

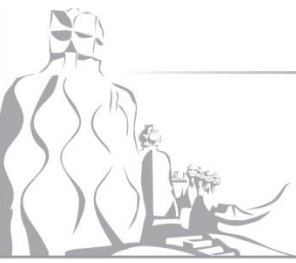
# Drug-Eluting Bead Irinotecan (DEBIRI) Therapy in Combination with Anti-EGFR Treatment in Patients with Refractory Colorectal Cancer and Predominant Liver Metastases

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Haematology and Oncology  
Martin-Luther-University  
Halle-Wittenberg, Germany



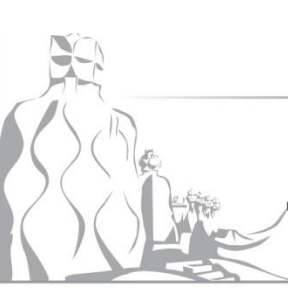
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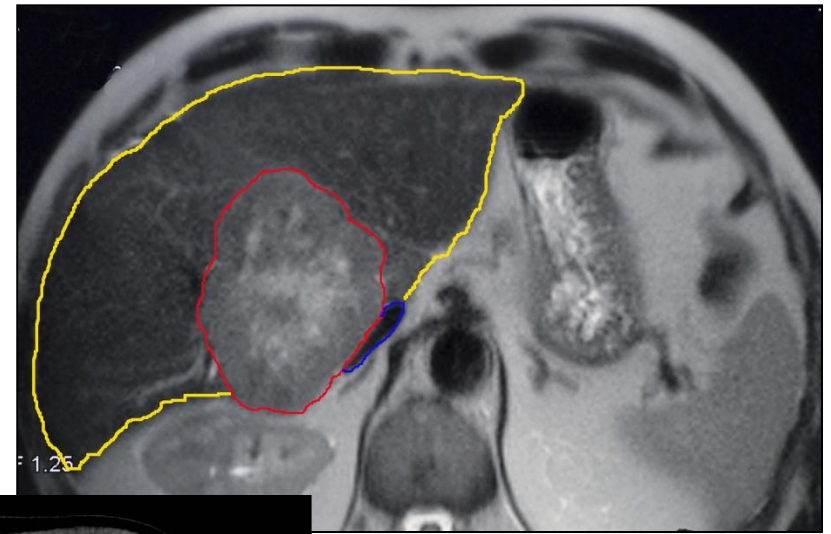
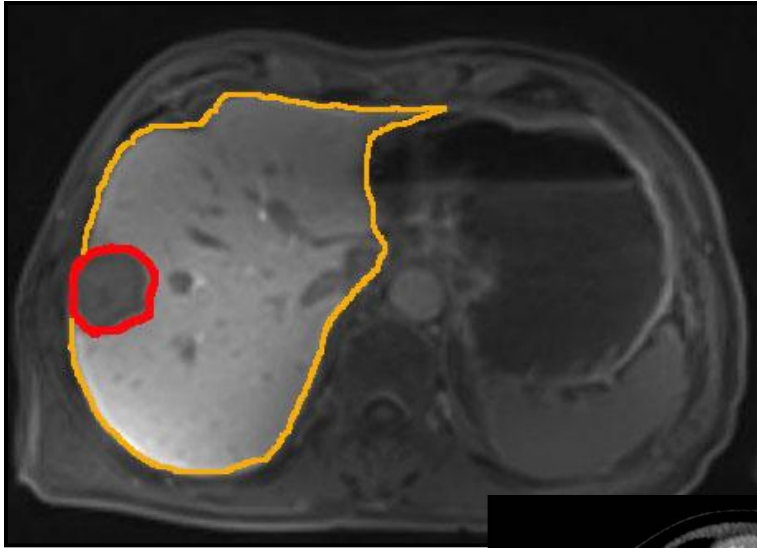


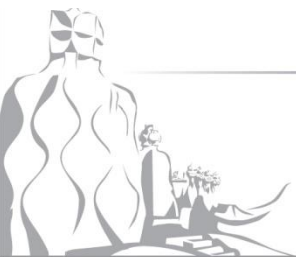
# Metastatic Colorectal Cancer: What are our Aims?

- **Improvement of overall survival**
- **Relief of symptoms**
- **Prevention from symptoms**
  - due to the disease
  - due to (unnecessary) toxicity
- **In patients with liver mets. only: enable cure**

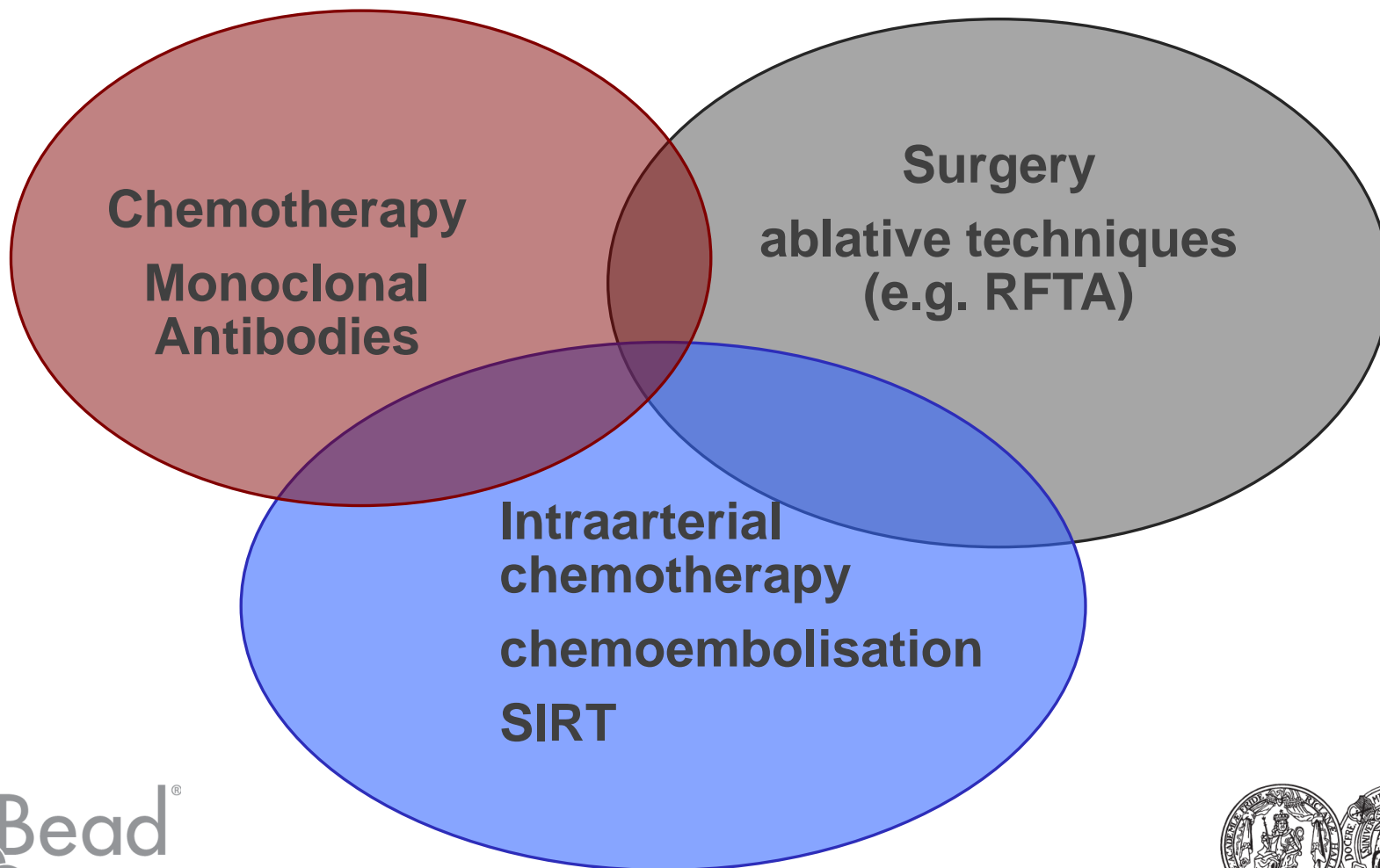


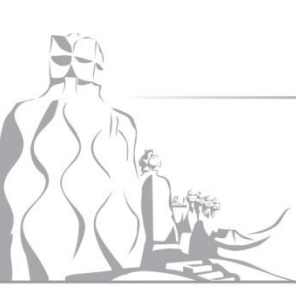
# CLM: Different Clinical Situations Determine Treatment Aim and Therapeutic Strategy





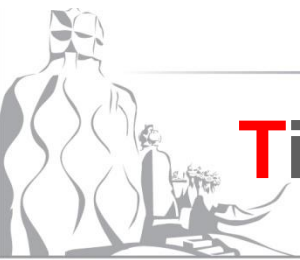
# Multimodal Therapy of mCRC: Armamentarium



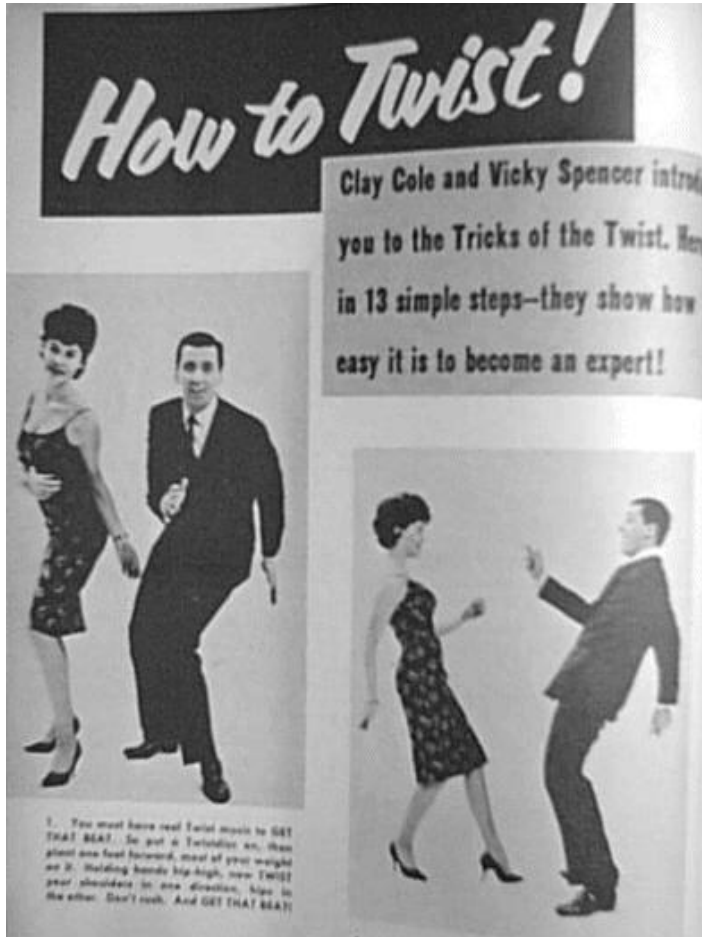


# Metastatic Colorectal Cancer: What are our Aims?

- **Improvement of overall survival**
- **Relief of symptoms**
- **Prevention from symptoms**
  - due to the disease
  - due to (unnecessary) toxicity
- **In patients with liver mets. only: enable cure**
- **Optimize treatment administration**



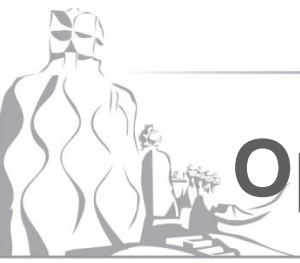
# Time **W**ithout **S**ymptoms or **T**reatment





# What Can “Better” Treatment do in Palliative Treatment of Incurable Disease?

- **Continue on treatment or allow a break?**
- **Use the best ablative technique available**
- **Situation dependent options:**
  - **Resection**
  - **Radiofrequency ablation**
  - **Chemoembolisation**



# Options for systemic treatment of MCRC

## Single agent chemotherapy

5-FU/FS

Capecitabine/UFT

(Oxaliplatin)

Irinotecan

## Combinations

infusional

FOLFOX

FOLFIRI

oral

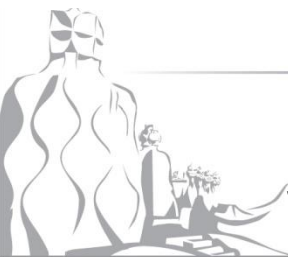
Cape-Ox / -iri

## “Biologicals”

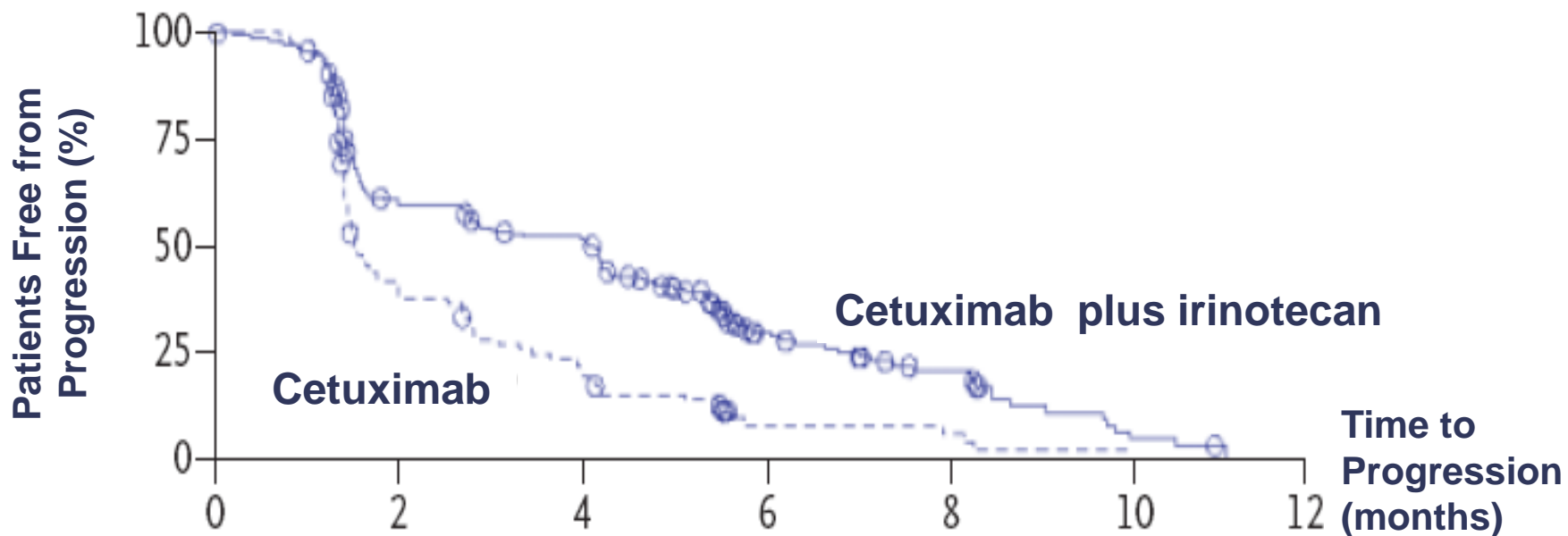
Bevacizumab

Cetuximab

Panitumumab



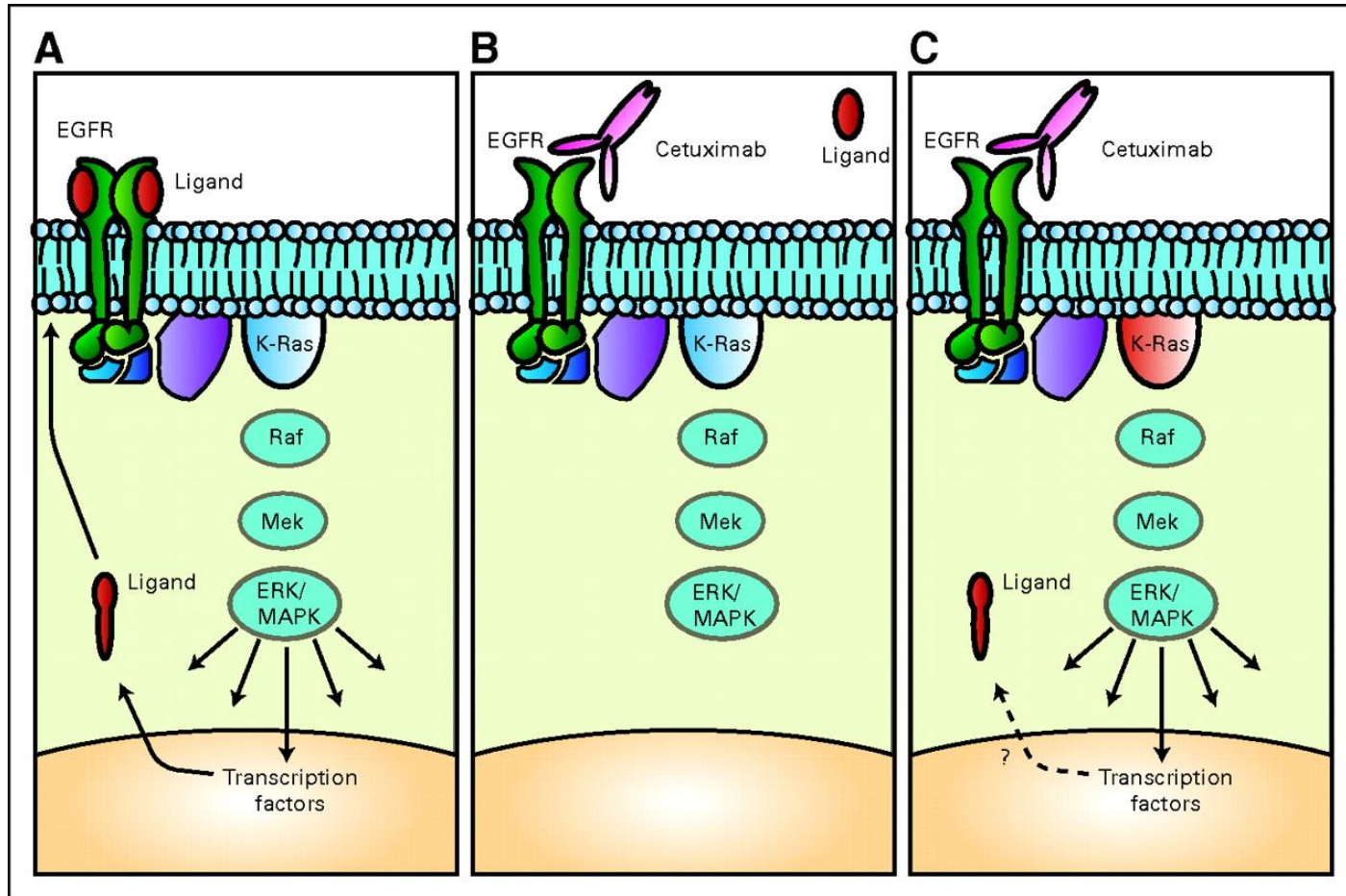
# Cetuximab plus Irinotecan – in Patients with mCRC and Irinotecan Pretreatment

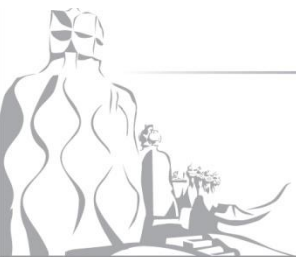


	n	RR	RR+SD	TTP (Mo.)	ÜL (Mo.)	
<b>Cetuximab</b>	111	11%	35%	1.5	6.9	<b>BOND Trial</b> Cunningham et al. New Engl J Med 2004
<b>Cetuximab + irinotecan</b>	218	23%*	55%	4.1*	8.6	

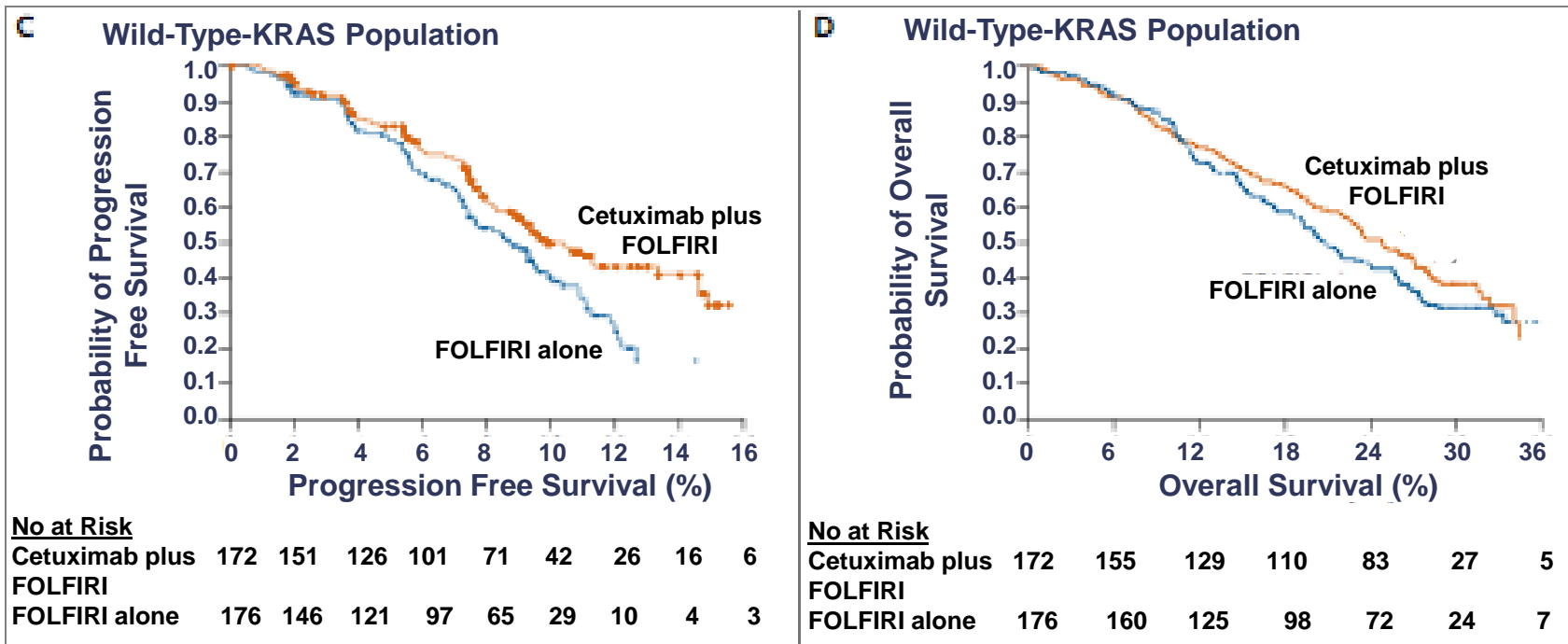


# EGF-Receptor and K-RAS Signaling in mCRC

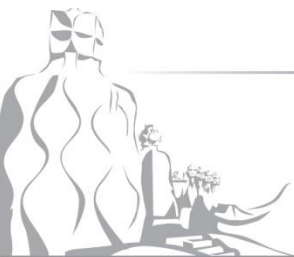




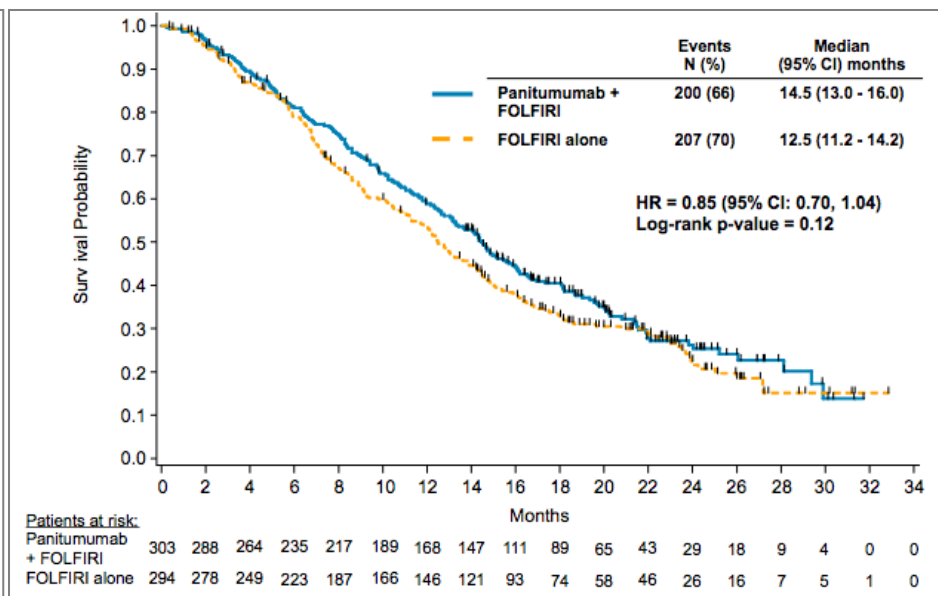
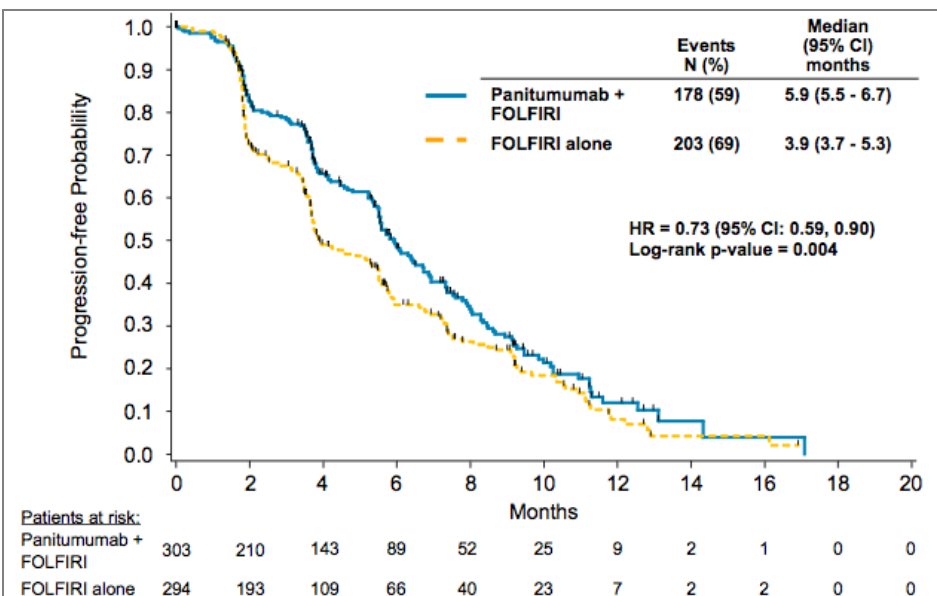
# CRYSTAL Trial: 1st line FOLFIRI +/- Cetuximab



Van Cutsem et al., New Engl J Med 2009



# 2nd line: FOLFIRI +/- Panitumumab K-ras WT Population Analysis

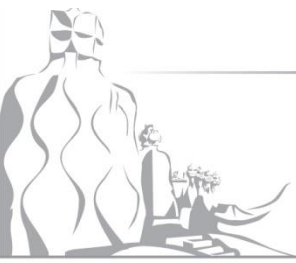




## 2<sup>nd</sup> and 3<sup>rd</sup> Line Regimens: Chemotherapy with Irinotecan +/- EGFR Antibodies

	N	RR	PFS	
FOLFIRI or FOLFOX	220	4 11	2.5 4.2	Tournigand et al., J Clin Oncol 2004
Irinotecan + Cetuximab*/**	648	16	4.0	Sobrero et al., J Clin Oncol 2008
FOLFIRI + Panitumumab* (KRAS WT only)	582	35	5.9	Peeters et al., ESMO/ECCO 2009

\* 2nd-line \*\* 3rd-line



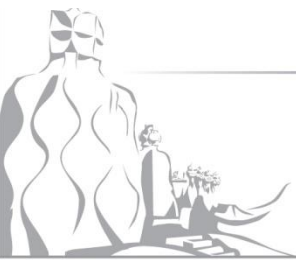
## Summary – and Rationale for a Trial

**In patients with KRAS wild type tumours, irinotecan plus EGFR inhibitors are active in all treatment lines**

**In patients with liver limited disease, local treatment may prolong interval without progression**

**Irinotecan Drug Eluting Beads may be the best way to administer intrahepatic irinotecan treatment**

**Combination of i.v. EGFR inhibitors with DEBIRI?**



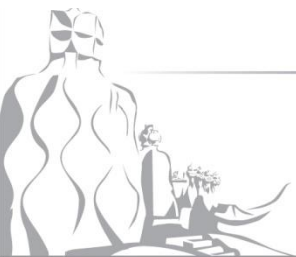
# A Randomized Phase II Trial

**Irinotecan drug-eluting beads administered by hepatic artery with cetuximab (i.v.) (*DEBIRITUX*)**

versus

**systemic treatment with cetuximab and irinotecan (i.v.)**

**in patients with refractory metastatic colorectal cancer  
and KRAS wild-type tumours**



# DEBIRITUX Trial: Design

## Randomization

Stratification criteria:  
Liver only disease vs. other sites included  
Bilobar vs. unilobar disease

Arm A (standard): N=25

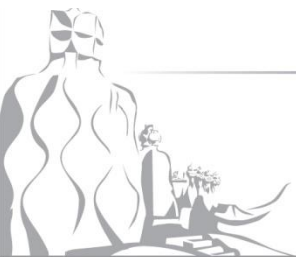
**i.v. Irinotecan:**  
Irinotecan 180 mg/m<sup>2</sup> day 1  
biweekly

**i.v. Cetuximab:**  
Initial dose 400mg/m<sup>2</sup>,  
followed by weekly 250 mg/m<sup>2</sup>

Arm B (experimental): N=49

**i.a. Irinotecan DEB:**  
Irinotecan 4 ml DEB every 4 weeks;  
2-6 cycles at investigator's discretion  
based on response, toxicity, tumour burden

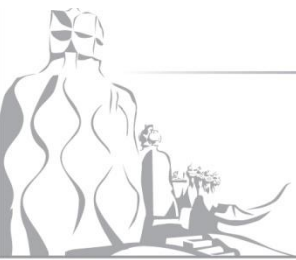
**i.v. Cetuximab:**  
Initial dose 400mg/m<sup>2</sup>,  
followed by weekly 250 mg/m<sup>2</sup>



# DEBIRITUX Trial: Treatment Arms

## Arm A:

- **Cetuximab IV: initial loading dose 400mg/m<sup>2</sup> and then 250mg/m<sup>2</sup> weekly. Prophylactic antihistamine**
- **Irinotecan IV: 180mg/m<sup>2</sup> every two weeks**

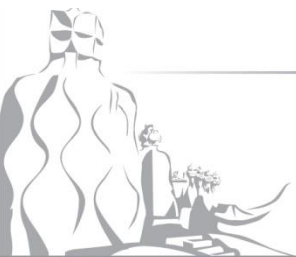


# DEBIRITUX Trial: Treatment Arms

## Arm B:

- **Cetuximab IV: initial loading dose 400mg/m<sup>2</sup> and then 250mg/m<sup>2</sup> weekly. Prophylactic antihistamine. First infusion day before CE**
- **DEBIRI:**
  - Minimum **of two treatments** (four bi-weekly sessions in the event of bilobar disease) at **week 0 and 4** with up to 4ml (100-300 µm DC Bead loaded with up to 200mg irinotecan) will be scheduled
  - **Further treatments** will be planned **based on tumour response until progression or unacceptable toxicity** develops.
  - **Treatment could be repeated** whenever residual tumour is found in the liver every 12 weeks. Presence of residual tumour will be assessed by contrast enhanced CT scan and if available PET scan.

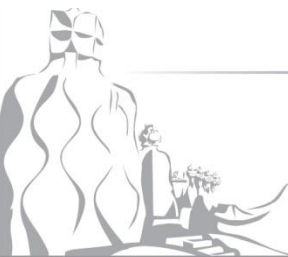




# DEBIRITUX Trial: Additional Question

Two different antiemetic regimens with steroids and 5-HT3-receptor antagonists with or without aprepitant will be evaluated in the experimental arm (B). Patients being randomized into arm B will be again randomized in a 1:1 ratio without further stratification.

- **Arm B 1**
  - 5 HT3 serotonin receptor antagonists (iv or po) on day 1
  - dexamethason 8mg (iv or po) on day 1-3
- **Arm B 2**
  - 5 HT3 serotonin receptor antagonists (iv or po) on day 1
  - dexamethason 8mg (iv or po) on day 1-3
  - aprepitant 125mg po on day 1 and 80mg po on day 2 and 3



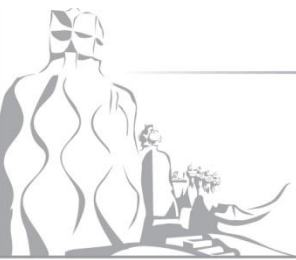
# DEBIRITUX Trial: Key inclusion Criteria

- **Confirmed stage IV, unresectable CLM**
- **KRAS wild-type tumours**
- **Refractory to 5FU (or Capecitabine), oxaliplatin, with / without irinotecan, with or without bevacizumab**
- **Liver only or liver dominant disease (defined as  $\geq 50\%$  tumor body burden confined to the liver)**
- **Patients with patent main portal vein**
- **Performance status  $\leq 2$  ECOG PS**
- **Life expectancy  $> 6$  months**
- **Adequate haematologic function**
- **Adequate liver function as measured serum transaminases (AST & ALT)  $\leq 3$  x ULN, total bilirubin  $\leq 1.5$  x ULN**
- **Adequate renal function: Serum creatinine  $\leq 1.5$  x upper limit of normal (ULN)**



# DEBIRITUX Trial: Key Exclusion Criteria

- **CNS or bone metastases**
- **Prior treatment with EGFR targeting antibodies**
- **Contraindications or severe preceding toxicity to irinotecan**
- **Contraindication for hepatic embolisation procedures:**
  - Porto-systemic shunt or hepatofugal blood flow
  - Large shunt (determined by investigator)
  - Severe atheromatosis
  - Hepatofugal blood flow
  - Main portal vein occlusion (eg by thrombus or tumour)



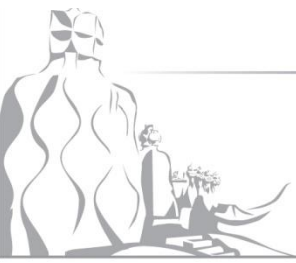
# DEBIRITUX Trial: Endpoints

## Primary Endpoint

- **Progression-free survival rate after 6 months (RECIST v1.1)**

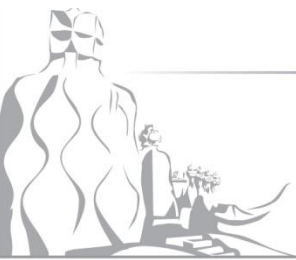
## Secondary Endpoints

1. **Safety of intra-arterial delivery with irinotecan DEB with cetuximab,**
2. **Tumour Response (according to RECIST v1.1)**
3. **Local tumour response (extent of necrosis in the treated lesions, according to EASL criteria 2001)**
4. **Time to progression**
5. **Time to liver progression (treated area)**
6. **Change in tumour markers (CEA)**
7. **Overall survival**
8. **Rate of acute and delayed emesis during chemoembolization with or without aprepitant**



# Summary

- **Irinotecan loaded beads are active in CLM treatment**
- **Synergy of (i.v.) irinotecan with EGFR antibodies is proven in 1<sup>st</sup> line and refractory mCRC**
- **Benefit may not be limited to the “curative” and the “purely palliative” situation**
- **May improve local control of the “critical” organ liver, prolong PFS and allow less frequent application of systemic treatment**



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