SERVIZIO SANITARIO REGIONALE
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DA SEICENTO ANNI GUARDIAMO AVANTI.

Malattia Metastatica del Carcinoma del Grosso Intestino
Tecniche e terapie Innovative

Come è cambiata la storia naturale della malattia

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Oncologia Clinica - Ferrara

29 ottobre 2011

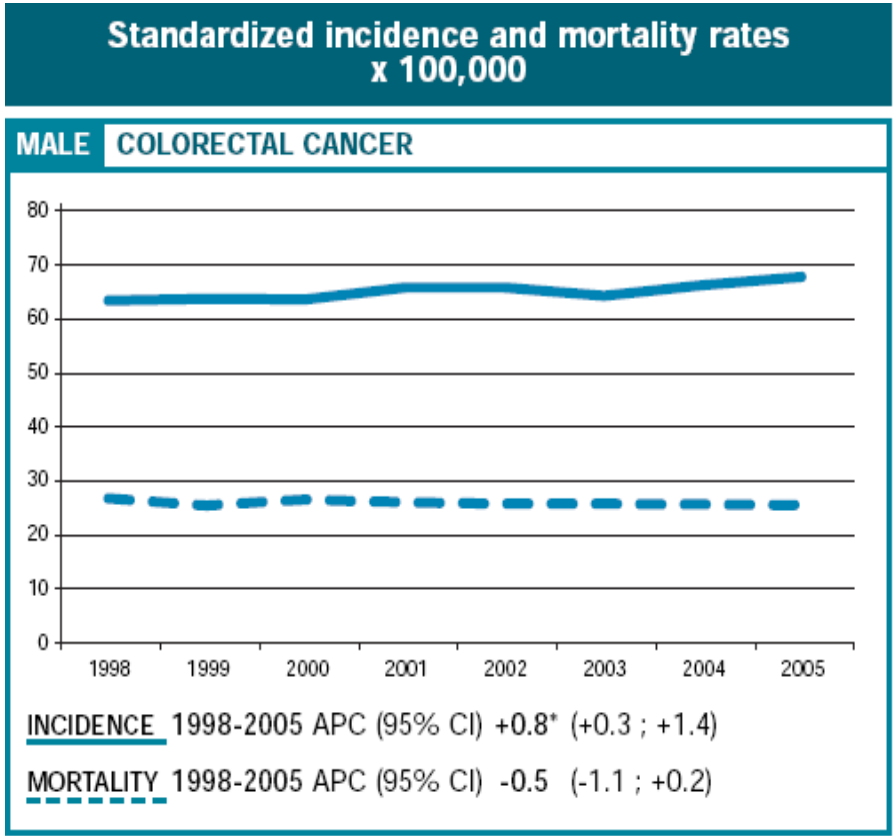
Colorectal Cancer: Survival

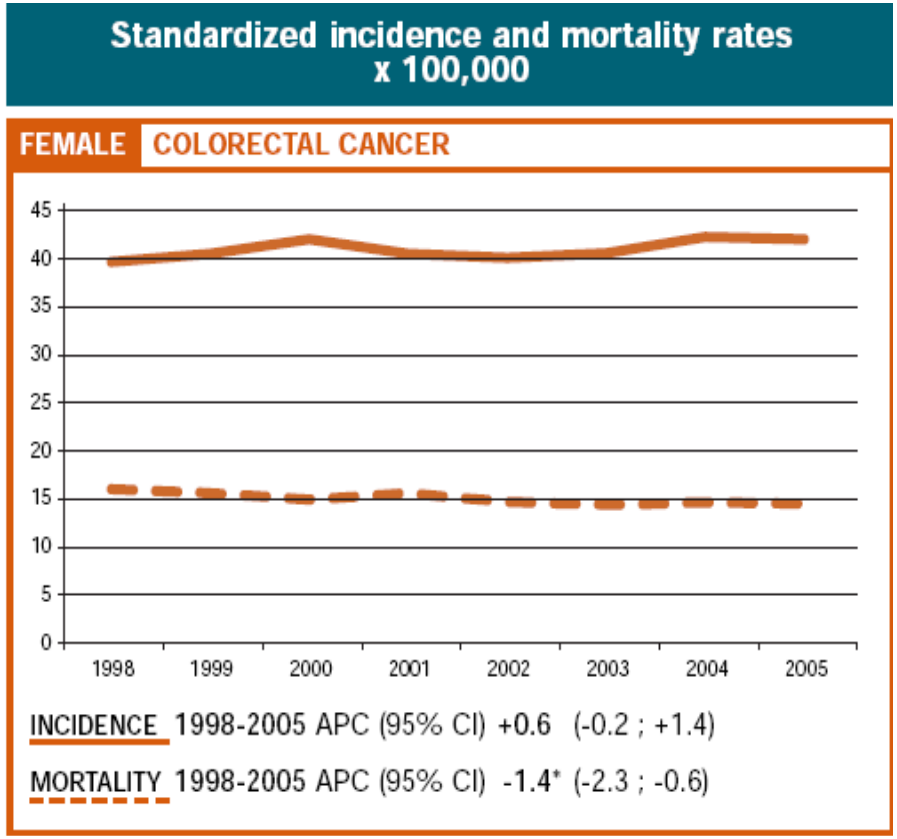
- CRC is second leading cause of all cancer deaths[1]
  - Estimated deaths in 2010[1]
    - Males: 26,580 (9%)
    - Females: 24,790 (9%)
- CRC-related deaths have declined steadily over past 20 yrs[1]
  - Due to improvements in screening, early detection, and

Overall 5-Yr Relative Survival,[2] %	65.0
• White males	66.0
• White females	65.7
• Black males	55.6
• Black females	56.6

1. American Cancer Society. Cancer facts & figures. 2010. 2. SEER stat fact sheets: colon and rectum. 2010.

Mortality trends show sligth decrease





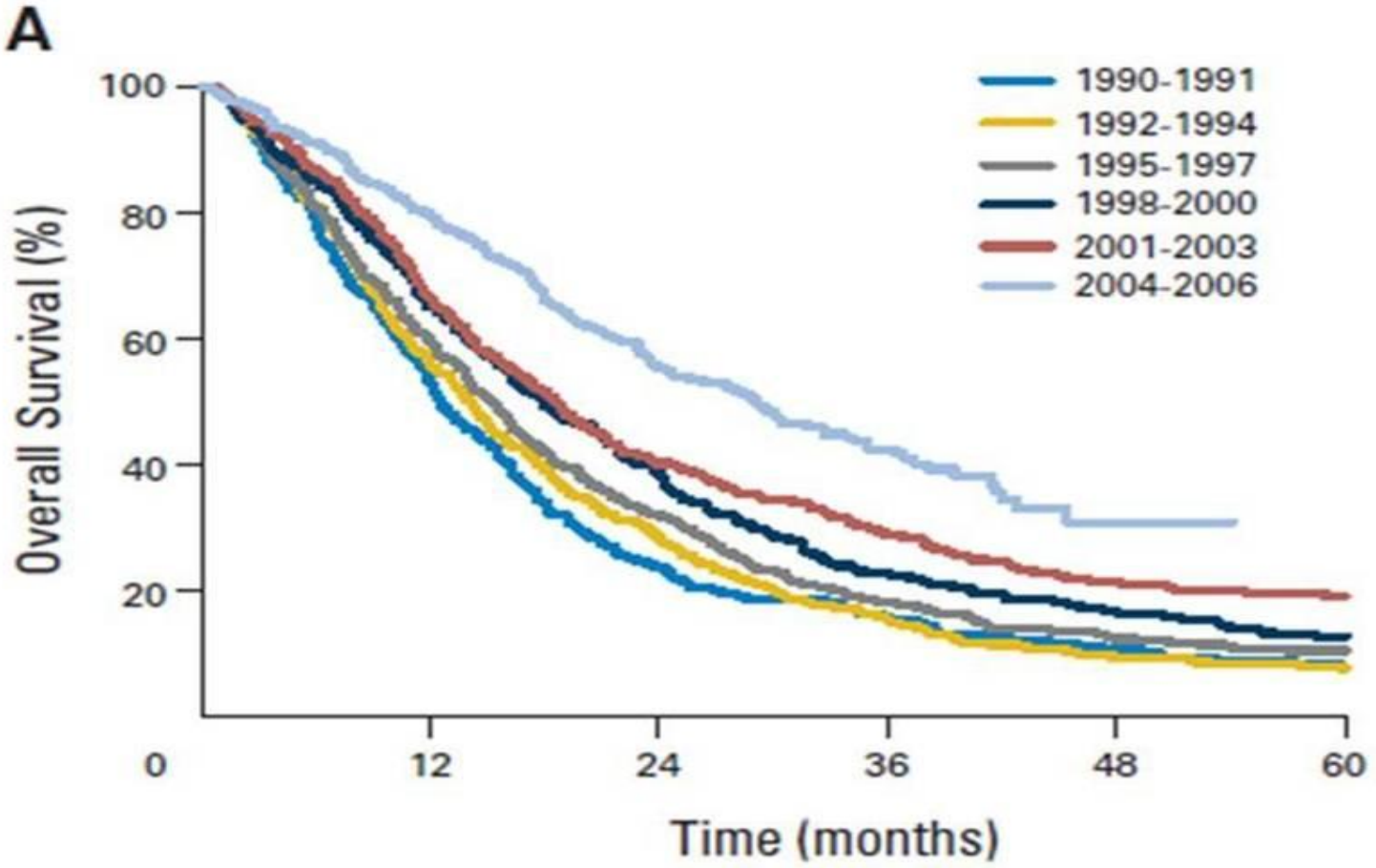
Fonte: AIRTUM

Trends of Incidence and Mortality in Europe, 1998-2005

Cancer site (sex)		Incidence				Mortality			
		Italy	USA	Northern Europe	UK	Italy	USA	Northern Europe	UK
All	men	↑	→↓	↑	→	↓	↓	↓	↓
	women	→	↓	↑	→	↓	↓	↓	↓
Lung	men	↓	↓	↓	↓	↓	↓	↓	↓
	women	↑	↓	↑	→	↑	↓	↑	→
Prostate	men	↑→	→↓	↑	↑→	↓	↓	↓	→
Breast	women	→→	↓	↑→	↑	↓	↓	↓	↓
Colorectal	men	↑	↓↓	↑	→	→	↓↓	↓	↓
	women	→	↓	↑	↓→	↓	↓↓	→↓	↓

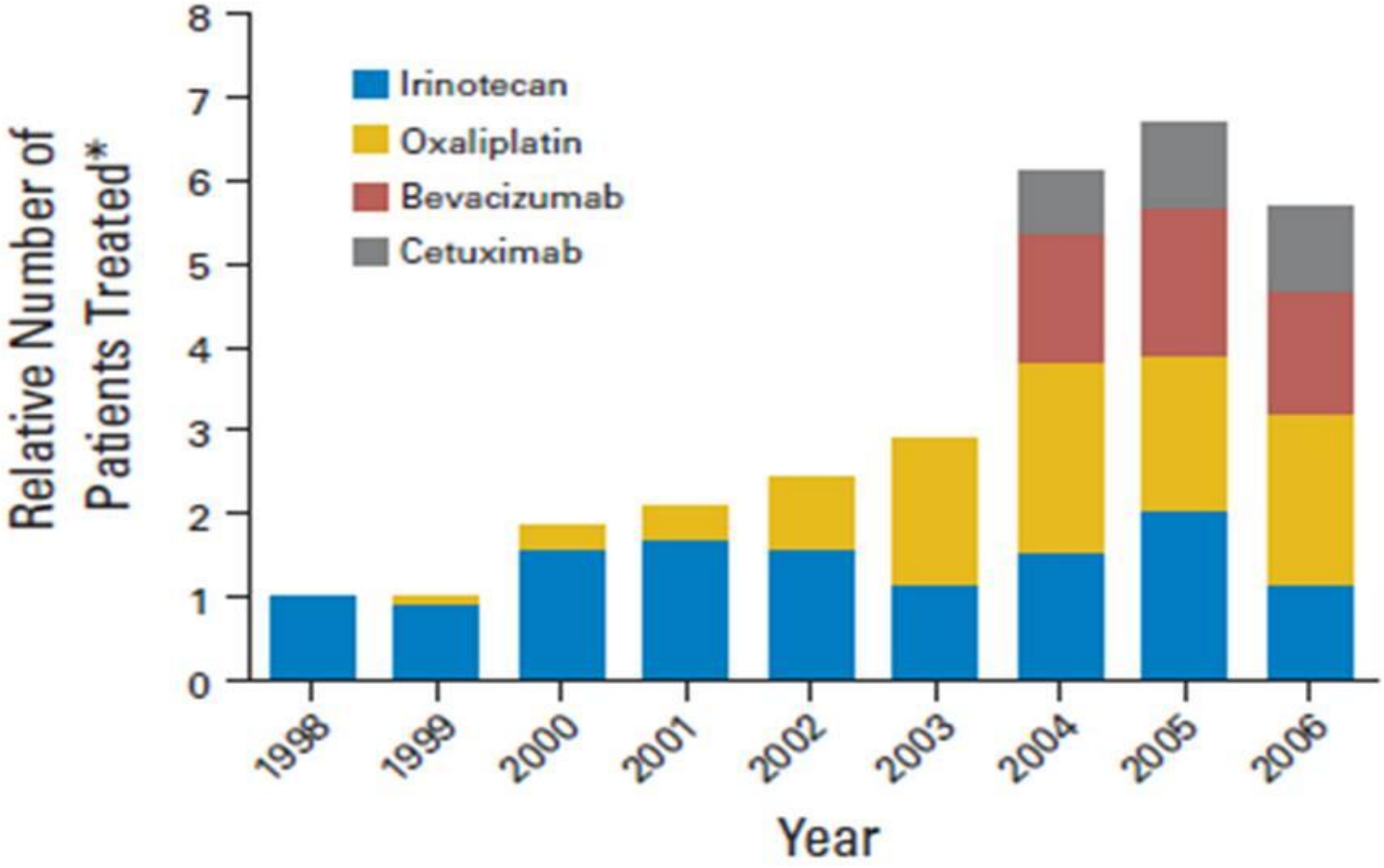
Fonte: AIRTUM

Improved survival with time

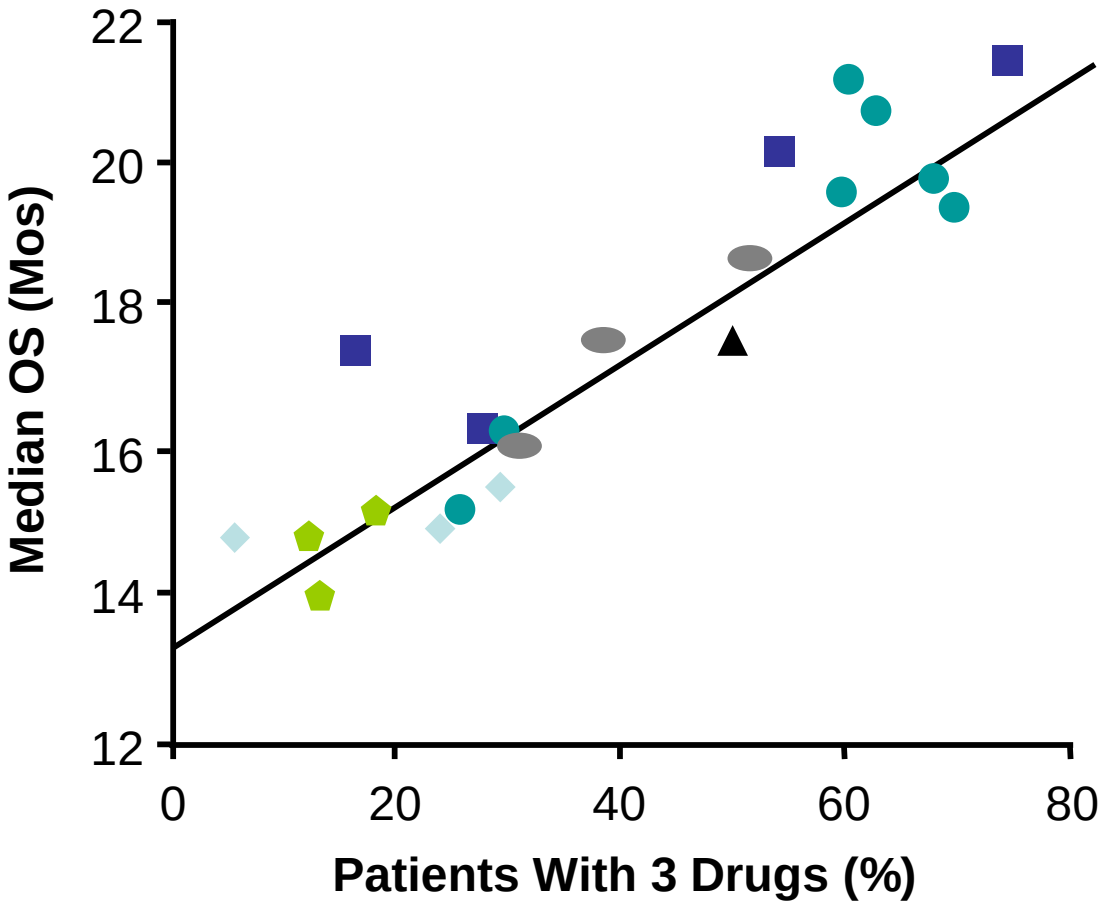


Kopetz S et al, J Clin Oncol 2009

Improved use of medical treatments



Access to Chemotherapy improves survival



First-line therapy

- Infusional 5-FU/LV + irinotecan
- Infusional 5-FU/LV + oxaliplatin
- Bolus 5-FU/LV + irinotecan
- Irinotecan + oxaliplatin
- Bolus 5-FU/LV
- LV5FU2

Grothey A, et al. J Clin Oncol. 2005;23:9441-9442.

Treatment paradigms in mCRC

Some patients with stage IV disease can be cured by an interdisciplinary approach

FOLFOX = XELOX = FOLFIRI
(XELIRI has problems with toxicity)

Most patients tolerate a chemotherapy doublet, but not all need it

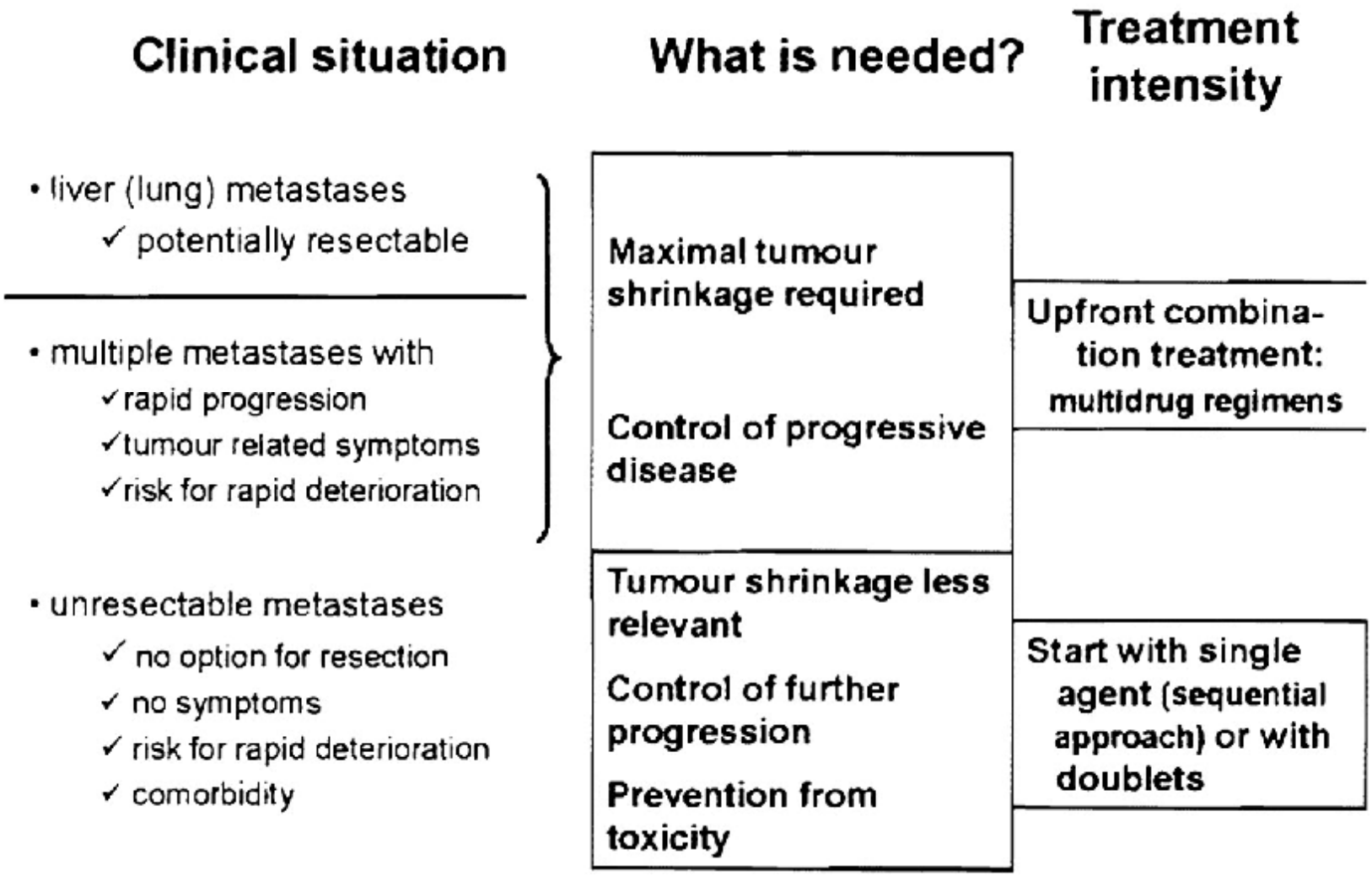
The addition of biologics to chemotherapy has improved outcomes, but not as much as we hoped

We are on the verge of individualized therapy based on molecular predictive factors

Patient Characteristics Drive Decision Making in mCRC Treatment

- Performance status
- Age
- Comorbid illnesses
- Extent of disease
- Intent of treatment: palliative vs potentially curative
- Previous adjuvant therapy within 1 yr
- Organ function: hepatic and renal
- Underlying/uncontrolled hypertension
- Bleeding risks/concerns
- KRAS status

Strategy for the treatment of metastatic CRC

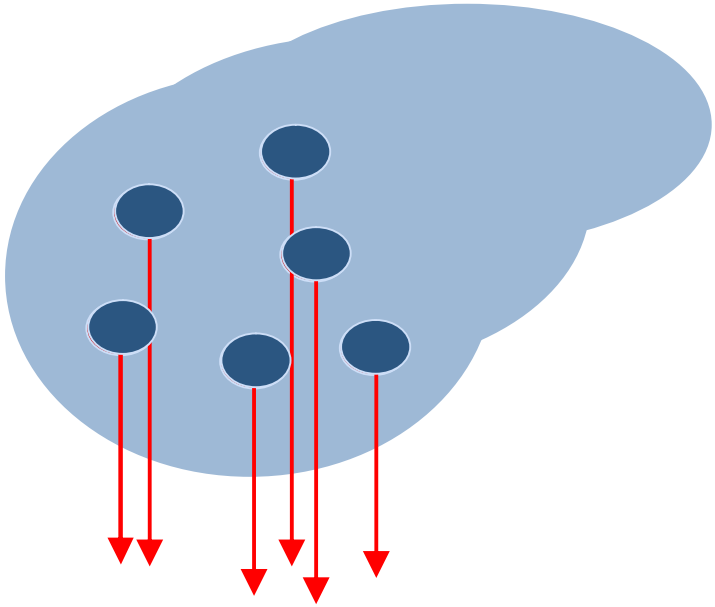


Van Cutsem E et al. Ann Oncol 2010;21:v93-v97

Liver Resection: New Perspectives

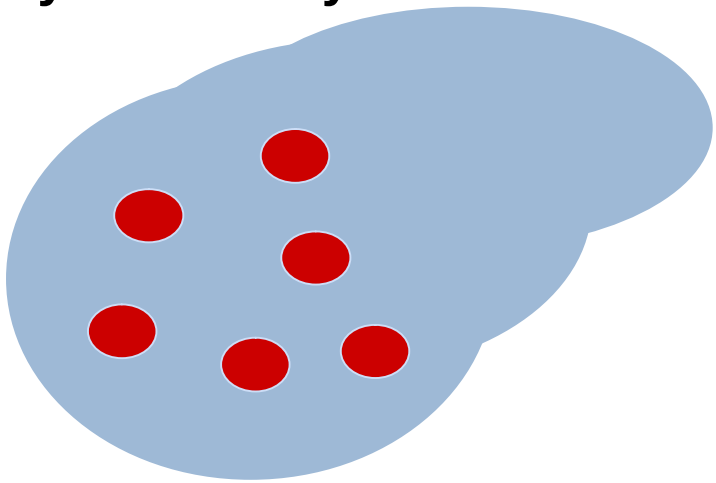
OLD

Resectability determined by “what comes out”

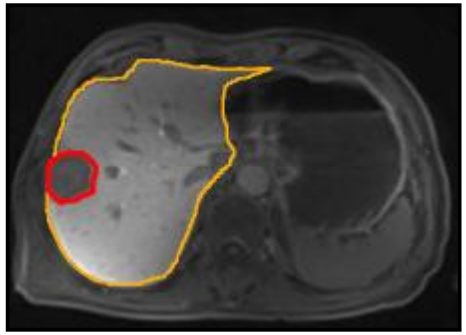


NEW

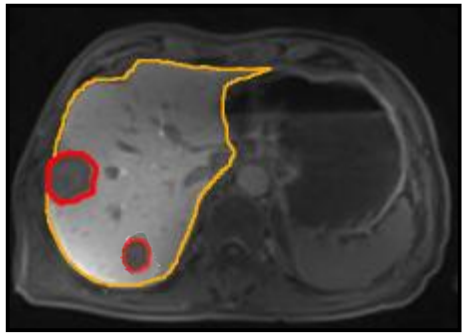
Resectability determined by “what stays in”



NOT all liver metastases are created equal

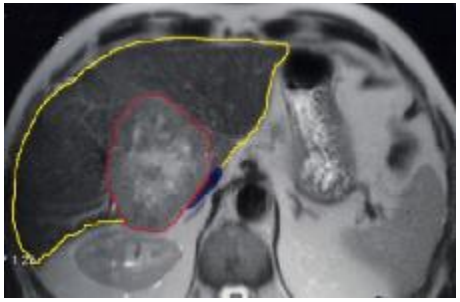


EASILY



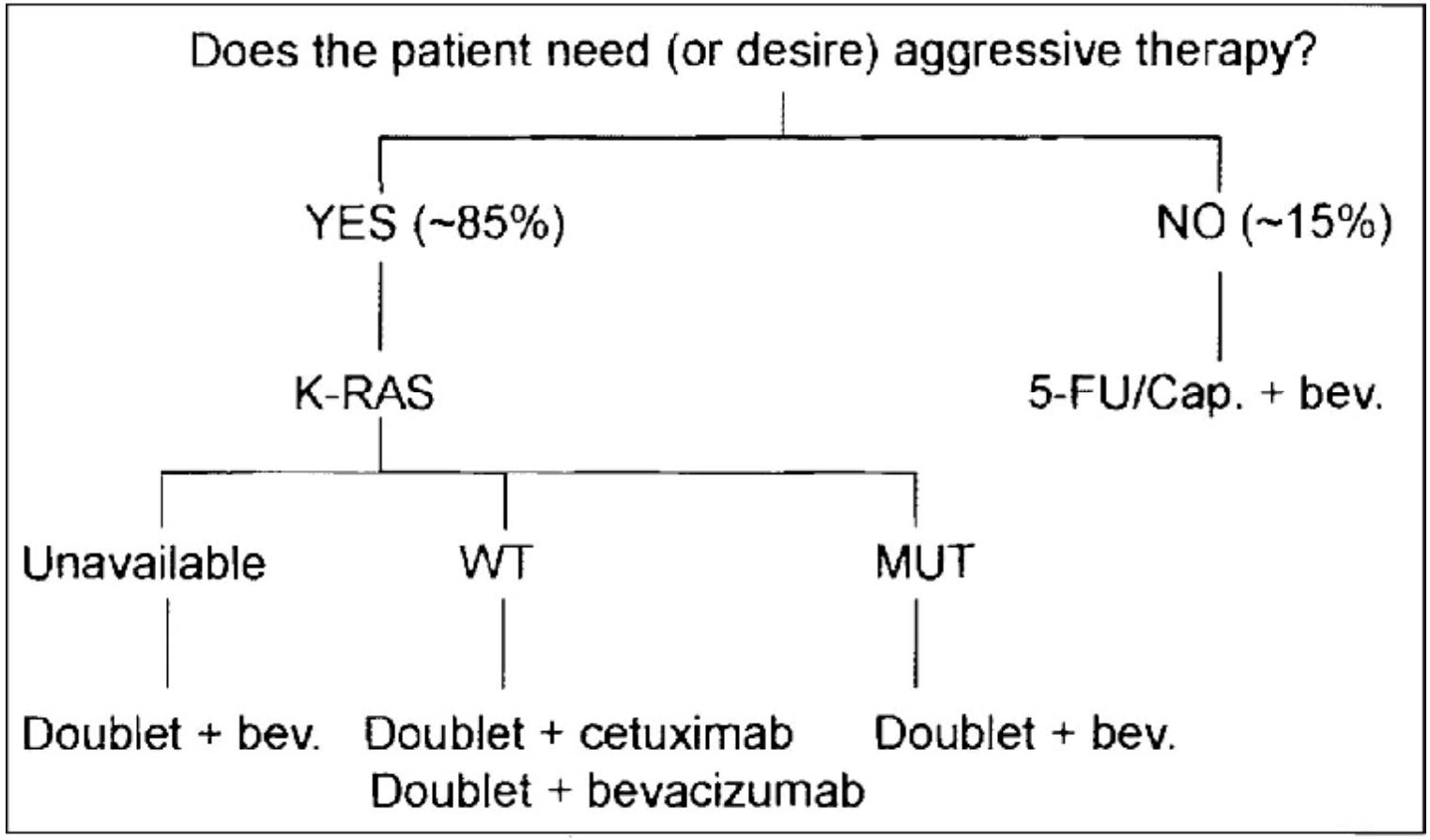
RESECTABLE HIGH RISK

MARGINALLY



POTENTIALLY

First line strategy of metastatic CRC



Modified Expert discussion ESMO/WCGIC Barcelona june 2009

Van Cutsem E et al. Ann Oncol 2010;21:v93-v97

Advanced/mCRC Patients Can Tolerate Intensive Therapy

First Line	Second Line	Third Line
FOLFOX ± bevacizumab FOLFOX ± cetuximab* CapeOx ± bevacizumab CapeOx ± cetuximab* FOLFIRI + bevacizumab FOLFIRI ± cetuximab* 5-FU/leucovorin + bevacizumab FOLFOXIRI (2B)	FOLFIRI Irinotecan FOLFIRI + cetuximab* (2B) Irinotecan + cetuximab*† FOLFOX CapeOx	Irinotecan + cetuximab*† FOLFOX CapeOx Irinotecan → Irinotecan + cetuximab*† Clinical trial BSC

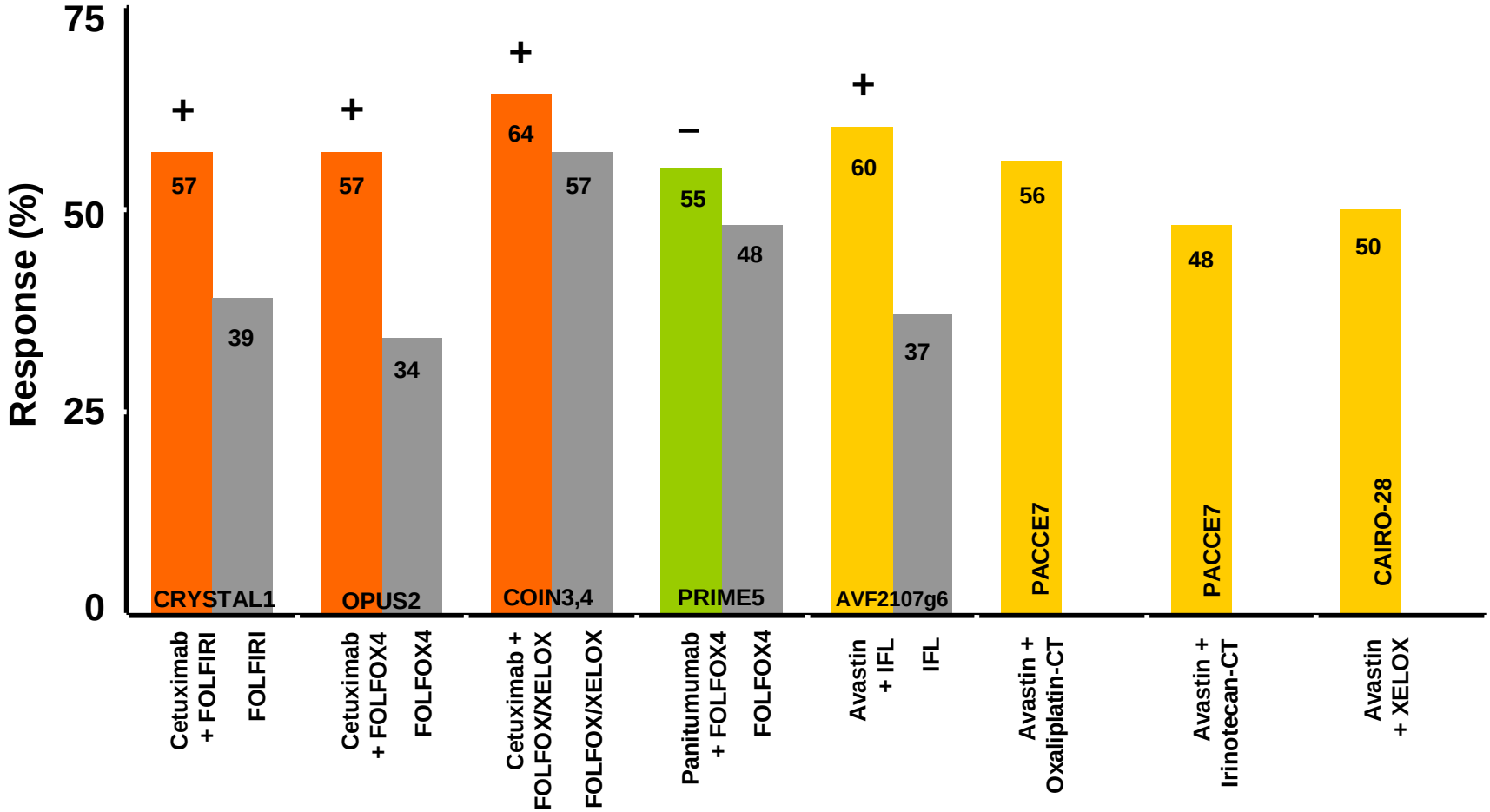
*Patients with wild-type *KRAS* only.
†In patients who cannot tolerate combination, consider either single-agent cetuximab (wild-type *KRAS* only) or single-agent panitumumab (wild-type *KRAS* only); cetuximab and panitumumab should not be used in combination.

NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. V1.2010.

Phase III randomized trials: gains in activity and efficacy in 1° line therapy

	N° of patients	RR	PFS
Bevacizumab			
Hurwitz	402	45 vs 35	10.6 vs 6.2
No16966	700	38 vs 38	9.4 vs 8
Cetuximab			
Crystal	599	58 vs 40	9.9 vs 8.7
COIN	2445	64 vs 57	8.6 vs 8.6
Nordic	566	47 vs 46	7.9 vs 8.7
Panitumumab			
Prime	656	55 vs 48	9.6 vs 8

Tumour response in patients with *KRAS* wild-type tumours



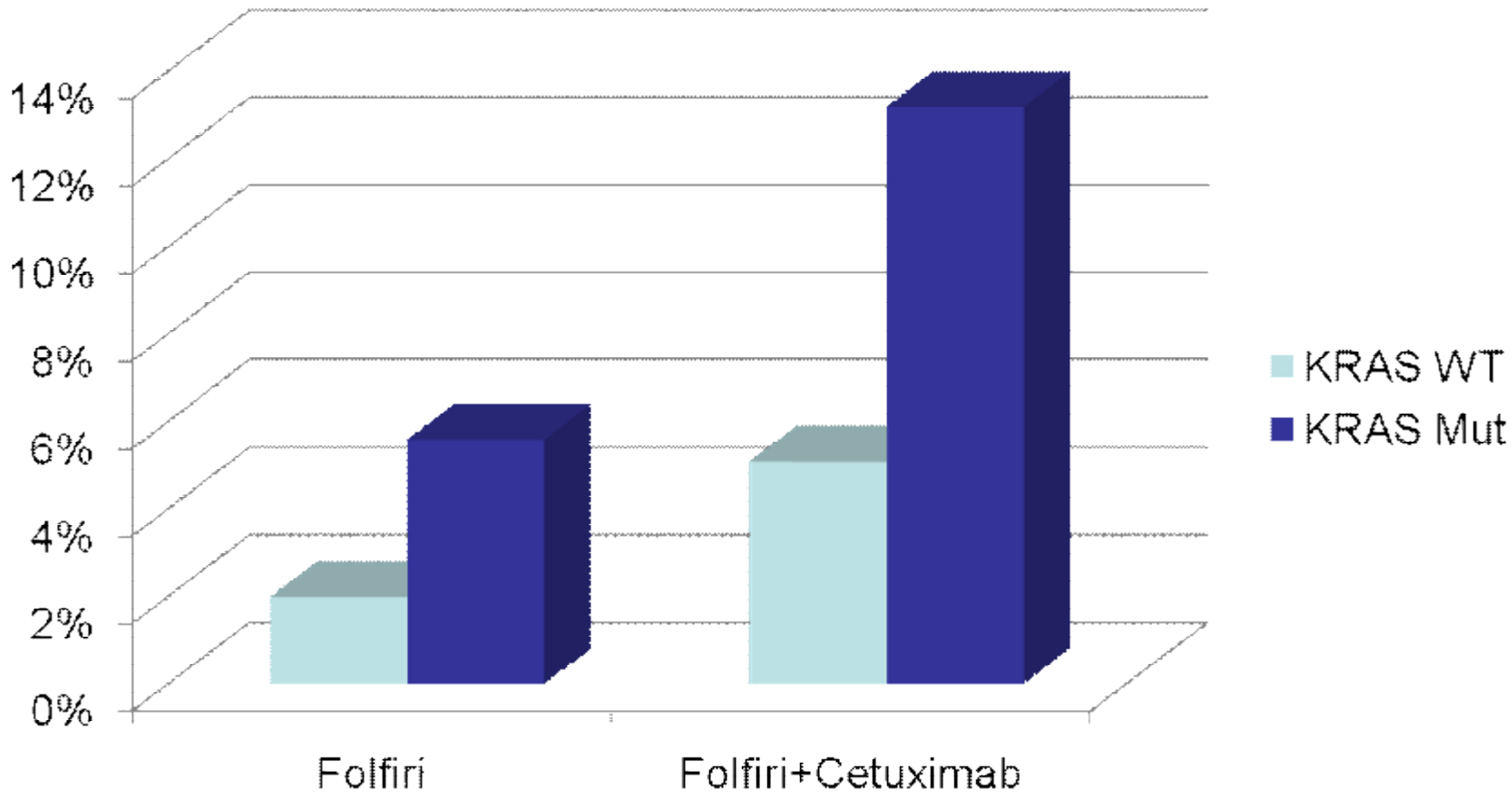
1. Van Cutsem, et al. NEJM 2009 2. Bokemeyer, et al. JCO 2009
3. Maughan, et al. ASCO 2010 (presentation 3502); 4. Maughan, et al. WCGC (presentation O-0022)5. Douillard, et al. JCO 2010
6. Hurwitz, et al. Oncologist 2009; 7. Hecht, et al. JCO 2009; 8.Tol, et al. NEJM 2009

OPUS-CRYSTAL Meta-Analysis

- Addition of cetuximab to chemotherapy showed PFS benefit in patients with wild-type *KRAS*
  - With > 90% of samples collected, addition of cetuximab reduced risk of disease progression by 34% (HR: 0.66; *P* < .001)
- OS results showed an advantage for patients with wild-type *KRAS* who received chemotherapy + cetuximab (HR: 0.81; *P* = .0062)

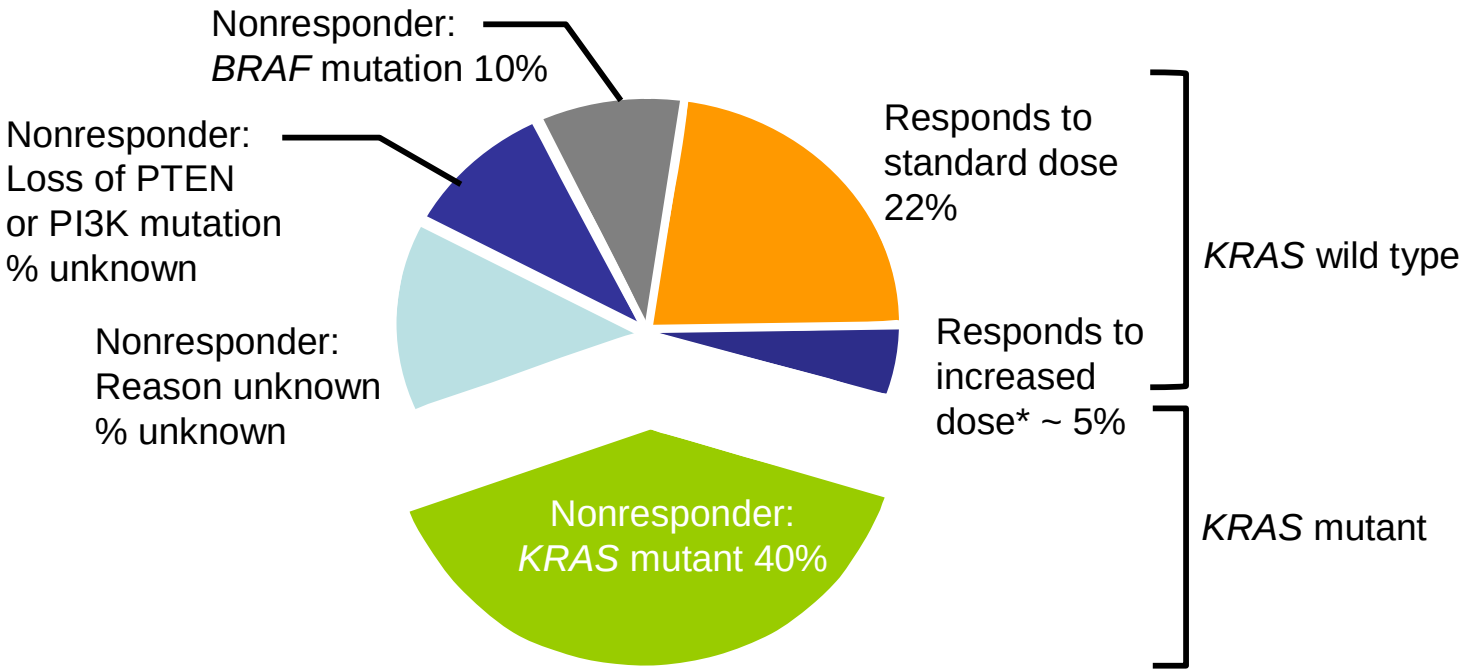
Van Cutsem E, et al. ECCO/ESMO 2009. Abstract P-6077.

Resectability according to KRAS and Cetuximab use



Van Cutsem, JCO 2011

KRAS Status and Response to EGFR mAbs ± Irinotecan: Chemorefractory Pts



Potential relationship between *KRAS* status and response to EGFR monoclonal antibodies, alone or in combination with irinotecan, in chemotherapy-refractive patients
* Possibly overcomes upregulated EGFR or circulating soluble EGFR.

KRAS and *BRAF* Mutational Status and EGFR Inhibitors

Subgroup	PR, %	*P* Value
Mutant *KRAS* (n = 34)	6	.011
Wild-type *KRAS* (n = 79)	28	.029
§ Mutant *BRAF* (n = 11)	0	.011
§ Wild-type *BRAF* (n = 68)	32	.029

- *KRAS* and *BRAF* mutations correlate with lack of response to treatment with monoclonal antibodies targeting EGFR

Di Nicolantonio F, et al. J Clin Oncol, 2008;26:5705-5712.

Phase III randomized trials: gains in activity and efficacy in 2° line therapy

	N° of patients	RR	PFS	OS
Bevacizumab				
Giantonio	**829**	**22.7 vs 8.6**	**7.3 vs 4.7**	**12.9 vs 10.8**
Cetuximab				
EPIC	**1298**	**16.4 vs 4.2**	**4 vs 2.6**	**10.7 vs 10**
Panitumumab				
Peeters	**597**	**35 vs 15**	**5.9 vs 3.9**	**14.5 vs 12.5**

Phase III randomized trials: gains in activity and efficacy in 3° line therapy

	N° of patients	RR	PFS	OS
Cetuximab				
	215	**13%**	**3.7**	**9.5**
Panitumumab				
	119	**17%**	**4.2**	**8.1**

Bevacizumab vs EGFR Antibodies in Advanced CRC

Agent	Strength	Weakness
Bevacizumab	Delay in tumor progression Gain in time Toxicity profile	Limited single agent activity Weak effect on RR (per RECIST)
EGFR antibodies	Single agent activity Consistent increase in RR Activity independent of line of therapy Predictive marker	Gain in time to progression moderate Toxicity profile

New thinking in mCRC have driven the changes in natural history of the disease

- The determination of the treatment goals and strategy are crucial
- Resection of (liver or lung) metastases should be considered
- Multidrug combination regimens should be proposed as aggressive therapy for many patients
- KRAS determination can clearly determine the selection of the best combination regimen
- The exposure to all available and indicated drugs (combination, sequential, maintainace, rechallenge) improves survival
- Further benefit will be obtained through a better selection of tumor and patients.