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Predicting survival in metastatic colorectal cancer

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Disclosures

- Consulting activities
 - Amgen
 - Pfizer
 - Roche/Genentech
 - Sanofi-Aventis
 - Genomic Health

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Personalized Medicine - Decision Tools -

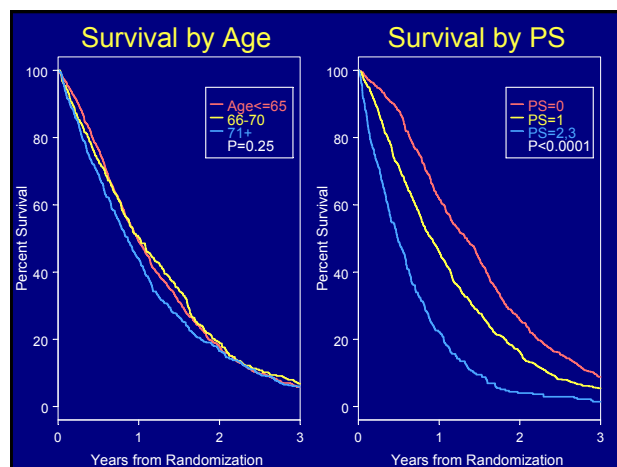
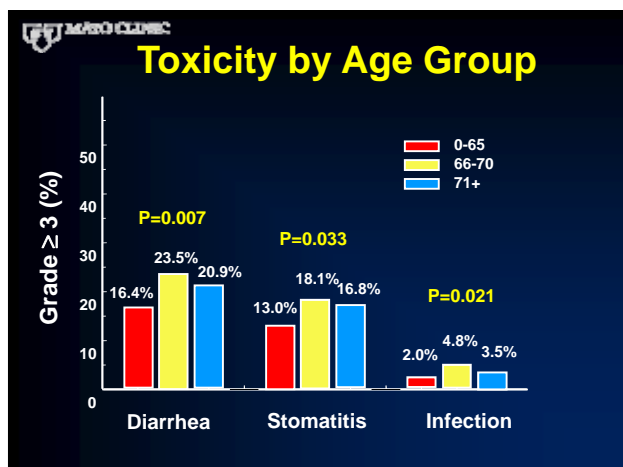
- Old: Clinical parameters
 - Patient-based
 - Age, PS, co-morbidities, experience with prior therapies, financial implications...
 - Tumor-based
 - Stage, differentiation, number and sites of metastases...
- New: Molecular Biomarkers
 - Patient-based (Pharmacogenomics)
 - Tumor-based

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Old Factor 1: Age

- Pooled analysis of four first-line advanced CRC trials testing 5-FU regimens
 - Bolus 5FU +/- LV, or 5EU
 - Studies conducted from 1984-97
 - Any age ≥ 18, PS 0-3
 - Total sample size: 1748

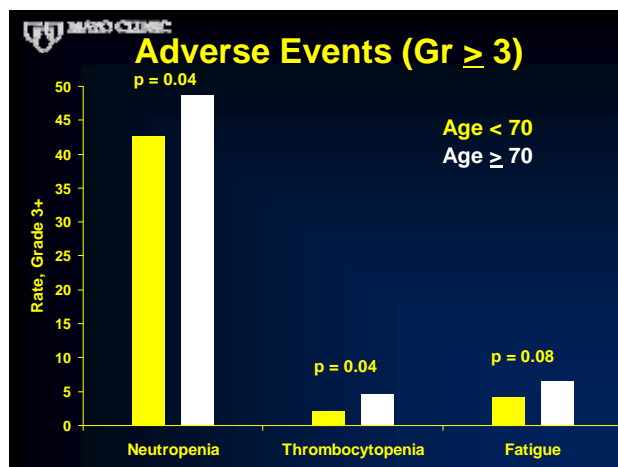
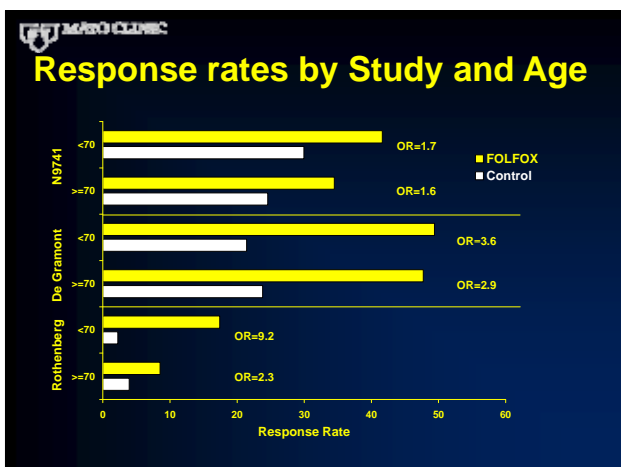
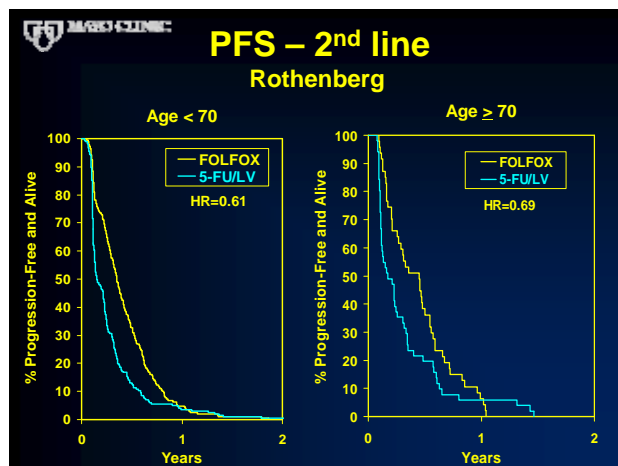
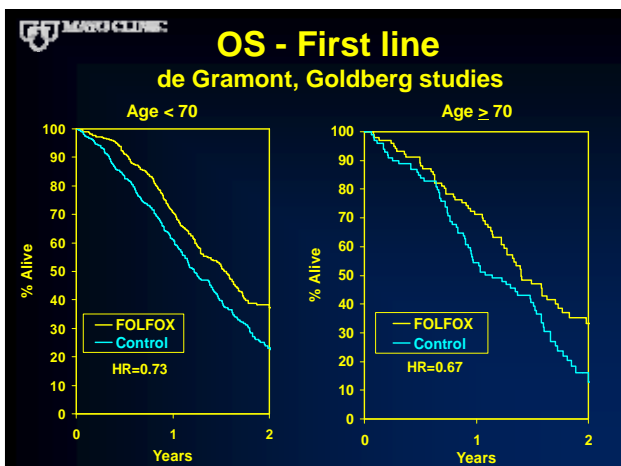
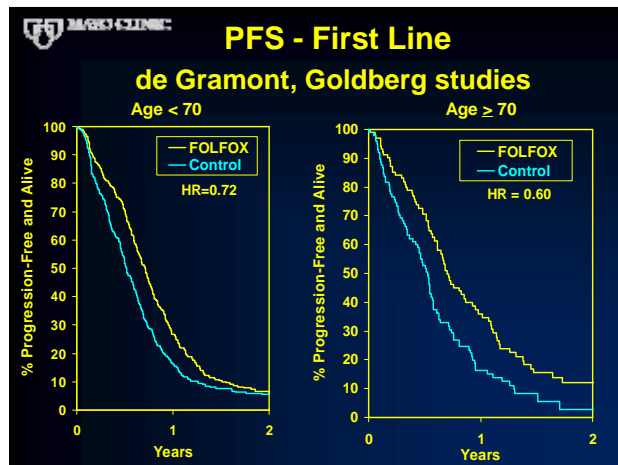
D'Andre et al CCC 2005

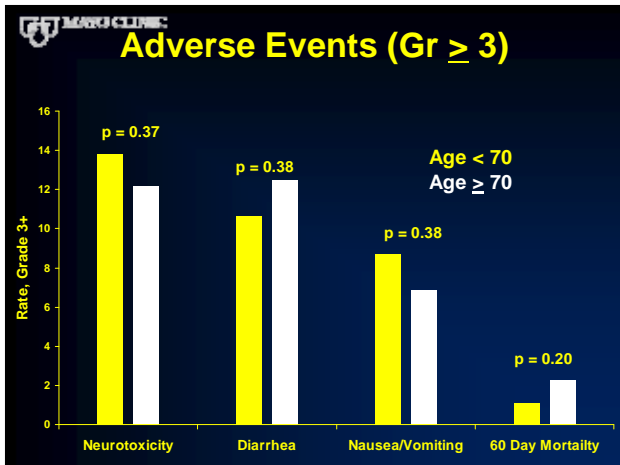


What about FOLFOX? Pooled analysis

Study	Comparator regimen	Setting	N
MOSAIC ¹	5-FU/LV	Adjuvant	2246
N9741 ²	IFL	1 st Line	546
de Gramont ³	5-FU/LV	1 st Line	420
Rothenberg ⁴	5-FU/LV	2 nd Line	531
Total			3743

¹Andre et al, NEJM 2004; ²Goldberg et al, JCO 2004; ³de Gramont et al, JCO 2000; ⁴Rothenberg et al, JCO 2003





- ### Age: Conclusions
- Among patients entered onto clinical trials
 - Younger and older patients accrue the same benefit from 5-FU/LV and FOLFOX4
 - Elderly patients do not experience clinically meaningful increased toxicity
 - Age alone should not exclude an otherwise healthy elderly patient from receiving FOLFOX chemotherapy

- ### Old Factor 2: PS
- Pooled analysis of 9 First Line Phase III Trials
 - Compare PS 0-1 to PS 2 patients
- Sargent et al, JCO 2009

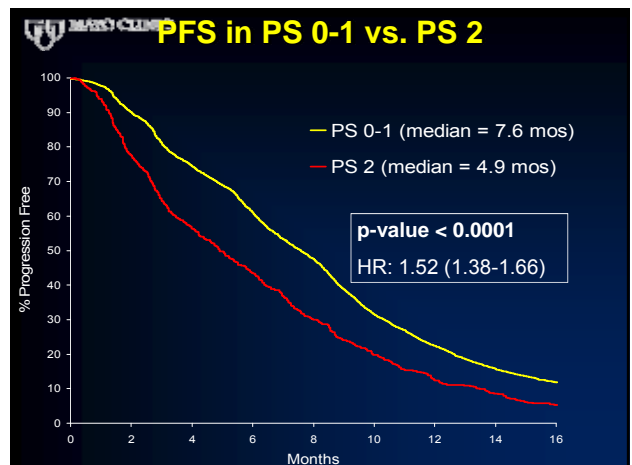
Trials Included

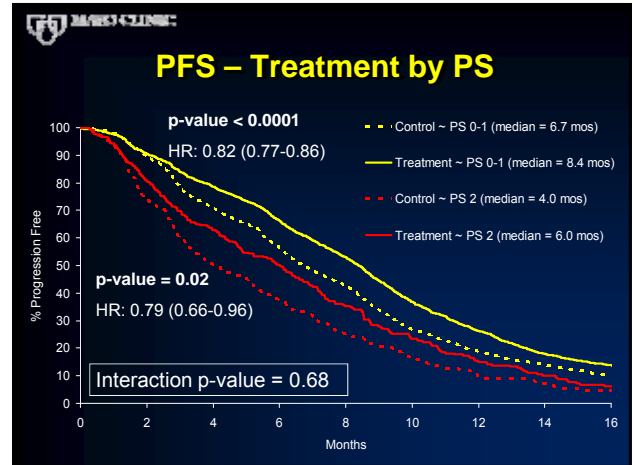
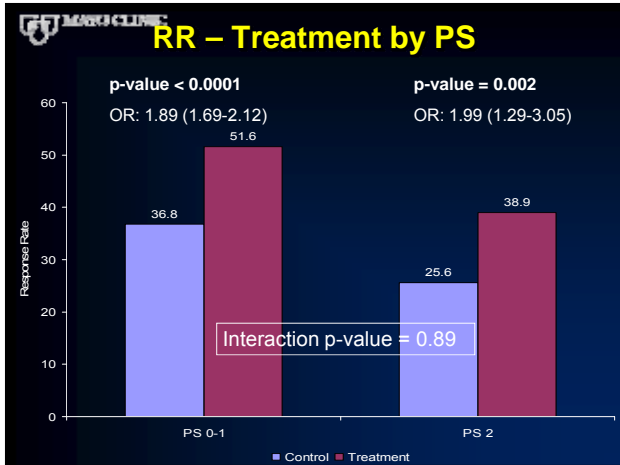
Trial	Treatment Arm	N	N, PS2
de Gramont	LVFU2 [†] , FOLFOX	420	44
Douillard	LVFU2 [†] , iFU/ir	385	27
FOCUS	iFU/LV [†] , iFU/Ox, iFU-Ir	2,135	180
N9741	IFL [†] , FOLFOX, IROX	1159	58
OPTIMOX	FOLFOX [†] +/-LVFU2	616	51
AIO	5FU/LV [†] +/- IRI	430	19
Porshen	FUFOX [†] , CAPEOX	471	39
Saltz	5-FU/LV [†] , IFL	444	65
Tournigand	FOLFOX [†] , FOLFIRI	226	26
Total		6286	509

***Defined Control**

Characteristics of 6,286 Patients

	PS 0-1	PS 2
No. Patients	5777	509
Age, Median Years (Range)	63 (19-88)	63 (24-84)
Sex, % Male	64	58
Study Arm, % Control	41	40



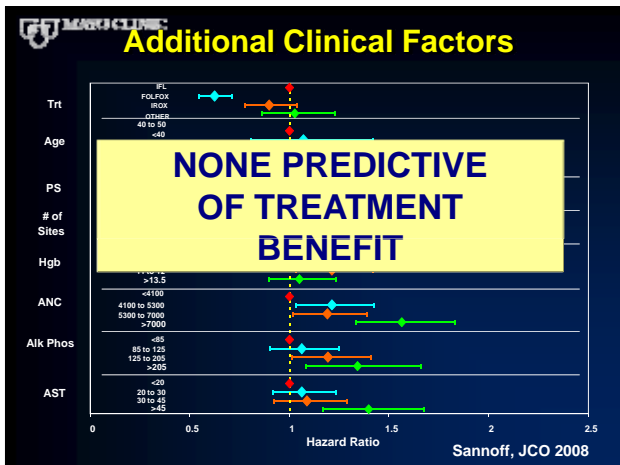


Grade ≥ 3 Toxicity by PS

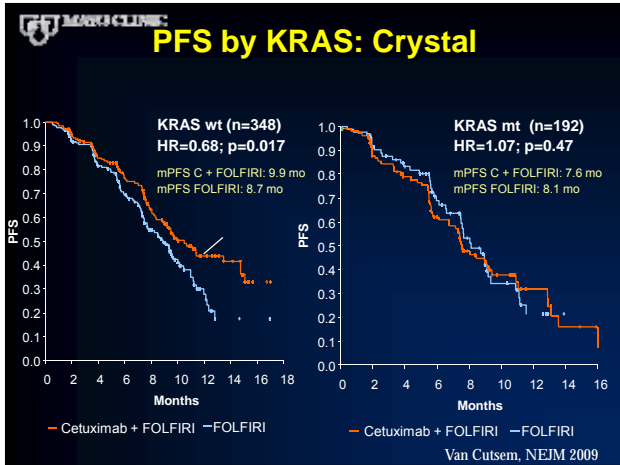
	PS 0-1	PS 2	P-value
Nausea*	8%	16%	< 0.0001
Vomiting*	8%	12%	0.006
Stomatitis*	2%	5%	0.11
Diarrhea*	17%	15%	0.32
N-penia*	34%	35%	0.51
60 day mortality	3%	12%	< 0.0001

*Note: FOCUS Trial Excluded

- ### PS: Conclusions
- Among patients entered onto clinical trials, PS 2 patients:
 - Have a poorer prognosis
 - Accrue similar benefit to PS 0-1 pts from superior Rx
 - Benefit more from 5-FU infusion with oxaliplatin or irinotecan
 - Have higher rates of nausea, vomiting, & 60-day mortality



New factor 1: KRAS



MARCO CLINE: No surprise: also for Pmab Press release 8/6/09

VECTIBIX® IN COMBINATION WITH CHEMOTHERAPY SIGNIFICANTLY IMPROVED PROGRESSION-FREE SURVIVAL IN FIRST-LINE METASTATIC COLORECTAL CANCER

Pivotal Study Meets Primary Endpoint of Progression-Free Survival in Wild-Type KRAS Population

Importantly, in patients with tumors harboring activating KRAS mutations, PFS was significantly inferior in the Vectibix arm. These data confirm previous findings when oxaliplatin-based chemotherapy and an anti-EGFR antibody are combined.

MARCO CLINE: New Factor 2: UGT1A1

MARCO CLINE: Severe Neutropenia Risk: 7/7 vs 6/6 + 6/7 Genotypes

Author	n/N (%)		Est. Odds Ratio	95% CI
	7/7	6/6 + 6/7		
Innocenti	3/6 (50%)	3/53 (6%)	16.7	2.3 - 120.6
Rouits	4/7 (57%)	10/66 (15%)	7.5	1.4 - 38.5
Marcuello ^a	4/10 (40%)	18/85 (21%)	2.5	0.6 - 9.7
Ando ^b	4/7 (57%)	22/111 (20%)	5.4	1.1 - 25.9

^aGr 3+ neutropenia.
^bGr 4 leukopenia and/or Gr 3+ diarrhea.

From Parodi et al, FDA Subcommittee presentation, November, 2004

MARCO CLINE: But not Irinotecan-specific: N9741

UGT1A1 genotype	IFL (n=109)	FOLFOX (n=285)	IROX (n=103)	All
6/6 (n=230)	7%	19%	10%	15%
6/7 (n=220)	11%	22%	15%	18%
7/7 (n=47)	18%	36%	55%	36%
p-Value*	0.46	0.11	0.004	0.007

McLeod, ASCO 2006

MARCO CLINE: Additional Potential Predictive Markers for Colon Cancer Treatment

Drug	Marker
Fluoropyrimidines	TS, DPD*, TP, MSI, MTHFR expression/polymorphisms
Irinotecan	UGT polymorphisms*, MSI, transporter polymorphisms
Oxaliplatin	ERCC1, GST P1, XPD expression, transporter polymorphisms
EGFR Antibodies	gene amplification/polymorphism, RAS mutation, BRAF mutation, ligand expression, PTEN expression, VEGF levels
VEGF inhibitors	VEGF polymorphisms, ICAM polymorphisms/levels, E-selectin levels, HIF1, Glut-1, VEGF gene expression
General	Circulating tumor cells

*FDA-recognized

Next Advance: identification of resistance markers in K-Ras Wild-type tumors

Acknowledgment: Lee Ellis

Bypass Pathways and EGFR Resistance

Camp et al Clin Ca Res 2005

B-raf mutations

All pts had progressed on at least one line of therapy

- ~50% received monotherapy with EGFR MoAB
- ~50 MoAB with chemotherapy

In patients with tumors with Mut B-raf, there were NO objective responses

Nicolantonio et al. JCO 2008

B-Raf Predicts for Benefit of Anti-EGFR Therapy in Patients with WT Ras and the Entire Cohort

Wild-type K-ras

All Patients

Bypass Pathways and EGFR Resistance

Camp et al Clin Ca Res 2005

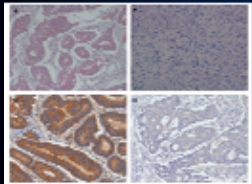
PTEN Expression and PFS

- PTEN in the metastasis was predictive of efficacy.
 - PTEN in the primary tumor was NOT predictive of efficacy.
- PTEN in the primary tumor and liver metastasis was concordant in only 60% of cases

Loupakis et al. JCO 2009

Challenges with PTEN

- Expression in primary tumors does not reflect expression in metastases
 - Although it is not lost or mutated in CRC, its expression can be regulated by methylation or miRNA
- Difficult to standardize IHC in different labs



Supplemental Figure 1: Representative examples of PTEN positive (A, B) and negative (C, D) cases. The cases reported in A and C panels were evaluated at Ospedale Niguarda Ca' Granda (Milan, Italy) whereas those in B and D at the Institute of Pathology in Locarno (Switzerland).

Sartore-Bianchi et al. Cancer Res 2009.

CAIRO -2 STUDY

CAPOX + Bevacizumab +/- Cetuximab
755 Pts

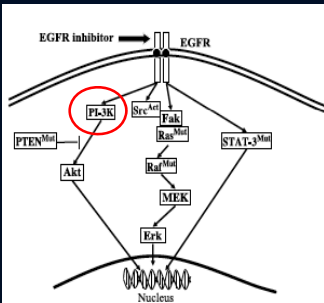
Tissue in 545

- ↑EGFR copy number 7%
no difference in PFS
among arms
- Loss PTEN 42%
no difference in PFS

EGFR amplification and PTEN did NOT predict for response to chemo + cetuximab therapy

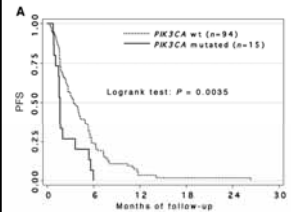
Tol et al. Proc AACR, 2009 Abstract 691

Bypass Pathways and EGFR Resistance



Camp et al Clin Ca Res 2005

PFS and PIK3CA Mutational Status in mCRC Patients Treated With Panitumumab and Cetuximab



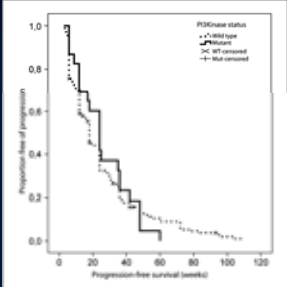
110 pts
> 85% received at least 1 prior Rx

Cetuximab	13%
Panitumumab	20%
Cetuximab/Irinotecan	67%

Sartore-Bianchi, A. et al. Cancer Res 2009

PIK3CA Mutations Are Not a Major Determinant of Resistance to the Epidermal Growth Factor Receptor Inhibitor Cetuximab in Metastatic Colorectal Cancer

Hans Prenen,¹ Jef De Schutter,¹ Bart Jacobs,² Wendy De Roock,² Bart Blesmans,² Bart Claes,² Doreen Lambrouck,² Erik Van Oosterom,² and Sabine Tejpar^{1,2}



Cetuximab	16
Cetuximab/Irinotecan	184

Prenen, H. et al. Clin Cancer Res 2009

The Role of PREDICTIVE Markers for Efficacy of EGFR MoABs

The sure thing	Probably Yes	Maybe, jury is still out	No
K-Ras	B-Raf	PI3K mutations	EGFR by IHC
		EGFR amplification	
		PTEN	
		Gene expression arrays	

- Excluding patients from EGFR MoAB Rx by use of multiple predictive factors will greatly increase the efficacy of EGFR MoABS
- It is imperative to PROSPECTIVELY include biomarkers and tissue procurement in clinical trials
 - When possible, biomarkers in primary tumors and liver metastasis should be compared

Predicting Survival in Advanced CRC: Conclusions

- Clinical factors of Age, PS should not exclude patients
- No factors to predict differential efficacy of Oxaliplatin vs irinotecan
- KRAS mutation definite exclusion for EGFR inhibitor
 - BRAF likely also will be validated, but lower prevalence
 - Other markers unclear
- No markers for anti-VEGF therapy