Review of the ESMO Consensus Conference on metastatic colo-rectal cancer
Basic strategy and groups (RASwt/mut, BRAF mut)

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Disclosure JY Douillard

• Compensated participations in:
  – Advisory Boards and Symposia:
    • Amgen
    • Bayer
    • Boehringer Ingelheim
    • Merckserono
    • Roche/Genentech
    • Sanofi
    • Takeda

  – Research Funding
    • Merckserono
## 5-Year Survival Rate for Stage IV CRC Remains Only 6%

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
<th>Overall Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>5-FU/LV bolus</td>
<td>12,6</td>
</tr>
<tr>
<td>2000</td>
<td>5-FU/LV infusion</td>
<td>14,1</td>
</tr>
<tr>
<td>2000</td>
<td>IFL</td>
<td>14,8</td>
</tr>
<tr>
<td>2000</td>
<td>LVFU2/irinotecan</td>
<td>17,4</td>
</tr>
<tr>
<td>2004</td>
<td>FOLFOX</td>
<td>19,5</td>
</tr>
<tr>
<td>2004</td>
<td>IFL + bevacizumab</td>
<td>20,3</td>
</tr>
<tr>
<td>2007</td>
<td>FOLFOX/FOLFIRI</td>
<td>22,6</td>
</tr>
<tr>
<td>2008</td>
<td>XELOX/FOLFOX + bevacizumab</td>
<td>21,3</td>
</tr>
<tr>
<td>2011</td>
<td>FOLFIRI + cetuximab</td>
<td>22.8*</td>
</tr>
<tr>
<td>2011</td>
<td>FOLFOX + panitumumab</td>
<td>23.9*</td>
</tr>
<tr>
<td>2011</td>
<td>FOLFIRI + bevacizumab</td>
<td>25.0 – 25.8*</td>
</tr>
<tr>
<td>2012</td>
<td>FOLFOX + panitumumab</td>
<td>26**</td>
</tr>
<tr>
<td>2012</td>
<td>FOLFIRI + bevacizumab</td>
<td>28.1 – 33.1**</td>
</tr>
<tr>
<td>2013</td>
<td>FOLFIRI + cetuximab</td>
<td>31</td>
</tr>
<tr>
<td>2013</td>
<td>FOLFOXIRI + bevacizumab</td>
<td>28.4**</td>
</tr>
<tr>
<td>2014</td>
<td>FOLFIRI + cetuximab or bevacizumab</td>
<td>29 – 29.9*</td>
</tr>
</tbody>
</table>

*KRAS wild type tumors; **Extended RAS wild type population. Note: Informal comparison as these are not head-to-head clinical trials.


Adapted from E Van Cutsem
Unresectable mCRC treatment in 2013

• Median expected OS: 20-30 months

• Most of the patients will receive several lines of treatment
  – From 100 in 1st line
    • 60-70 will receive a 2nd line
    • 30-40 will receive a 3rd Line
    • 15-20% will receive 4+ lines
ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making

## Groups according to clinical presentation

<table>
<thead>
<tr>
<th>Groups</th>
<th>Clinical Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 0</td>
<td>Upfront resectable metastasis,</td>
</tr>
<tr>
<td></td>
<td><strong>Goal:</strong> cure, reduced relapse rate</td>
</tr>
<tr>
<td>Group 1</td>
<td>Potentially resectable metastasis</td>
</tr>
<tr>
<td></td>
<td><strong>Goal:</strong> Objective Response, tumor shrinkage.</td>
</tr>
<tr>
<td>Group 2</td>
<td>Multiple metastasis, rapid progression, associated symptoms even in patients</td>
</tr>
<tr>
<td></td>
<td>without major co-morbidities</td>
</tr>
<tr>
<td></td>
<td><strong>Goal:</strong> Disease control, symptom improvement.</td>
</tr>
<tr>
<td>Group 3</td>
<td>Multiple metastasis or organ involved, definitely never resectable, Mild symptoms</td>
</tr>
<tr>
<td></td>
<td>associated, co-morbidities</td>
</tr>
<tr>
<td></td>
<td><strong>Goal:</strong> Disease control, increased survival with preserved quality of life,</td>
</tr>
<tr>
<td></td>
<td>regimen with mild toxicity profile prefered..</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Treatment aim</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>0</strong></td>
<td>Clearly R0-resectable liver and/or lung metastases</td>
</tr>
<tr>
<td><strong>1</strong></td>
<td>Not R0-resectable liver and/or lung metastases only which&lt;br&gt;• Might become resectable after response to induction chemotherapy&lt;br&gt;• ±Limited/localized metastases to other sites, e.g. loco regional lymph nodes&lt;br&gt;• Patient is physically able to undergo major surgery (biological age, heart/lung condition) and more intensive chemotherapy</td>
</tr>
</tbody>
</table>
Clinical Groups 2 and 3

**Clinical presentation**

2. Multiple metastases/sites, with
   - Rapid progression and/or
   - Tumour-related symptoms and/or risk of rapid deterioration
   - Co-morbidity allows intensive treatment

3. Multiple metastases/sites, with
   - Never option for resection
   - and/or no major symptoms or risk of rapid deterioration
   - and/or severe comorbidity (excluding from later surgery and/or intensive systemic treatment, as for groups 1 + 2)

**Treatment aim**

- Clinically relevant tumour shrinkage as soon as possible
- At least achieve control of progressive disease

**Treatment intensity**

- Upfront active combination: at least doublet
- Abrogation of further progression
- Tumour shrinkage less relevant
- Low toxicity most relevant

- Treatment selection according to disease characteristics and patients preference re toxicity and efficacy:
  - “Watchful waiting” (exceptional)
- Sequential approach: start with
  - Single agent, or
  - Doublet with low toxicity
- Exceptional triplets
Hierarchy of factors for definition of treatment aim/group.

A. Potentially resectable after chemotherapy?
   - no
   - yes
      - Pat. can tolerate intensive CTx?
        - no
        - yes
        - Pat. can tolerate major surgery?
          - no
          - yes
          - Pat. can tolerate intensive CTx?
            - no
            - yes
          - INTERMEDIATE (group 2)
            - INTERMEDIATE (group 3)

B. Symptoms present or imminent? Aggressive tumor dynamics?
   - no
   - yes
   - Far advanced/ bulky disease
     - no
     - yes
     - Pat. can tolerate intensive CTx?
       - no
       - yes
     - INTERMEDIATE (group 2)
       - INTERMEDIATE (group 3)
Factors influencing the choice of 1st-line treatment in group 1, 2 and 3

Tumour biology-related factors

• Localization
  • Liver- or lung-only metastases versus multiple sites
  • Potentially R0-resectable lesions after induction chemotherapy and sufficient downsizing versus massive disease extension

• Growth dynamics
  • Aggressive versus indolent growth
  • Asymptomatic versus symptomatic disease
  • Imminent relevant tumour symptoms if low active or inactive treatment

• Second-line treatment after ineffective first-line single-agent treatment may not be possible anymore

• Chemosensitivity (not detectable before start of chemotherapy)

• Prognostic molecular or biochemical markers (e.g. BRAF mutation)
Factors influencing the choice of 1st-line treatment in group 1, 2 and 3

*Patient-related factors*
- Biological age
- Co-morbidity
- Physical capacity to tolerate more intensive treatment
- Eligibility for potential secondary resection of liver/lung
- Psychological capacity/willingness to undergo more intensive treatment

*Drug efficacy/toxicity profile of chemotherapy*
- Potential to induce maximal regression of metastases size/number
- Potential to prolong PFS or OS
- Toxicity profile
- Drug sensitivity/predictive biomarkers

*Drug availability and cost*
- Availability (depending on region)
- Reimbursement
- Cost/economic reasons
## 1st-line options according to clinical groups

<table>
<thead>
<tr>
<th>Group</th>
<th>RAS wild-type</th>
<th>RAS mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recommendation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Recommendation&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td>FOLFIRI + Pan/Cet ++ +</td>
<td>FOLFOX/XELOX + Bev +++</td>
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<tr>
<td></td>
<td>FOLFOX + Pan/Cet ++ +</td>
<td>FOLFOXIRI ++(+)&lt;sup&gt;b&lt;/sup&gt;</td>
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<td></td>
<td>FOLFOXIRI ++(+)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>FOLFOXIRI ++&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>FOLFIRI/XELIRI + Bev ++(+)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>FOLFIRI/XELIRI ++</td>
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<td></td>
<td>FOLFOX/XELOX +</td>
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<td></td>
<td>FOLFIRI/XELIRI +</td>
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<tr>
<td></td>
<td>IRIS +</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>FOLFIRI + Cet ++ +</td>
<td>FOLFOX/XELOX + Bev +++</td>
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<tr>
<td></td>
<td>FOLFOX + Pan/Cet ++ +</td>
<td>FOLFIRI/XELIRI + Bev ++(+)&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>IRIS +</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>FUFOL/Cape (mono) +++</td>
<td>FUFOL/Cape (mono) +++</td>
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<tr>
<td></td>
<td>FUFOL/Cape + Bev +++</td>
<td>FUFOL/Cape + Bev +++</td>
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<td>XELOX/FOLFOX ++</td>
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<tr>
<td></td>
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<td>IRIS +</td>
</tr>
<tr>
<td></td>
<td>Cet/Pan (mono) (+)</td>
<td>watchful waiting + selected pts.&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Watchful waiting + selected pts.&lt;sup&gt;d&lt;/sup&gt;</td>
<td>triplets (±Bev) + option for spec. situation</td>
</tr>
<tr>
<td></td>
<td>Triplets (+/−Bev or Cet/Pan) + option for spec.</td>
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</table>
ESMO consensus patients groups

• Additional predictive biomarkers should be incorporated in treatment decision
  – Ras phenotype allows to select for anti-EGFR therapy
  – Braf phenotype for chemotherapy intensification?
ESMO Group 2 mCRC

- Need for an active regimen for an aggressive tumor to stop tumor growth
  - Doublets or Triplets chemo-regimen are preferred
    - To be selected according to tolerance profile/pre-existing conditions
  - Targeted agents may be used in combination with chemotherapy for improved efficacy
    - Decision should be based on RAS phenotype and contra-indications

- In some cases, patient file should be reviewed in a MDT to discuss possible resection.
Preceptorship program: colorectal cancer

Group 3 patients
Clinical Group 3 for 1st-line treatment stratification

Clinical presentation

3. Multiple metastases/sites, with
   - Never option for resection
   - and/or no major symptoms or risk of rapid deterioration
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<td>FUFOL/Cape (mono)</td>
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<td>FUFOL/Cape (mono)</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>FUFOL/Cape + Bev</td>
<td>+++</td>
<td>FUFOL/Cape + Bev</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>XELOX/FOLFOX</td>
<td>++</td>
<td>XELOX/FOLFOX</td>
<td>++</td>
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</tr>
<tr>
<td>FOLFIRI/XELIRI</td>
<td>++</td>
<td>FOLFIRI/XELIRI</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>IRIS</td>
<td>+</td>
<td>IRIS</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Cet/Pan (mono)</td>
<td>(+)</td>
<td>watchful waiting</td>
<td>+ selected pts.&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Watchful waiting</td>
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<td>triplets (±Bev)</td>
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<td></td>
</tr>
<tr>
<td>Triplets (+/−Bev or Cet/Pan)</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Proposal for sequence of salvage-chemotherapy.


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ESMO Group 3 mCRC

• Multiple strategies are possible

• Several lines will be used

• The important points are:
  – To try to use all available agents
  – Drug re-introduction may apply
  – To improve survival and preserve quality of life

• Stop and Go strategies are convenient and may allow longer treatment overall
ESMO Group 3 mCRC
Targeted agents + Chemotherapy

- Bevacizumab is active in combination with chemotherapy
  - Survival benefit is not constantly seen but PFS is
  - Risk factors should be considered
  - If used, should be preferred in early lines
  - No activity as single agent
  - To be discussed if maintenance is used
ESMO Group 3 mCRC

• Anti-EGFR Monoclonal Antibodies are generally used at a later line of treatment in this patients population
  – Patients should be selected according to K and N RAS wt
  – No sequential trials in this group of patients are available
  – Upfront use of anti EGFR MoAb has been reported in small trial with high efficacy
  – Most frequently used in 3rd or 4th line
State of Art for treatment strategy in mCRC

• ESMO consensus guidelines as a reference in clinical practice

• Each individual patient should be referred to 1 of the 4 groups
  – Treatment goal will be stated upfront
  – Treatment options will be identified for discussion
ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making


Annals of Oncology Advance Access published September 4, 2014

clinical practice guidelines

Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

E. Van Cutsem, A. Cervantes, B. Nordlinger & D. Arnold, on behalf of the ESMO Guidelines Working Group*

1Digestive Oncology, University Hospitals Leuven, Leuven, Belgium; 2Department of Hematology and Medical Oncology, INCLMA, University of Valencia, Valencia, Spain; 3Department of General Surgery and Surgical Oncology, Hôpital Ambroise Paré, Assistance Publique – Hôpitaux de Paris, Paris, France; 4Klinik für Tumorbiologie, Freiburg, Germany

Updated Consensus conference to be published in Annals: Summer 2015
Metastatic Colorectal cancer
Basic strategy and groups (RASwt/mut, BRAF mut)

- Based on present molecular profile and treatment availability
  - mCRC should be split according to:
    - Mutational status of RAS and Braf
    - Metastatic spread
      - Single organ (LLD) potentially resectable
      - Multiple organs never resectable
  
- Treatment strategy should be offered accordingly
  - After MultiDisciplinary Team discussion
  - Patients characteristics and desire