
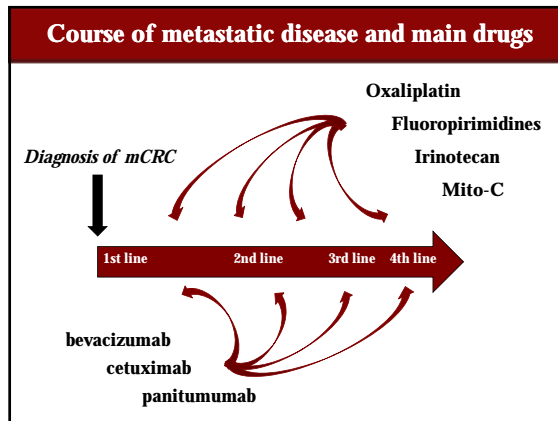


WCGIC 24-27 June 2009 Barcelona, Spain
 "Session XV - ESMO session: focus on young medical oncologists"

How to select patients on the basis of molecular factors: the perspective of a YMO in advanced disease

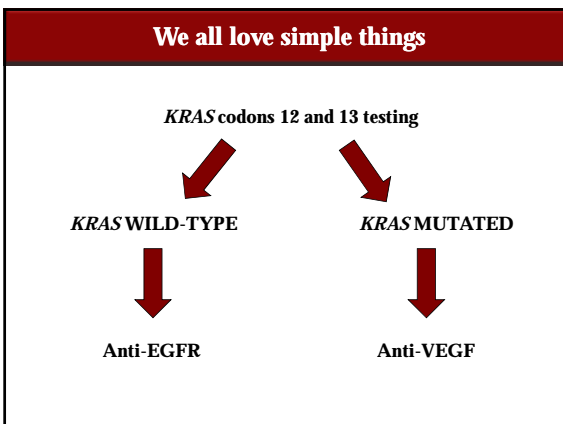
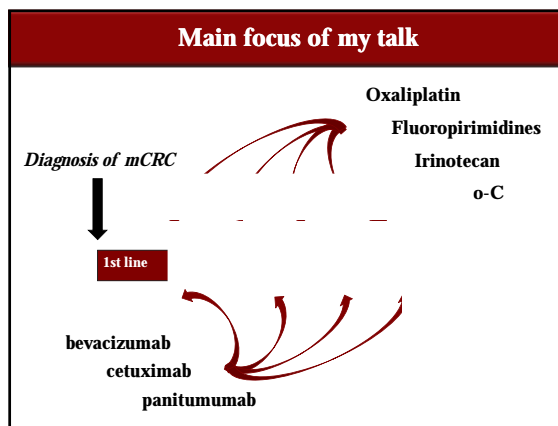
Fotios Loupakis
 U.O. Oncologia 2 Universitaria - Azienda Ospedaliero-Universitaria Pisana
 Istituto Toscano Tumori


Selection for chemo: where do we stand?

Review
A review on the use of molecular markers of cytotoxic therapy for colorectal cancer, what have we learned?
 Results: With the exception of mismatch repair deficiency, these molecular markers showed divergent and inconsistent results on their prognostic and/or predictive value.
 M. Koopman et al. Eur J Cancer '09

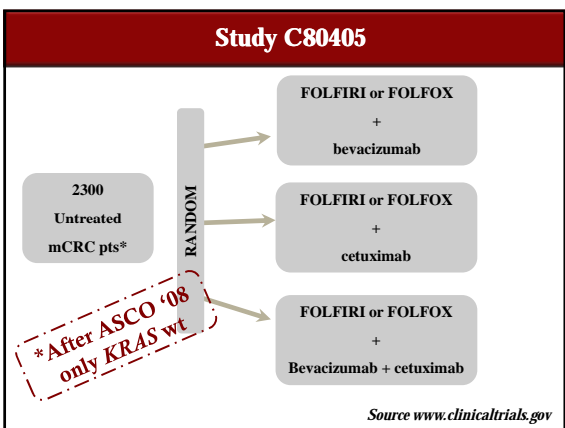
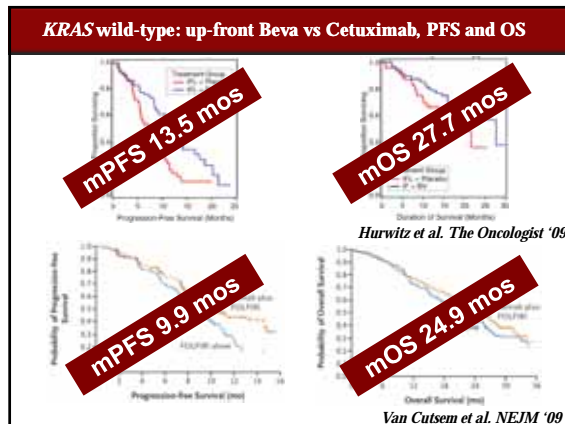
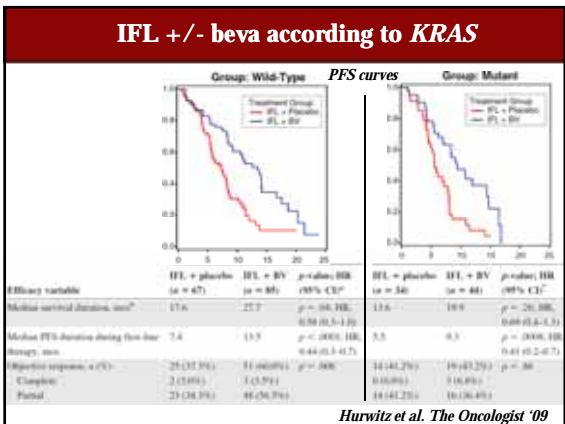
Editorial Comment
Molecular markers of chemotherapy in advanced colorectal cancer: Back to square one
 A. Sobrero Eur J Cancer '09



Since ancient times ...simplicity has raised questions



1. What is the best for KRAS wt patients?



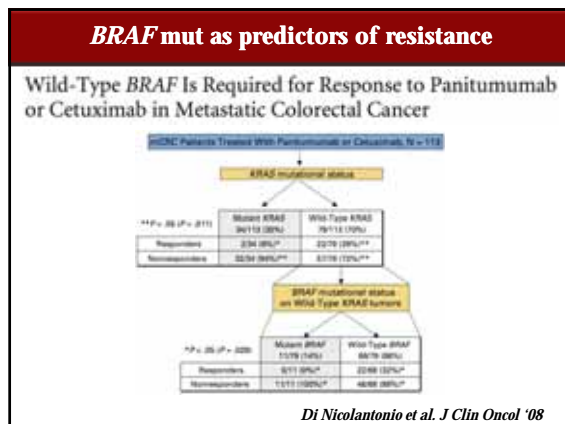
Since ancient times ...simplicity has raised questions

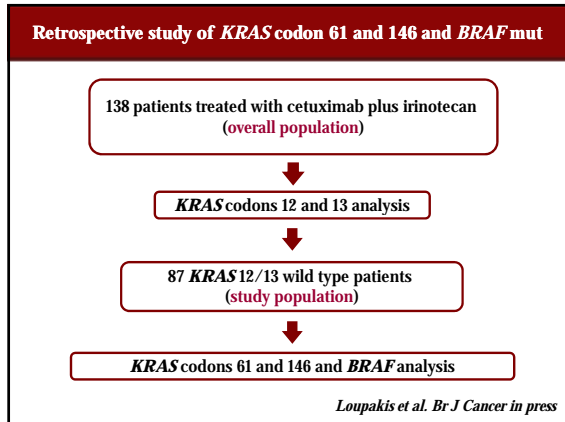
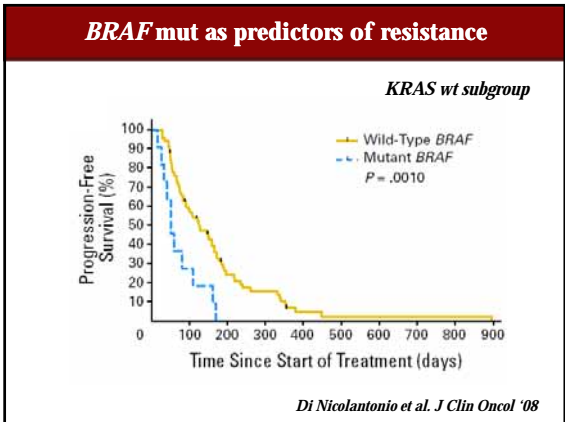
...and answers have been a mixture of science and philosophy...

1. What is the best for *KRAS* wt patients?
Up today no direct comparisons beva vs anti-EGFRs, similar benefits vs chemo alone, therefore consider clinical risks for toxicities and patients preferences

Since ancient times ...simplicity has raised questions

2. Do all *KRAS* wt patients benefit from anti-EGFRs?





Activity: main results

KRAS 12 and 13 mutations in the overall population			
N=138			
	KRAS 12/13 mut (n=63)	KRAS 12/13 wt (n=75)	Fisher's exact test: p=0.304
Non responders	48 (76%)	63 (77%)	
Responders	7 (11%)	24 (29%)	

STUDY POPULATION (n=87)				
KRAS 61 and 146 mutations		BRAF V600E mutation		
N=76 (11 not evaluable)		N=67		
	KRAS 61/146 mut (n=6)	KRAS 61/146 wt (n=70)	BRAF mut (n=12)	BRAF wt (n=55)
Non responders	6 (100%)	46 (66%)	13 (100%)	40 (73%)
Responders	0 (0%)	22 (31%)	0 (0%)	21 (37%)

Fisher's exact test: p=0.008 (KRAS 61/146); p=0.016 (BRAF)

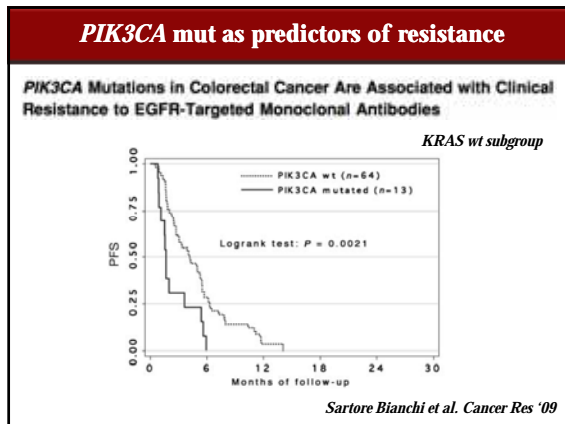
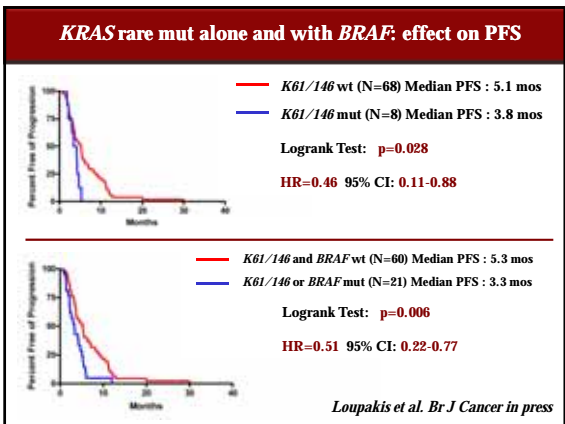
Loupakis et al. *Br J Cancer in press*

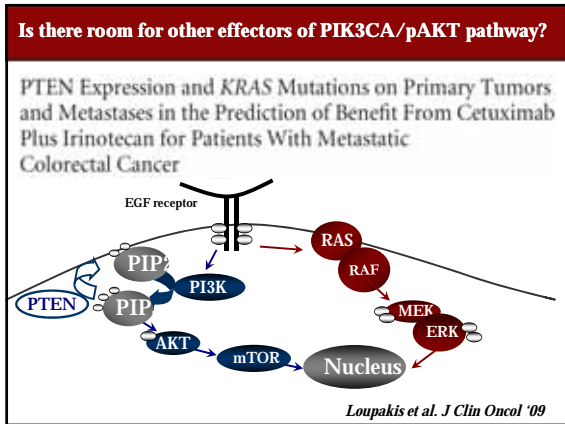
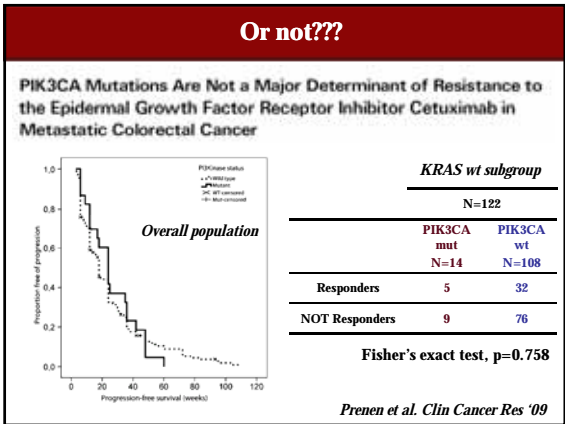
Activity: combined analysis of BRAF and KRAS rare mut

N= 87 (6 not evaluable) → 81 evaluable		
	KRAS 61/146 or BRAF mut (N=21)	KRAS 61/146 and BRAF wt (N=60)
Non responders	21 (100%)	38 (63%)
Responders	0 (0%)	22 (37%)

Fisher's exact test: p=0.0005

Loupakis et al. *Br J Cancer in press*





PTEN-IHC: concordance between prim and mets

45 primaries and related mets evaluable

	PTEN + Primary	PTEN - Primary
PTEN + Mets	16 (36%)	11 (24%)
PTEN - Mets	7 (16%)	11 (24%)

Concordance: 27/45 = 60% (95% CI: 46-74%)

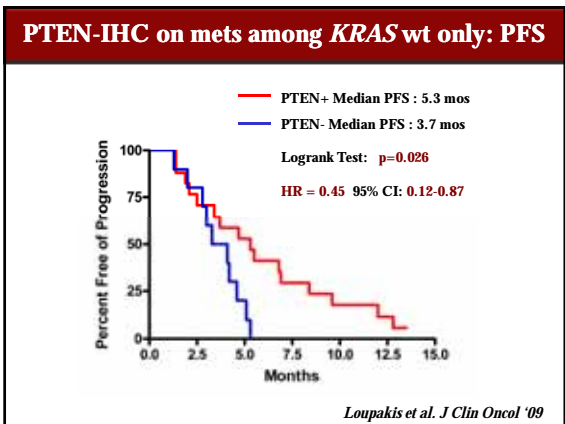
Loupakis et al. J Clin Oncol '09

PTEN-IHC on mets: activity

	N=55 (4 not evaluable)	
	PTEN + n=33	PTEN - n=22
Responders <small>(8 RECIST + 5 SD0)</small>	12 (36%)	1 (5%)
NOT Responders	21 (64%)	21 (95%)

Responders vs NOT Responders
Fisher's Exact Test: p=0.007

Loupakis et al. J Clin Oncol '09



Since ancient times ...simplicity has raised questions

2. Do all KRAS wt patients benefit from anti-EGFRs?

No. Rare *KRAS* mutations as well as *BRAF* mutations are the most promising markers to further refine patients' selection

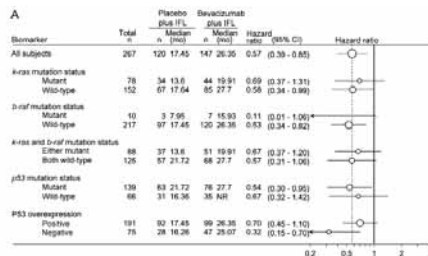
Since ancient times ...answers have raised new questions



3. What about beva?

Molecular analyses of phase III IFL +/- beva

KRAS, BRAF and p53 mutations



Ince et al. JNCI '05

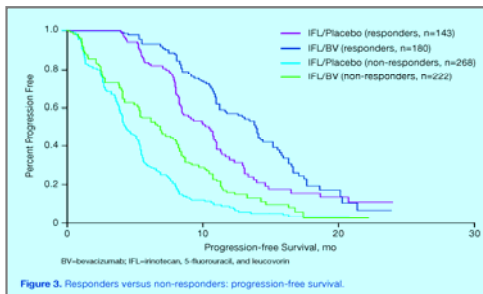
Molecular analyses of phase III IFL +/- beva

VEGF and Thrombospondin-2 expression and microvessel density

Stratification	Number	Placebo (n=133)	IFL (n=134)	Microvessel Density Ratio	Hazard Ratio
VEGF (201) VEGF expression score					
< 3	62	35	27	1.22	0.98
≥ 3	71	31	40	1.28	0.91
Thrombospondin-2 (201) Thrombospondin-2 expression score					
< 3	62	35	27	1.22	0.98
≥ 3	71	31	40	1.28	0.91
Microvessel density (201) Microvessel density score					
< 3	62	35	27	1.22	0.98
≥ 3	71	31	40	1.28	0.91

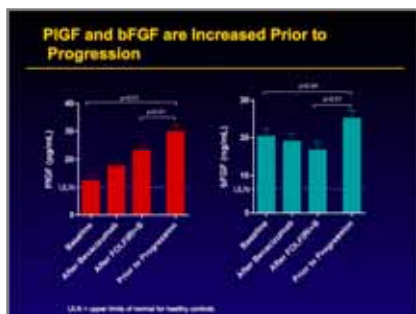
Jubb et al. JCO '06

Do even non responders "respond" to beva?



Mass et al. ASCO '05

Maybe possible markers of "acquired resistance" ...



Kopetz et al. ASCO Gastrointestinal '09

Maybe multiple along the way




PREDICTIVE vs PROGNOSTIC

PREDICTIVE FACTOR
Predicts likelihood of response to tx

PROGNOSTIC FACTOR
Correlates with outcome regardless of tx

PREPRODIGNOSTIC FACTORS

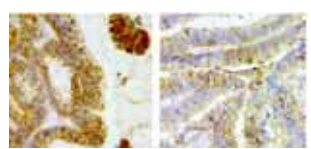


Stage of disease (II vs III vs IV (1st vs 2nd vs 3rd etc...))

Received tx (actually or Even previously!!!)

EGFR-IHC: technical...

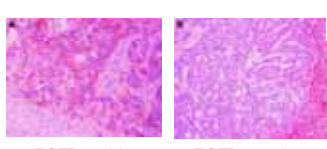
- ✓ Different epitopes bound (Chung 2005)
- ✓ Tissue fixation (Stein 1996)
- ✓ Storage time (Atkins 2004)
- ✓ Non-homogeneous pattern of expression



EGFR-positive EGFR-negative

...and biological limitations


Lack of concordance between primaries and related metastases in 26 out of 99 analysed pairs (26%)



EGFR-positive EGFR-negative

Scartozzi et al. J Clin Oncol '05

BRAF mutations in the CRYSTAL trial: size matters

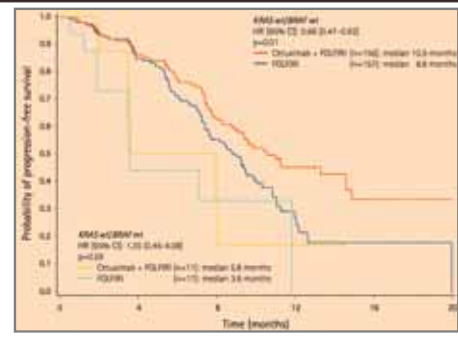


Response rate (%)

Legend: Cetuximab + FOLFIRI (orange), FOLFIRI (blue)

Kohne et al. ASCO '09 #4068

BRAF mutations in the CRYSTAL trial: size matters



Probability of progression-free survival

Time (months)

Kohne et al. ASCO '09 #4068

BRAF mutations in the CRYSTAL trial: premises & conclusions

Results for the *BRAF* population should be interpreted with caution due to the small numbers of patients with *BRAF* mutant disease

↓

BRAF tumor mutation status was not predictive of cetuximab efficacy in terms of PFS and OS in this analysis

...the routine testing of mCRC tumors for *BRAF* mutation status is unlikely to be useful for directing tx in the 1st-line tx of mCRC in combination with CT

Kohne et al. ASCO '09 #4068

BRAF mutations in the CRYSTAL trial: premises & conclusions

Results for the *BRAF* population should be interpreted with caution due to the small numbers of patients with *BRAF* mutant disease

↓

BRAF tumor mutation status was not predictive of cetuximab efficacy in terms of PFS and OS in this analysis

↓

...

Rougier et al. WCGIC '09

New markers: the problem of the possible overlap

KRAS WILD-TYPE SUBGROUP			
	N	Amphiregulin IHC Mean Score	p
<i>BRAF</i> wild type	39	79.7	0.0023
<i>BRAF</i> mutated	10	18	

Cremolini et al. WCGIC '09

PTEN-IHC on primaries: the importance of pts' selection

	PTEN+	PTEN-
Responders	10	0
NOT Responders	6	11


Fisher's Exact Test: p=0.001

Loss of PTEN expression significantly predicts resistance to cetuximab...

117	M	72	FOLFIRI/CAPRI	3rd	CPT11+Amfresumab (C7)	28
118	F	72	SF/ULV/CPT11	3rd	CPT11+Amfresumab (C7)	30
120	F	43	None	1st	CAPRI+Amfresumab (C7)	28
121	F	88	CAP/CPT11	3rd	CPT11+Amfresumab	10
122	M	59	CAP/OKR/FOLFIRI	3rd	CPT11+Amfresumab	30

Frattini et al. BJC '07

Always the same awaited "happy ending"!



Our retrospective analysis suggests that Marker X is **very promising**...

...it deserves further investigation in
Well-conducted
Adequately powered
Prospective clinical trials
...To be validated.

... and we loved the happy ending too!

PTEN Expression and KRAS Mutations on Primary Tumors and Metastases in the Prediction of Benefit From Cetuximab Plus Irinotecan for Patients With Metastatic Colorectal Cancer

In conclusion, it is urgent to plan adequately dimensioned trials to confirm and to prospectively validate the integrated analyses of EGFR signaling pathways, eventually combined with other promising predictive factors (ie, EGFR polymorphisms⁴¹ and EGFR ligand expression¹²) as useful tools to select patients undergoing cetuximab-containing treatments.

Loupakis et al. J Clin Oncol '09

The well conducted, prospective, validating clinical trial

Pretreated KRAS wt mCRC pts With mts samples assessable for PTEN - IHC

2-tailed Alfa: 5%
Power: 80%
24 months enrollment
12 months F-up

SCREENING

50% PTEN +

RANDOM

CETUXIMAB (HR: 0.45)
BSC

50% PTEN -

RANDOM

CETUXIMAB (HR: 1)
BSC

Considering that...

1050
 60% of CRISPRAS-wt
 patients
 should be screened

To be "adequately" powered!

...the road from "ideas" to "bedside" is winding

- ✓ Conflicting results from retrospective analyses
- ✓ Methodological difficulties (cut-offs, reproducibility, expertise, costs)
- ✓ No "black or white" association with benefit from Tx
- ✓ No real influence on the choice of a "better alternative"
- ✓ Validating trials usually utopian
- ✓ No immediate economic interest

...the road is winding...and we have to walk it uphill

Most drugs are approved after *overpowered studies* demonstrating small *statistically significant but clinically questionable* advantages

And then, it is *almost impossible* to validate reliable molecular markers for selection



Efficacy of BSI-201, a PARP Inhibitor, in Combination with Gemcitabine/Carboplatin in Triple Negative Metastatic Breast Cancer: Results of a Phase II Study

Joyce O'Shaughnessy^{1,2,4}, Cynthia Osborne^{1,2,4}, John Pippin^{1,2,4}, Debra Platt^{1,4}, Christine Hochs¹, Valeria Ossoskovskaya¹, Barry M. Sherman¹, Charles Bradley¹

¹Baylor Sammons Cancer Center, ²Texas Oncology, Dallas, TX, ³Texas Oncology Cancer Center, Austin, Texas, ⁴US Oncology Dallas, TX, ⁵MPiPharm Sciences, Inc., Brisbane, CA

ASCO Annual Meeting

Since ancient times ...every "young" has had his own mentor



The School of Athens, fresco Raffaello 1509 - Vatican City

