

## Poster discussion on colorectal cancer: ECLU july 2007



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## Maximising patient outcomes in CRC



- Colorectal cancer treatment in a context of a *Continuum of Care*:
  - Treatment plan throughout the continuum of care, based on best available evidence
  - More effective drugs now available and trend towards a targeted and possibly “tailored” therapy
  - Multi-Disciplinary Approach: i.e. *resection of liver metastases*

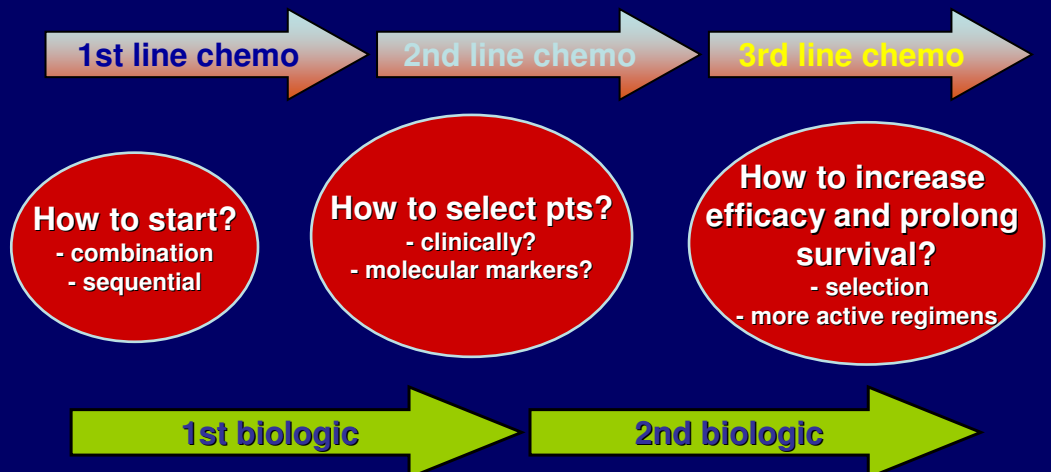
Goldberg R, Rothenberg M, Van Cutsem E et al. Oncologist 2007



## Treatment of metastatic CRC

	Survival		
	Med (mo)	1 yr (%)	2 yr (%)
- Best Supp. Care	6	< 30	< 10
- 5-FU + FA	11-12	45	20-30
• Capecitabine	12	50	20-30
• Irinotecan	18	60-70	30-40
• Oxaliplatin	18	60-70	30-40
• Bevacizumab	20-24	70	40-50
• Cetuximab	?	?	?
• Panitumumab	?	?	?

## The issues that face us to achieve a continuum of care



modified from Van Cutsem E. Editorial *J Clin Oncol*. 2006

# Challenges in CRC

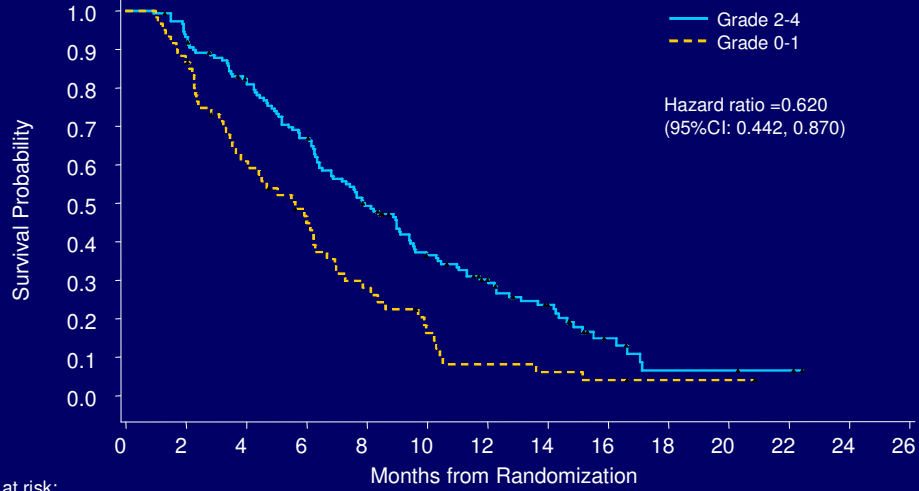
- Strategy:
  - 2 agents **vs** 3 agents
  - 3 cytotoxics **vs** 2 cytotoxics + 1 biological
  - 2 cytotoxics + 1 biological **vs** 2 cytotoxics + 2 biologicals
  - 1 cytotoxic (later sequential use) **vs** 2 cytotoxics
  - 1 cytotoxic **vs** 1 cytotoxic +1 biological
- Strategy
  - Which cytotoxic first
  - Which biological first: VEGF inhibitor or EGFR inhibitor
  - **Resection of unresectable disease: 36 PD, Bosch**
  - Drug holidays
  - **Optimizing regimen: 35 PD Martin-Martorell**
- Selection of patients and of tumors
  - **Markers: 32 PD Buhmeida, 34 PD Gevorgyan**
  - Pharmacogenomics
- ....

## Patient selection after EGFR inhibitors



- Skin rash
- EGFR - IHC
- Downstream markers
- Gene Mutations
- K-ras
- EGFR gene copy number, as assessed by FISH
- Amphiregulin, epiregulin
- ...

## Overall Survival by Worst Severity of Skin Toxicity in the Panitumumab Patients

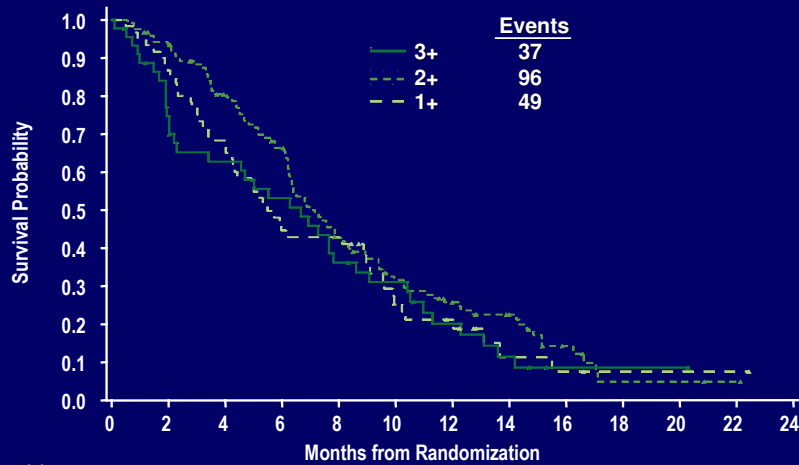


Patients at risk:  
Grade 2-4  
Grade 0-1

Note: Hazard ratio adjusted for ECOG score and geographic region  
Analysis restricted to patients with at least grade 0 skin toxicity and with progression-free survival of at least 28 days

Van Cutsem E et al. J Clin Oncol, 2007

## Overall Survival<sup>a</sup> for Panitumumab by EGFr Tumor Membrane Staining Intensity



Patients at risk:  
3+  
2+  
1+

<sup>a</sup>12-month analysis

Siena S, Van Cutsem E et al. Ann Oncol 2006 abstract ESMO

## Epidermal Growth Factor Receptor (EGFR) and *KRAS* mutations as predictors of clinical benefit on cetuximab-based therapy in patients (pts) with advanced colorectal cancer

*Arpine Gevorgyan, MD  
Unit of Medical Oncology 2  
Milan, Italy*

*PD 34*



### Patients and Methods

- ❖ 40pts previously treated with Oxaliplatin, Irinotecan, 5FU for metastatic disease received: **Cetuximab 400-250 mg/m<sup>2</sup>/w; Irinotecan 300 mg/m<sup>2</sup> d1 q 21**
- ❖ Disease evaluation according to RECIST
- ❖ EGFR-IHC expression on primary and metastatic tissue specimen (where available)
- ❖ FISH for EGFR Gene status
- ❖ Direct sequencing of exon1 of the *KRAS*-gene

Gevorgyan et al, ECLU 2007

## Conclusions

- ❖ According to our experience, IHC and FISH are unable to provide adequate selection criteria for the pts with different EGFR-status expression who can benefit from cetuximab therapy
- ❖ No information on K-Ras

Gevorgyan et al, ECLU 2007

## Treatment with Cetuximab or Panitumumab in Advanced *EGFR* Gene Amplified mCRC

	Responder*	Non-responder	Total
<i>EGFR</i> amplification	8	1	9
No <i>EGFR</i> amplification	1	20	21

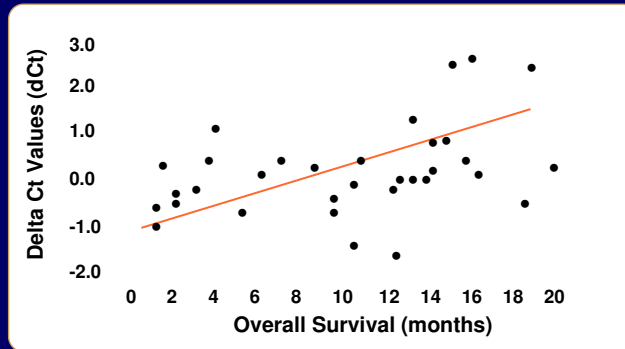
\*9 of 10 responders were assessable by FISH

- There was a correlation between *EGFR* amplification and response to cetuximab ( $p < 0.0001$ )
- However, the frequency of *EGFR* amplification in colorectal cancer is less than that observed by Moroni et al. (2005)<sup>1</sup>. The actual frequency may be about 10%<sup>2,3</sup>

<sup>1</sup>Moroni M. *et al.* Lancet Oncol 2005; 6:279-86; <sup>2</sup>Shia J. Mod Pathol 2005; 18:1350-6; <sup>3</sup>Sauer T. Histopathology 2005; 47:560-4.

## EGFR Gene Copy Number Correlated with OS, Not with PFS or RR

346 pts, refractory to irinotecan, oxaliplatin and fluoropyrimidines, were treated with cetuximab Quantitative PCR in 34 pts



Results

**EGFR gene copy number correlated significantly with OS (p=0.03)**

**EGFR gene copy number did not relate to RR or PFS**

Lenz J, Van Cutsem E, et al Clin Oncol 2006; 24:4914-21.

## Predictive Markers for Cetuximab in Refractory MCRC Patients

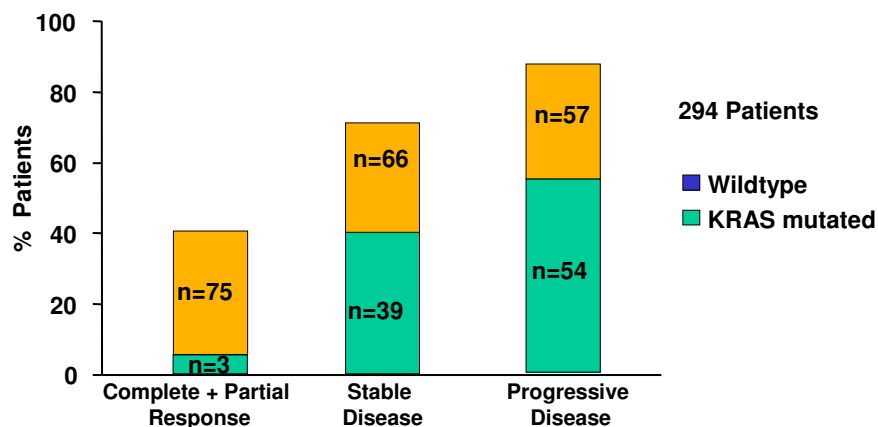
n = 85	RR	PFS	OS
EGFR FISH	++	trend	no
K ras mutations	+	trend	no
EGFR FISH & K ras	+++	+	no

Correlation of expression profile between metastasis and primary tumor

Finocchiaro et al, Proc ASCO 2007

## Negative Association of KRAS Mutation with Response to Anti-EGFR Antibodies:

Pooled Data from 5 Mono and Combination Therapy Studies



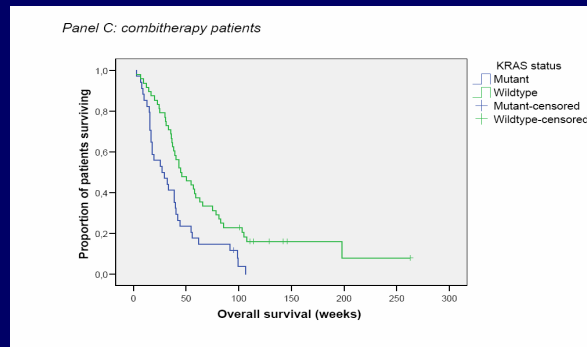
Moroni M *et al.* Lancet Oncol 2005; 6:279-86; Lièvre A. *et al.* Cancer Res 2006; 66:3992-5; Benvenuti S. *et al.* Cancer Res 2007; 67:2643-8; Di Fiore F. *et al.* Br J Cancer 2007; 96:1166-9; De Roock W... Van Cutsem E. JCO 2007; 25(18S):4132; Lièvre A. *et al.* AACR 2007. Abstract 5671. (borrowed from P Laurent-Puig)

## K-RAS Mutations in Refractory CRC

	N	K-RAS mutations	RR all pts.	RR pts. with mutations	survival
Lièvre	30	43%	37%	0%	OS 7 vs. 16 mos.
Di Fiore	59	27%	20%	0%	PFS 3 vs. 5.5 mos. p<0.015
De Roock	113	41%	41%	0%	OS 7 vs. 11 mos.

Lièvre, Cancer Res 2006; Di Fiore, Br J Cancer 2007; De Roock...Van Cutsem E, Tejpar S, ASCO 2007

## K-RAS in irinotecan refractory mCRC treated with cetuximab + irinotecan



**OR:**

**Med OS:**

27/66 K-Ras wild type pts vs 0/42 in K-Ras mutants.  
K-Ras WT vs mutants: 43.0 v 27.3 weeks; p 0.020  
(all patients: n = 113; combination cetuximab/irinotecan = 83)  
HR= 0.620 (95% CI 0.41 – 0.92)

De Roock , Van Cutsem, Tejpar; ASCO 2007

## Expression Patterns of $\beta$ -catenin in primary and their corresponding metastatic colorectal carcinomas

Buhmeida Abdelbaset et al  
Turku University Hospital  
Turku, Finland  
ECLU July 5-8, 2007

**Aim:**  $\beta$ -catenin by IHC in 33 pairs of primary and metastatic CRC

## RESULT: Different levels of $\beta$ -catenin expression in Primary and their corresponding metastatic lesions

82% of primary cancer lesions revealed (high MI P and low or absent NI P), while 18% revealed the opposite (low MI P and high NI P).

66 % of Secondary cancer lesions revealed the same behaviour which is (high MI M and low or absent NI M). 34% revealed the opposite (low MI M and high NI M)

Similarly, 70% of the primary tumours had high MI P and low CI P, whereas in the metastatic lesions only 45% of cases revealed high MI M and low CI M.

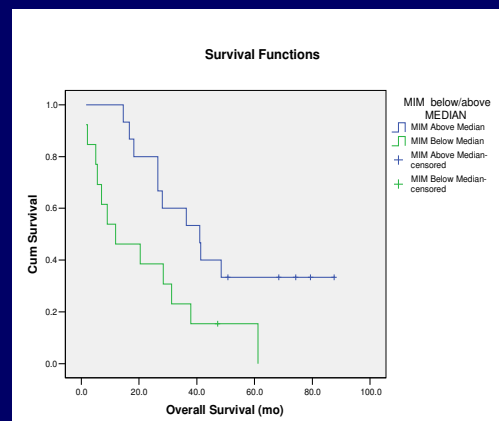
Buhmeida Abdelbaset et al, ECLU July 5-8, 2007

## RESULT: Survival and Membranous Index Metastases

Membranous Index Metastases < median = 21 months

Membranous Index Metastases > median = 49 months

$p < 0.01$



Buhmeida Abdelbaset et al, ECLU July 5-8, 2007

## **BIWEEKLY CETUXIMAB (500mg/m<sup>2</sup>) AND IRINOTECAN (180mg/m<sup>2</sup>) FOR THE TREATMENT OF REFRACTORY METASTATIC COLORECTAL CANCER**

P. Martín Martorell, E. Rodríguez Braun, A. Pérez Fidalgo, I. Chirivella, A. Insa, A. Cervantes  
University Hospital Valencia, Dept. of Hematology and Medical Oncology, Valencia, Spain.

ECLU Conference Lugano 5-8 July 2007

## **CONCLUSIONS**

**Biweekly administration of cetuximab 500mg/m<sup>2</sup> and irinotecan 180mg/m<sup>2</sup> is feasible in CRC (n = 25)**

**Overall response rate and time to progression are comparable to weekly administration schemes**

**Similar pharmacodynamic and pharmacokinetic behaviour (EMR 62-202045 – ASCO 2007)**

**Acceptable toxicity profile**

P. Martín Martorell et al, ECLU 2007

## Weekly vs every-second-week Cetuximab schedule: efficacy

	Cetuximab + irinotecan schedule		
	Every 2 weeks (n=40)	Weekly (n=65)	BOND <sup>1</sup> (n=218)
Duration of therapy	<b>16 w<sup>a</sup></b>	<b>16 w</b>	<b>18 w</b>
Response rate (CR + PR)	<b>22%</b>	<b>20%</b>	<b>23%</b>
TTP	<b>4.8 m</b>	<b>5.4 m</b>	<b>4.1 m</b>
OS	<b>9.8 m</b>	<b>10.4 m</b>	<b>8.6 m</b>

<sup>a</sup>8 courses (q2w)

<sup>1</sup>Cunningham... Van Cutsem EI. NEJM 2004;351:337-345;  
Pfeiffer P, et al. ASCO GI 2007 (Abstract No. 305)

## RESECTION OF LIVER METASTASES IN COLORECTAL CANCER (CRC). ANALYSIS OF PROGNOSTIC FACTORS IN AN INSTITUTIONAL SERIES OF PATIENTS MANAGED WITH SURGERY OR NEOADYUVANT CHEMOTHERAPY (NC) IN A MULTIDISCIPLINARY TEAM APPROACH

**DESIGN:**

**RETROSPECTIVE OBSERVATIONAL STUDY in 104 patients**

Bosch A et al, ECLU 2007

## Outcome in 2 groups of patients with resected metastases of CRC

	PRIMARY SURGERY	PREOP-CT	p
MEDIAN PROGRESSION FREE SURVIVAL	26.2 m	20.5 m	0.23
MEDIAN OVERALL SURVIVAL	53.9 m	30.1 m	0.01
OVERALL SURVIVAL AT 5 YEARS	34%	16%	

- Pts who needed pre-op. Chemotherapy: worse outcome  
Why Chemotherapy needed? Probably selection

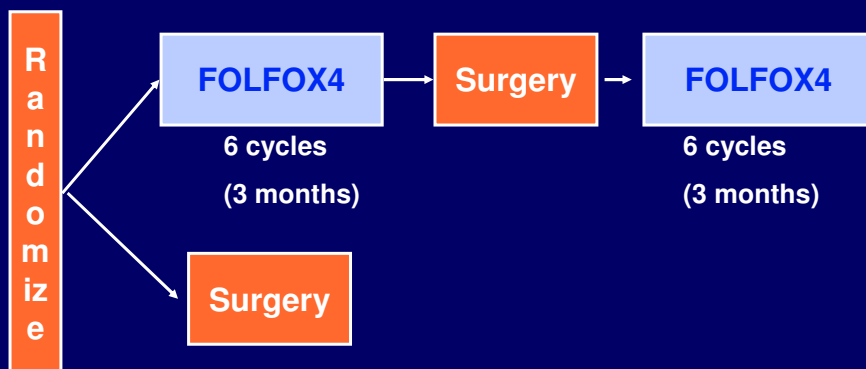
Bosch A et al, ECLU 2007

## Colorectal liver metastases

Disease is limited to the liver:

- **Unresectable** liver metastases
  - Neoadjuvant or induction chemotherapy followed by resection if response?
- **Resectable** liver metastases
  - Neoadjuvant and/or adjuvant chemotherapy?

## EORTC 40983: Study design



N=364 patients with  $\leq 4$   
resectable livermetastases

Nordlinger B et al, Proc ASCO 2007

## EORTC 40983: Results

	N pts CT	N pts Surgery	% absolute difference in 3-year PFS	Hazard Ratio (Confidence Interval)	P-value
<b>All patients</b>	<b>182</b>	<b>182</b>	<b>+7.2%</b> (28.1% to 35.4%)	<b>0.79</b> (0.62-1.02)	<b>P=0.058</b>
<b>All eligible Patients</b>	<b>171</b>	<b>171</b>	<b>+8.1%</b> (28.1% to 36.2%)	<b>0.77</b> (0.60-1.00)	<b>P=0.041</b>
<b>All resected Patients</b>	<b>151</b>	<b>152</b>	<b>+9.2%</b> (33.2% to 42.4%)	<b>0.73</b> (0.55-0.97)	<b>P=0.025</b>

Nordlinger B et al, Proc ASCO 2007