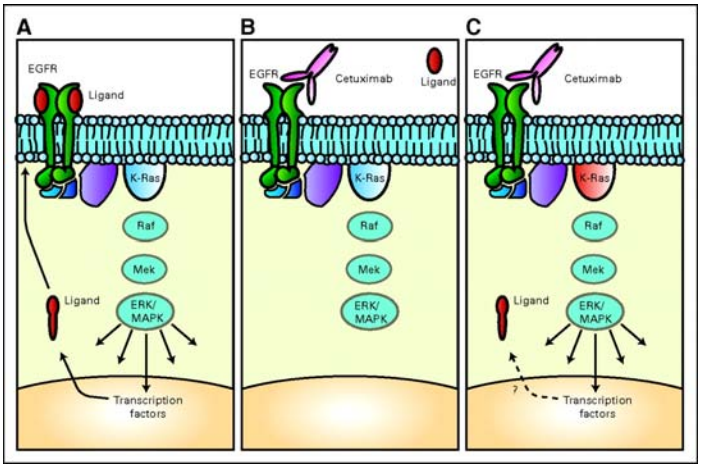
The Ras Mutation



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

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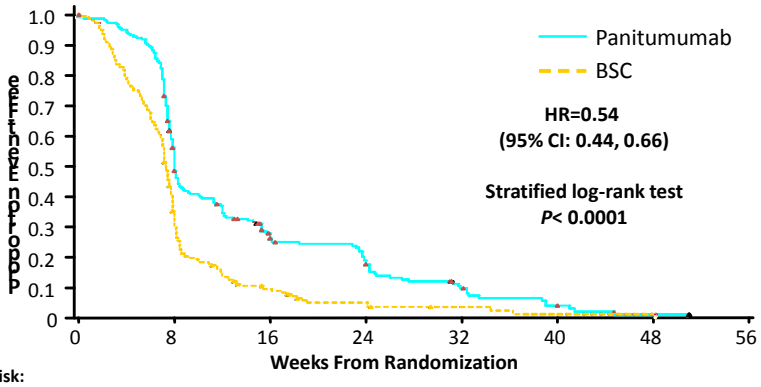
Panitumumab vs BSC in mCRC: PFS



Patients at risk:							
Panitumumab	231	118	49	31	13	5	1
BSC	232	75	17	7	3	1	1

76% of BSC patients crossed over to panitumumab therapy

No significant difference in OS between arms
(median follow-up of 72 weeks)

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Van Cutsem. *J Clin Oncol.* 2007;2 1658.

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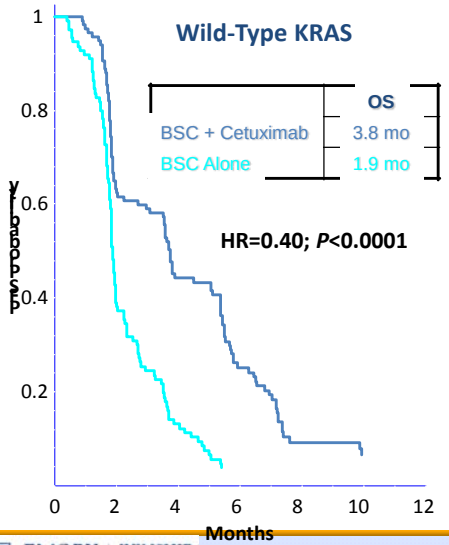
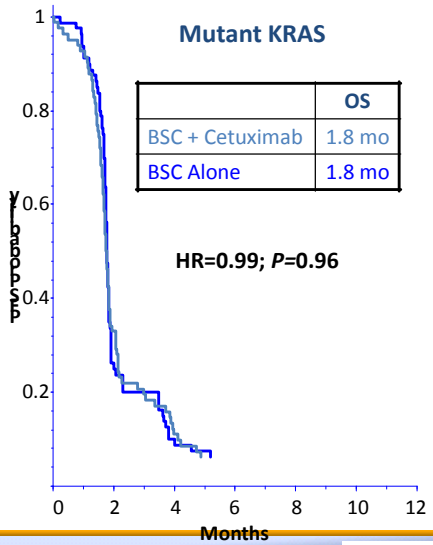
NCIC CTG C0.17: PFS and KRAS Status





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Karapetis. Presented at 10th *WCGIC*, June 25-28, 2008; Barcelona, Sp

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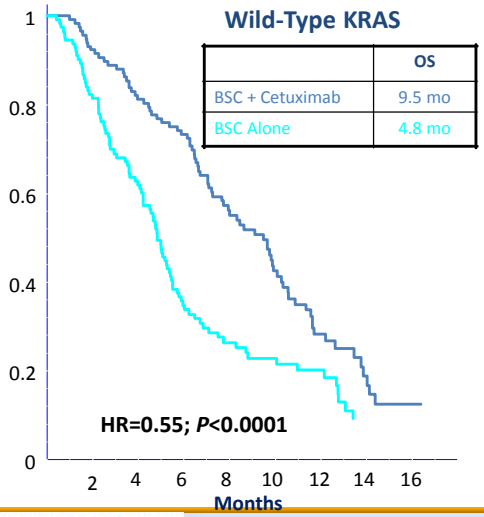
NCIC CTG C0.17: Overall Survival in Patients With Wild-Type KRAS



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Karapetis. Presented at 10th *WCGIC*, June 25-28, 2008; Barcelona, Spain (abstr O-037).

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Is KRAS status predictive of antiangiogenic therapy?

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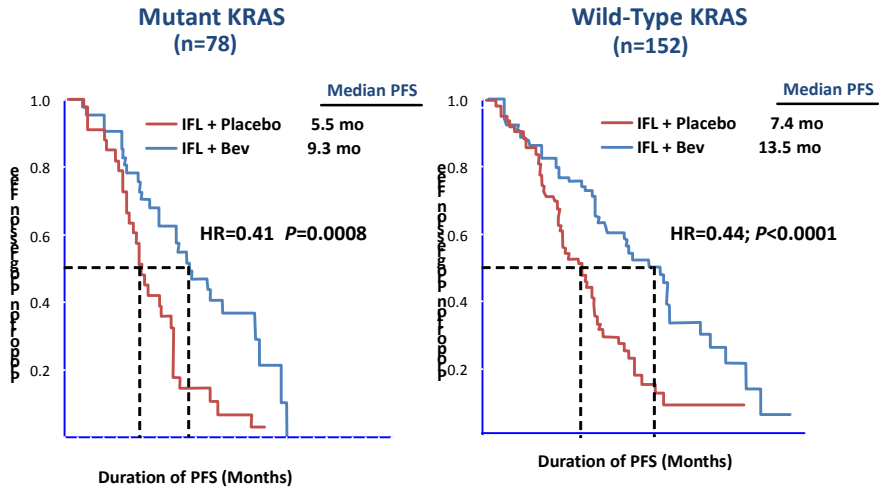
Bevacizumab Shows PFS Benefit Regardless of KRAS Status



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Rosen. *Ann Oncol.* 2008;19:vi19 (abstr O-035)

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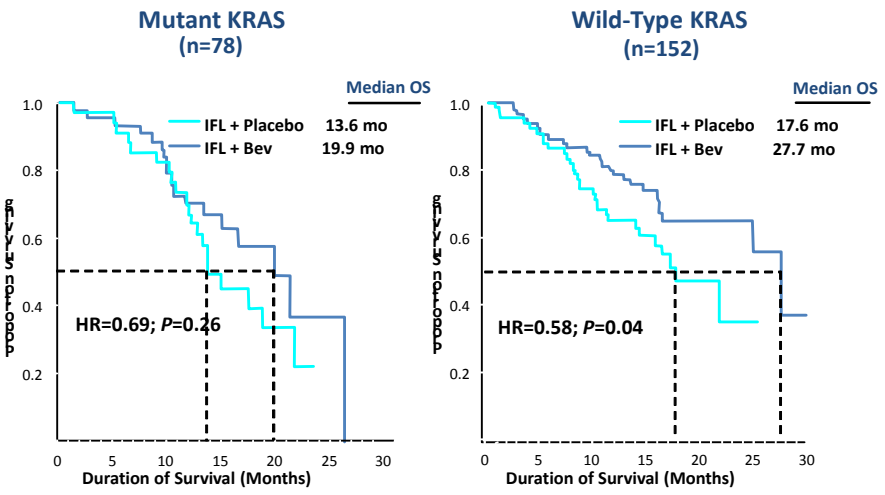
Bevacizumab Shows OS Benefit Regardless of KRAS Status



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Rosen. *Ann Oncol.* 2008;19:vi19 (abstr O-035).

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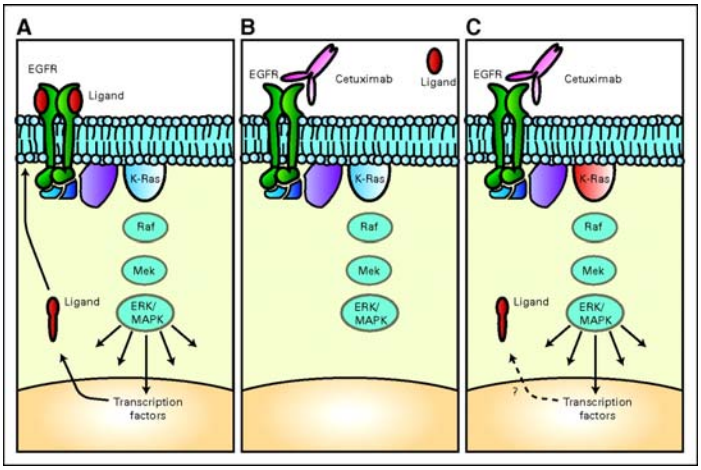

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Khambata-Ford, S. et al. J Clin Oncol; 25:3230-3237 2007

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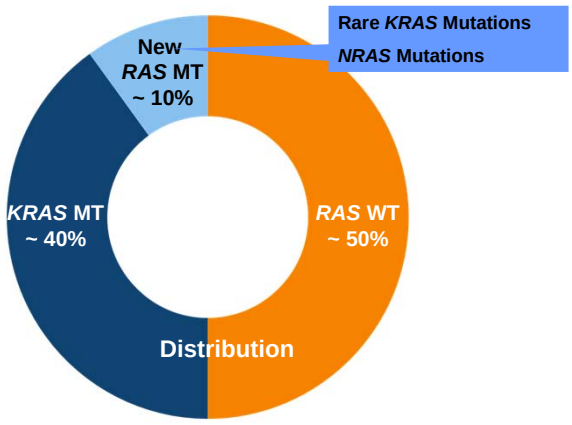
EGFR Biomarkers



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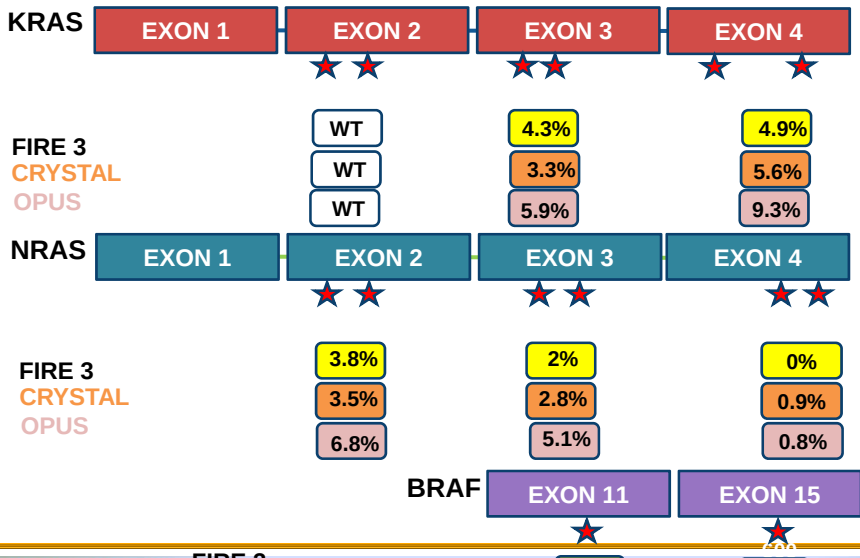
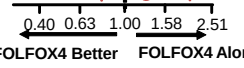
Extended Mutational Analysis



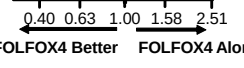
Analysis of KRAS/NRAS Mutations

PFS		
Subgroup	n	HR for Progression or Death (95% CI)
Primary analysis		
Nonmutated KRAS exon 2	656	0.80 (0.66-0.97)
Mutated KRAS exon 2	440	1.29 (1.04-1.62)
Prospective-retrospective analysis		
Nonmutated RAS	512	0.72 (0.58-0.90)
Mutated RAS	548	1.31 (1.07-1.60)
Nonmutated KRAS exon 2, mutated other RAS	108	1.28 (0.79-2.07)



Panitumumab-FOLFOX4 Better FOLFOX4 Alone Better

OS		
Subgroup	n	HR for Progression or Death (95% CI)
Primary analysis		
Nonmutated KRAS exon 2	656	0.83 (0.67-1.02)
Mutated KRAS exon 2	440	1.24 (0.98-1.57)
Prospective-retrospective analysis		
Nonmutated RAS	512	0.78 (0.62-0.99)
Mutated RAS	548	1.25 (1.02-1.55)
Nonmutated KRAS exon 2, mutated other RAS	108	1.29 (0.79-2.10)



Panitumumab-FOLFOX4 Better FOLFOX4 Alone Better

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

BRAF Mutation Status

CRYSTAL Trial	KRAS WT/**BRAF WT** (n = 566)		KRAS WT/**BRAF MT** (n = 59)	
	FOLFIRI (n = 289)	Cetuximab + FOLFIRI (n = 277)	FOLFIRI (n = 33)	Cetuximab + FOLFIRI (n = 26)
Median OS, mos (95% CI)	21.6 (20.0-24.9)	25.1 (22.5-28.7)	10.3 (8.4-14.9)	14.1 (8.5-18.5)
HR (95% CI) P value*	0		0	
Median PFS, mos (95% CI)	8.8 (7.6-9.4)	9 (9.4-11.8)	5.6 (3.5-8.1)	(3.6-9.1)
HR (95% CI) P value*	0.673 (0.528-0.858) .0013		0.934 (0.425-2.056) 0.8656	
OR rate, % (95% CI)	42.6 (36.8-48.5)	61.0 (55.0-66.8)	15.2 (5.1-31.9)	19.2 (6.6-39.4)
P value†	< .0001		.9136	

Median OS: 23 mos

Median OS: 12 mos

*Stratified log-rank test. †Cochran-Mantel-Haenszel test.

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

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Molecular Markers in CRC

Marker	Description	Prognostic/Predictive value
Microsatellite instability (MSI)[1,2]	• In 15% sporadic colorectal cancers cases • Change in length of DNA microsatellites due to insertions or deletions of repeating units	• Better outcomes in stage II and III patients vs MSS • Associated with improved prognosis vs intact MMR patients • No benefit with 5-FU adjuvant treatment
Loss of heterozygosity at chromosome 18q and 17p [2]	• In > 70% of colorectal cancers • Allelic loss of portions of chromosomes 18q and 17p • Site of deleted in colon cancer (DCC) protein	• Associated with worse prognosis
Genomic tests Oncotype DX Coloprint	• 12 or 18 gene signatures	• Predict risk of recurrence of patients with resected stage II or III colon cancer

1. Watanabe T, et al. *N Engl J Med*. 2001;344(16):1196-1206. 2. Wilson PM, et al. *Gastrointest Cancer Res*. 2007;1(6):237-246. 3. Kopetz S, et al. *Oncology*. 2008;22(3):260-270.

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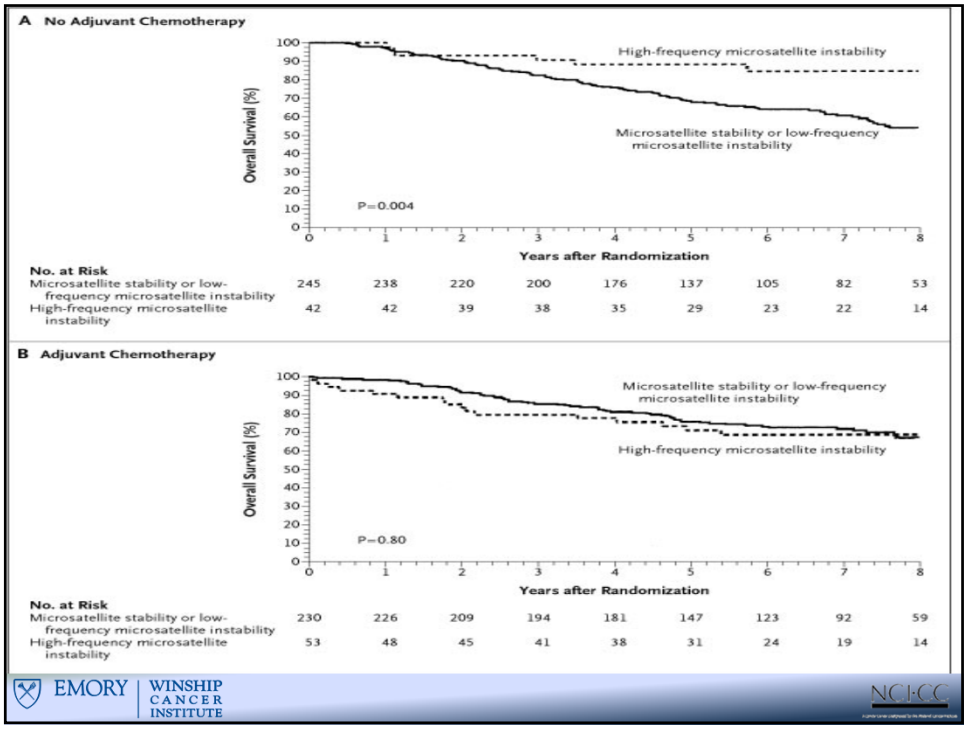

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Thank You