

## Expert discussion on molecular markers and biologicals in metastatic colorectal cancer

ESMO / World Congress on  
Gastrointestinal Cancer  
June 24- 27, 2009, Barcelona

## Expert meeting

- Experts: opinion leaders from different countries and different disciplines selected on scientific merits and recognition as international opinion leaders
- Questions were sent around to all experts and returned before meeting
- Analysis of answers
- Analysis discussed in Barcelona
- Presentation re-discussed

## Expert meeting

- Expert opinion should be based on scientific studies and on evidence coming from well performed clinical trials
- Decisions of experts:
  - evidence based medicine
  - often also influenced by clinical experience more than minimal guidelines
- Strengths: can help guide clinicians for treatment choices
- Caveat: these are not official guidelines nor true consensus statements

## Expert panel members

Jordan Berlin Andres Cervantes Fortunato Ciardiello Aimery De Gramont Eduardo Diaz-Rubio Mario Dico* Michel Ducreux Bengt Glimelius Robert Glynne Jones Axel Grothey Thomas Gruenberger Dan Haller	Karin Haustermans Roberto Labianca Heinz Lenz Bernard Nordlinger Nicolas Pavlidis Philippe Rougier Hans-Joachim Schmoll Alberto Sobrero Josep Tabernero Eric Van Cutsem* Wolff Schmiegel
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\* chairmen

## Prognostic versus predictive markers

**Prognostic**

Provides information on disease outcome, regardless of which treatment is used

**Predictive**

Provides information on efficacy of a specific treatment

Markers have often both a predictive and a prognostic value

## Metastatic CRC Clinical prognostic markers

- Patients related factors
  - Performance status and symptoms
  - Comorbidity
  - Age
  - Socio-economic status
- Center related factors
  - Center experience / volume
  - Deviation from normal clinical practise
- Tumor related factors
  - Rectal versus colon primary
  - Stage of primary tumor if metachronous
  - Extent of metastatic disease
  - Synchronous vs metachronous presentation
  - Previous adjuvant treatment with oxaliplatin / early relapse after adjuvant therapy
  - Previous lines of treatment

### Metastatic CRC Biochemical prognostic markers

- Alkaline phosphatase
- LDH
- WBC
  
- Bilirubin
- Albumin
- CEA

### Metastatic CRC Molecular prognostic markers

- No real validated prognostic markers
  
- Data available on potential prognostic value of
  - BRAF mutations: worse prognosis
  - MSI-H tumors: better prognosis

### Metastatic CRC Clinical predictive markers

- Markers for outcome
  - Performance status
  - Multiple sites of metastases/ very extensive disease
  - Symptomatic peritoneal carcinomatosis
  - Deviation from standard practise
  - Previous lines of treatment
  - Skin rash for anti-EGFR(occurs only after start of therapy)
  
  - Very preliminary data: hypertension for anti-VEGF (occurs only after start of therapy)
  
- Markers for toxicity
  - Cardiovascular disease/ATE

### Metastatic CRC Biochemical predictive markers

- Limited data
  
- For efficacy
  - LDH
  - WBC for cytotoxic therapy
  - Alkaline phosphatase for cytotoxic therapy
  
  - CEA flare and CEA drop
  
- For toxicity:
  - renal function for capecitabine
  - bilirubin for irinotecan

### Metastatic CRC Molecular predictive markers

- KRAS mutation (codon 12 & 13) validated for predicting resistance to anti-EGFR
- Emerging predictive markers
  - BRAF mutations: predictive for resistance to anti-EGFR in chemorefractory CRC
    - Early lines of treatment: not validated
    - BRAF mutations mutually exclusive with KRAS mutations
  - ligands: amphi- and epiregulin (linear correlation)
- Potential markers under investigation for anti-EGFR
  - PI3K
  - PTEN
  - NRAS
- Potential markers for chemotherapy toxicity and efficacy:
  - ERCC1 for oxaliplatin
  - UGT1A1 for irinotecan
  - DPD for 5-FU

### Metastatic CRC Molecular predictive markers

- KRAS mutation analysis should be done before chemotherapy for metastatic CRC is given
  
- KRAS analysis can be done on paraffin embedded tumor block of primary tumor or metastases

### Metastatic CRC Molecular predictive markers

- Which markers to routinely determine?
  - KRAS before chemotherapy for metastatic CRC is given
  - MSI:
    - Emerging information in adjuvant treatment of colon cancer
    - Metastatic colon cancer: young patients (<50) or suspicion of Lynch syndrome
  - BRAF: emerging data; not yet routine determination

### Treatment of unresectable mCRC

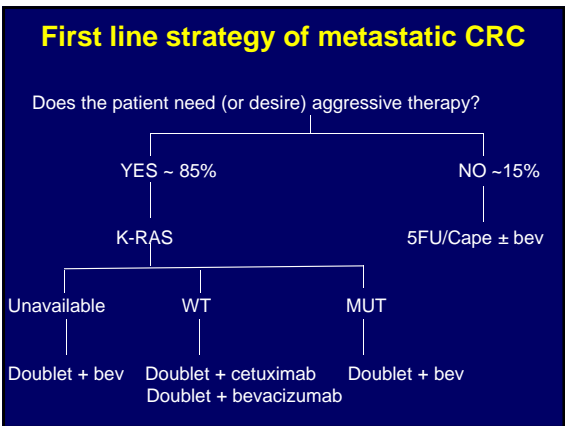
- Determined by multidisciplinary discussion and management by expert teams !!!
- Outcome may be related to experience of the team
- Determination of goals of treatment though all lines of therapy is crucial at the initiation of the first treatment:
  - Strategic choices determine the therapeutic options**
    - Cure or palliation

### Treatment of unresectable mCRC

- Use of biologicals added to cytotoxic partners improves the outcome in many patients
- Take into consideration safety profile of biologicals and cytotoxic partners
- Both FOLFIRI and FOLFOX/XELOX are in many patients the preferred partners for biologicals.

### Strategy according to treatment aim

Clinical situation	What is needed?	Treatment intensity
<ul style="list-style-type: none"> <li>• liver (± lung) metastases</li> <li>• potentially resectable</li> </ul>	Maximal tumor-shrinking required	Upfront combination: multidrug regimens
<ul style="list-style-type: none"> <li>• multiple metastases</li> <li>• rapid progression</li> <li>• tumor related symptoms</li> <li>• (risk for) deterioration</li> </ul>	Control of progressive disease	Start with single agent Sequential approach or doublets
<ul style="list-style-type: none"> <li>• unresectable metastases</li> <li>• no option for resection</li> <li>• no symptoms or risk for rapid deterioration</li> <li>• comorbidity</li> </ul>	Tumor shrinkage less relevant Control of further progression Prevention from toxicity	



### Treatment of unresectable mCRC

- Patients needing or desiring an aggressive approach:
  - patients with potentially resectable metastases
  - patients with clearly symptomatic disease in whom tumor regression is needed
- KRAS wild type patients:
  - CT + cetuximab
  - CT + bevacizumab
  - evidence for response is greater for cetuximab in neoadjuvant approach
- KRAS mutant patients
  - CT + bevacizumab
  - FOLFIRI may be an option if contraindications for bevacizumab and downsizing is desired

### Treatment of unresectable mCRC Later lines of therapy

- Change cytotoxic partner
- Second line:
  - no systematic use of biologicals
  - bevacizumab, if no bevacizumab in first line
- Third line in KRAS wild type patients not yet exposed to anti-EGFR antibody
  - cetuximab/irinotecan: most active combination
  - cetuximab
  - panitumumab

### Treatment of unresectable mCRC Specific issues

- Treat with biologicals until progression or toxicity, or until metastases become resectable
- Continue treatment until progression with biologicals, even if one of the cytotoxic partners (oxaliplatin, irinotecan) is stopped
- No clear evidence to administer biologicals beyond progression
- Correlation of rash and activity after anti-EGFR antibodies has no immediate practical implications in clinical practise

### Treatment of unresectable mCRC Specific issues

- Irinotecan-based chemotherapy in first line if oxaliplatin is given in adjuvant treatment
- Elderly patients: capecitabine ± bevacizumab
- Last line 5FU/capecitabine + mitomycin (low level of evidence or agreement)

### Treatment of resectable mCRC Resectable liver (lung) metastases

- There are limited data on the systematic use of biologicals in the treatment of resectable liver or lung metastases
- Strategies:
  - Perioperative (pre- and post) chemotherapy
  - Postoperative chemotherapy
    - EU: perioperative chemotherapy
    - US: postoperative chemotherapy
- Total duration 6 months FOLFOX (perioperative or postoperative)

### Monitoring metastatic CRC treated with biologicals

- Similar to patients not treated with biologicals
- Clinical, biochemical (including CEA) and CT scan every 2-3 months
- Monitoring for toxicity
  - Clinical
    - hypertension
    - skin
  - Biochemical
    - hematology
    - liver function
    - renal function
    - magnesium
    - proteinuria

### Clinical research agenda

- First-line comparison of biologicals
- Optimal molecular selection:
  - what is beyond KRAS?
  - markers for angiogenesis inhibitors
- Defining the optimal strategy
- Continuation vs drug holidays
  - Maintenance
- Intermittent treatment with biologicals
- Optimal strategy in neoadjuvant and adjuvant treatment
- Strategies for KRAS mutant patients
  - e.g. MEK, mTOR
- Evaluation of new targets and new agents interfering with these targets
- .....
- .....

